reduced activity of the variant enzyme with Thr^{70} might have resulted in the abnormal pharmacokinetics in patient 1.

The allelic frequency of the 208G>A polymorphism of the *CDA* gene in the Japanese population is 4.3% (10). Recently, genetic polymorphisms in the gemcitabine metabolic pathway, including *CDA* SNPs in Europeans and Africans, were reported by Fukunaga et al. (15). The SNP 208G>A was not detected in Europeans, whereas the allelic frequency of 208A was 0.125 in Africans (15). According to the two previous studies (10, 15), frequencies of homozygous 208G>A individuals in the Japanese and African populations were estimated to be about 0.18% and 1.56%, respectively. Therefore, severe toxicity caused by 208G>A could occur more frequently in Africans than in Japanese.

Based on the results of the analyses of the pharmacokinetic profiles and the 208G>A SNP, we can conclude that decreased CDA activity might have been responsible for the severe drug toxicity observed in this Japanese cancer patient.

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Phase I Study of Fixed Dose Rate Infusion of Gemcitabine in Patients with Unresectable Pancreatic Cancer

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Objective: The purpose of this study was to determine the feasible dose of gemcitabine when administered as a fixed dose rate infusion (10 mg/m^2/min) on a weekly schedule to Japanese patients with unresectable advanced pancreatic cancer.
Methods: Patients were required to have histologically or cytologically proven locally advanced or metastatic pancreatic cancer for which they had received no previous chemotherapy. Gemcitabine was administered intravenously weekly for three consecutive weeks every 4 weeks. Patients at three dose levels were scheduled to receive escalating doses of gemcitabine: 1000 mg/m^2 over 100 min (Level 1), 1200 mg/m^2 over 120 min (Level 2) and 1500 mg/m^2 over 150 min (Level 3).
Results: A total of 16 patients were enrolled in this study between December 2003 and September 2004. Maximum-tolerated dose was not reached during the first course. Dose-limiting toxicity was Grade 4 neutropenia. Grade 3 or 4 neutropenia was observed at Level 3 in all six patients in the first course, and administration of gemcitabine on Day 8 or 15 was skipped in all six patients. Non-hematologic toxicity was mild and the most common symptoms were anorexia, nausea and vomiting. Partial response was achieved in 1 of the 17 patients (7%). Median overall survival was 7.3 months.
Conclusions: Gemcitabine administered at a rate of 10 mg/m^2/min was tolerated up to 1500 mg/m^2, but 1200 mg/m^2 represented a more appropriate recommended dose in further studies owing to neutropenia in Japanese patients with advanced pancreatic cancer.

Key words: advanced pancreatic cancer – systemic chemotherapy – gemcitabine – fixed dose rate infusion

INTRODUCTION

Pancreatic cancer is the fifth most common cause of cancer death in Japan, with an estimated 19 000 deaths annually (1). Early-stage diagnosis of pancreatic cancer is difficult because of the lack of specific early symptoms, and surgery with curative intent can be performed in only 5–20% of patients (2). The prognosis for unresectable pancreatic cancer remains extremely poor.

Gemcitabine (2′,2′-difluorodeoxycytidine) is a novel pyrimidine antimetabolite with a broad spectrum of antitumor activity against various solid tumors, such as pancreatic and lung cancer (3). This prodrug is initially phosphorylated by deoxycytidine kinase to gemcitabine monophosphate, with subsequent phosphorylation steps yielding gemcitabine di- and triphosphate (4). Gemcitabine triphosphate inhibits DNA synthesis by competing with deoxycytidine triphosphate for incorporation into DNA by DNA polymerase (5). A dose of 790 mg/m^2 gemcitabine weekly for 3 weeks every 28 days was recommended for Phase II studies on the basis of a Phase I study in which gemcitabine was administered as a once-weekly 30 min bolus infusion (6). This dosing schedule was used in subsequent Phases II and III studies, and once-weekly 30 min infusion of the 1000 mg/m^2 dose was subsequently selected as the standard schedule (7,8). In a randomized clinical trial, gemcitabine was confirmed to provide a survival advantage over 5-FU in addition to symptom-relieving benefits in patients with advanced pancreatic cancer (8). Based on these results, gemcitabine has generally been accepted as the standard chemotherapeutic agent for advanced pancreatic cancer. However, the advantages in terms of survival rate are inadequate, and various chemotherapeutic regimens have been investigated in clinical studies in efforts to prolong survival.

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The cellular pharmacokinetics of the active metabolite, gemcitabine triphosphate, in mononuclear cells have been examined in previous studies, and the rate of gemcitabine triphosphate accumulation and peak intracellular concentration were highest at a dose rate of 350 mg/m^2 over 30 min, during which steady-state gemcitabine levels of 15–20 μmol/l were achieved in plasma (6,9). A dose ~10 mg/m^2/min that achieves plasma gemcitabine concentrations of 15–20 μmol/l would thus maximize the intracellular rate of accumulation for gemcitabine triphosphate. This schedule of gemcitabine administration, with fixed dose rate (FDR) infusion of 10 mg/m^2/min, would enable exposure to higher concentrations of gemcitabine, and should improve clinical efficacy.

Phase I studies of FDR infusion of gemcitabine in the United States recommended a Phase II dose of 1500 mg/m^2 (10,11). A subsequent randomized Phase II trial comparing this FDR gemcitabine infusion schedule and high-dose gemcitabine (2200 mg/m^2) using a standard 30 min infusion showed improved median survival time for the FDR arm (12). The FDR infusion schedule is expected to become the optimal method of gemcitabine administration, but has not previously been assessed in Japan. We, therefore, conducted a Phase I study to determine whether FDR infusion of gemcitabine would be tolerated in Japanese patients with unresectable advanced pancreatic cancer. The primary objectives of this study were to confirm whether the recommended dose in the United States, 1500 mg/m^2 over 150 min, would be feasible in Japanese patients and to determine the relationship between dose and toxicity for gemcitabine administered using the FDR infusion schedule. The secondary objective was to evaluate antitumor activity of the schedule.

PATIENTS AND METHODS

Patients Eligibility

Eligibility criteria for enrollment in the study were as follows: (i) histologically confirmed pancreatic ductal adenocarcinoma; (ii) unresectable locally advanced or metastatic disease; (iii) no previous treatment for pancreatic cancer except surgery; (iv) age ≥20 and ≤74 years old; (v) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (vi) adequate bone marrow (leukocyte count ≥4000 cells/mm^3, platelet count ≥100 000 cells/mm^3 and hemoglobin ≥9.0 g/dl), renal function (serum creatinine concentration ≤upper limit of normal) and hepatic function (serum bilirubin level ≤2.0 mg/dl, serum albumin level ≥3.0 g/dl, serum aspartate and alanine transaminase (AST and ALT) levels ≤2.5 times upper limit of normal); (vii) life expectancy ≥8 weeks; and (viii) written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice, and these patients were required to have serum bilirubin levels of ≤2.0 mg/dl and serum AST and ALT levels ≤5 times the upper limit of normal before enrollment. Exclusion criteria comprised serious complications such as active infection, active gastrointestinal ulcer, cardiac disease or renal disease; central nervous system metastasis; marked pleural effusion or ascites; symptomatic interstitial pneumonitis; and pregnancy or lactation for women. This protocol was approved by the National Cancer Center's institutional review board for clinical investigation.

Treatment Methods

Gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) was administrated intravenously at 10 mg/m^2/min, weekly, for three consecutive weeks, followed by a week of rest. This cycle was continued until disease progression or serious adverse effects developed or until the patient requested discontinuation. When patients developed leukopenia of <2000/mm^3, neutropenia of <1000/mm^3, thrombocytopenia of <70 000/mm^3, total bilirubin >2.0 mg/dl or AST and ALT levels >5 times the upper limit of normal, gemcitabine administration was suspended until the patient recovered. If a rest period of >4 weeks was required owing to toxicity, the patient was withdrawn from the study.

Study Designs

Patients at three dose levels were scheduled to receive escalating dose of gemcitabine. At the first dose level (Level 1), gemcitabine was administered at a dose of 1000 mg/m^2. The dose level was increased to 1200 mg/m^2 for Level 2 and 1500 mg/m^2 for Level 3. Patient cohorts had a minimum of three patients at each level. If no dose-limiting toxicity (DLT) was observed in the initial three patients during the first cycle of treatment, the dose was advanced to the next level. If DLT occurred in the initial three patients, three additional patients were studied at the same dose level. If two or more of these six patients experienced DLT at that level, the dose was escalated to the next level. The maximum-tolerated dose (MTD) was defined as the highest dose level at which more than two of the six patients experienced DLT during the first cycle of treatment. If DLT occurred in three patients at Level 1, the dose was reduced to 800 mg/m^2 (Level 0). DLT was defined as follows: (i) Grade 4 leukopenia or neutropenia; (ii) febrile neutropenia; (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion; (iv) ≥Grade e 3 non-hematological toxicity with the exception of nausea, vomiting, anorexia, fatigue and constipation; and (v) any toxicity requiring two consecutive skips of administration or a >4 week delay in treatment. Toxicity was graded according to the National Cancer Institute common toxicity criteria version 2.0.

Clinical Assessments

Physical examination, complete blood cell counts, serum chemistries and urinalysis were performed at baseline and at least once weekly after initiating treatment. Patients underwent dynamic computed tomography (CT) to evaluate response at 4–8 week intervals after start of treatment. CT was performed by obtaining contiguous transverse sections using the helical scanning method at a section thickness of 5 mm. Tumor response was assessed according to the World Health Organization criteria (13). Serum carbohydrate antigen (CA)19-9

levels were measured monthly by immunoradiometric assay. Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression or death owing to any cause. Overall survival was calculated from the first day of treatment until death owing to any cause. Survival data were analysed using the Kaplan–Meier method.

RESULTS

PATIENT CHARACTERISTICS

Between December 2003 and September 2004, a total of 16 patients were enrolled in this study. Dose escalation schedule and the number of patients at each level are shown in Table 1. The first administration of 1200 mg/m^2 of gemcitabine in one patient receiving Level 2 was later found to have been infused over 90 min, departing from the FDR of 10 mg/m^2/min. As a result, an additional patient was added to Level 2 and ultimately seven patients were treated at Level 2. Patient characteristics are shown in Table 2. The 16 patients received 60 courses of gemcitabine. Median number of courses administered per patient was 3 (range 1–9 courses). All 16 patients were evaluable for toxicity, but the Level 2 patient not infused with gemcitabine at a rate of 10 mg/m^2/min was excluded from the evaluation of DLT.

TOXICITY

Toxicities of the 15 patients evaluated for DLT during the first course are shown in Table 3. The first three patients enrolled on Levels 1 and 2 did not experience any DLT, but one of the six patients at Level 3 experienced DLT. MTD was not reached in this study. However, since all six patients at Level 3 (1500 mg/m^2 over 150 min) experienced Grade 3 or 4 neutropenia after Day 1 or 8 of the first course and did not receive the second or third dose of gemcitabine, an additional three patients were entered at Level 2 to accurately determine the recommended FDR for gemcitabine. Finally, no Grade 4 hematological toxicity was observed in any of the six patients at Level 2, and Grade 3 neutropenia developed in three of these patients. While five of the six patients received the full three doses of gemcitabine in the first course, the remaining patient did not receive the third dose owing to Grade 3 neutropenia. Level 2 (1200 mg/m^2) was therefore selected as the recommended dose for further studies of this FDR gemcitabine regimen in Japan.

Table 1. Dose escalation scheme

Dose levels	Gemcitabine (mg/m^2/wk)	Infusion time (min)	*n*
1	1000	100	3
2	1200	120	7
3	1500	150	6

Table 2. Patient characteristics

Variable	No. of patients (n = 16)
Gender	
Male	7
Female	9
Median age (range)	62 (47–74) years
ECOG performance status	
0	11
1	4
2	1
Disease stage	
Locally advanced	3
Metastatic	13
Site of metastatic disease	
Liver	10
Lung	3
Distant lymph nodes	2
CA19-9 before treatment (U/ml)	
≤37	4
>37, ≤1000	6
>1000	6

ECOG, Eastern Cooperative Oncology Group; CA19-9, carbohydrate antigen 19–9.

Table 3. Toxicities across first course by patient

	Dose levels											
	Level 1 (n = 3)				Level 2 (n = 6)				Level 3 (n = 6)			
	Grades				Grades				Grades			
	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	0	0	2	0	3	1	2	0	0	2	4	0
Neutropenia	0	0	2	0	1	2	3	0	0	0	5	1
Anemia	1	1	2	0	2	3	0	0	4	2	0	0
Thrombocytopenia	1	2	0	0	2	0	1	0	0	2	1	0
Anorexia	1	1	0	0	2	0	1	0	2	2	0	0
Nausea	1	1	0	0	1	0	1	0	4	1	0	0
Vomiting	0	1	0	0	0	0	1	0	1	1	0	0
Rash	0	0	0	0	2	2	0	0	1	3	0	0
Fatigue	2	0	0	0	2	0	0	0	0	1	0	0
Fever	0	1	0	0	0	0	0	0	1	0	0	0
Mucositis	0	1	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	1	0	0	0
AST, ALT elevation	0	1	0	0	1	1	0	0	0	1	0	0

AST, serum aspartate transaminase; ALT, serum alanine transaminase.

Toxicities throughout the entire period of this protocol were assessed in all 16 patients enrolled in this study (Table 4). The most common toxicity was leukopenia, particularly neutropenia, with 13 of the 16 patients (81%) developing Grade 3 or 4

Table 4. Toxicities during entire course by patient

	Dose levels											
	Level 1 (n = 3)				Level 2 (n = 7)				Level 3 (n = 6)			
	Grades				Grades				Grades			
	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	0	0	2	0	2	2	3	0	0	1	4	1
Neutropenia	0	0	2	0	1	1	5	0	0	0	3	3
Anemia	1	0	2	0	1	5	1	0	3	2	1	0
Thrombocytopenia	1	2	0	0	2	1	1	0	0	2	2	0
Anorexia	1	0	1	0	4	0	1	0	4	2	0	0
Nausea	1	0	1	0	4	0	1	0	5	1	0	0
Vomiting	0	0	1	0	2	0	1	0	1	1	0	0
Constipation	0	0	0	0	0	1	0	0	1	0	0	0
Diarrhea	0	0	0	0	1	0	0	0	0	0	0	0
Rash	0	0	0	0	3	2	0	0	1	2	0	0
Fatigue	1	1	0	0	2	0	0	0	0	1	0	0
Fever	0	1	0	0	0	0	0	0	2	0	0	0
Mucositis	0	1	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	1	1	0	0	3	0	0	0
AST, ALT elevation	0	1	0	0	1	1	0	0	0	1	0	0

AST, serum aspartate transaminase; ALT, serum alanine transaminase.

neutropenia during treatment. Non-hematological toxicities were generally mild at all levels, and one patient developed Grade 3 nausea, vomiting, and anorexia at Level 1 and Level 2, respectively. Skin rashes were mild, but tended to occur in a larger number of patients as the dose was escalated.

Tumor Response and Survival

Partial response was achieved in 1 of the 16 patients (6.3%), but no complete responses were observed. Overall response rate was thus 6.3% (95% confidence interval = 0.2–30.2%). No change was noted in 12 patients (75.0%), and progressive disease was in two patients (12.5%). The patient with DLT was not evaluated for tumor response because she received standard gemcitabine chemotherapy as second-line chemotherapy before the evaluation. Serum CA19-9 levels were reduced to >50% in 2 of the 12 patients (16.7%) in whom pretreatment level was elevated to above the upper limit of normal.

Disease progression was finally observed in all patients and 12 of the 16 patients died of disease progression. Median progression-free survival was 3.2 months, and overall median survival time (MST) was 7.3 months (Figs 1 and 2).

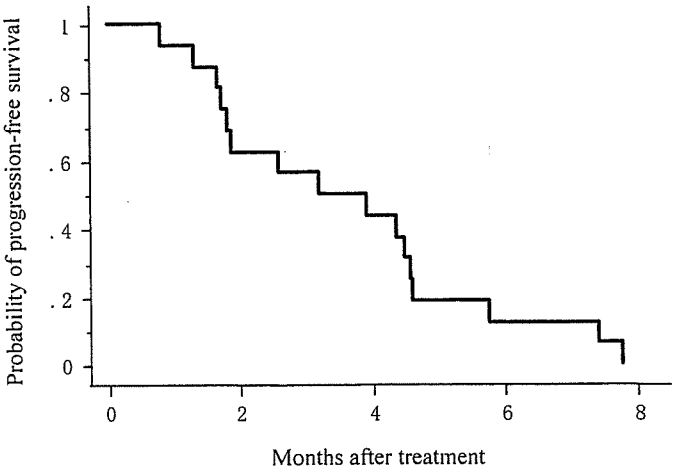

Figure 1. Progression-free survival of all 16 patients.

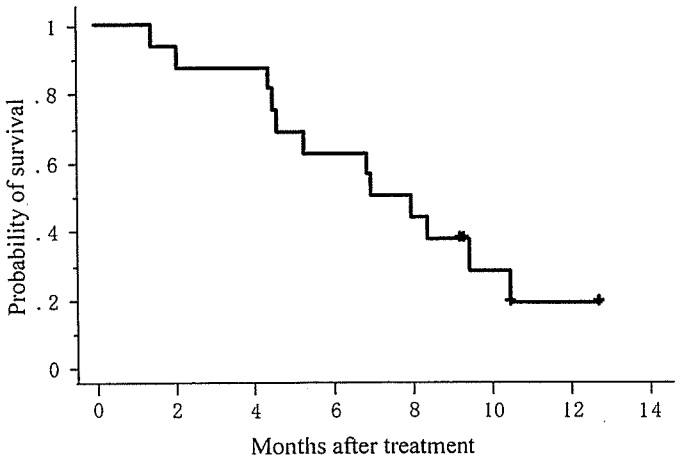

Figure 2. Overall survival of all 16 patients.

DISCUSSION

Gemcitabine is a prodrug that requires initial intracellular phosphorylation by deoxycytidine kinase, ultimately undergoing phosphorylation to the active gemcitabine triphosphate, a cytotoxic agent that inhibits DNA synthesis. Tempero et al. (12) reported on intracellular concentrations of gemcitabine triphosphate in peripheral blood mononuclear cells in a randomized trial comparing FDR infusion over 150 min and high-dose gemcitabine (2200 mg/m^2) using a standard 30 min infusion. The rate of gemcitabine triphosphate accumulation in patients who received conventional infusion decreased markedly after the end of infusion (30 min), whereas patients who received gemcitabine as FDR infusion exhibited linear accumulation of the triphosphate throughout the infusion. Intracellular gemcitabine triphosphate concentration in the FDR arm was 2-fold higher than that in the conventional infusion arm.

In the United States, two Phase I studies have been performed to determine the recommended dose for FDR infusion of gemcitabine (10,11). Brand et al. (11) conducted a Phase I study at dose levels of 1200 mg/m^2, 1500 mg/m^2 and 1800 mg/m^2, administered on Days 1, 8 and 15 of a 28 day cycle. MTD was defined as 1500 mg/m^2, with granulocytopenia and thrombocytopenia representing the DLTs. Brand et al. concluded that myelosuppression was more severe than

anticipated based on previous reports regarding standard gemcitabine administration. Touroutoglou et al. (10) conducted the other Phase I study of FDR infusion of gemcitabine in which the weekly dose was escalated from 1200 to 2800 mg/m^2 for 3 weeks every 4 weeks. They reported that MTD was 1800 mg/m^2, and recommended a Phase II starting dose of 1500 mg/m^2 owing to myelosuppressive effects.

The present study evaluated the safety of FDR infusion of gemcitabine and identified the feasible dose for Japanese patients with unresectable advanced pancreatic cancer. This Phase I study was conducted using dose levels of 1000, 1200 and 1500 mg/m^2, administered on Days 1, 8 and 15 of the 28 day cycle. DLT was observed in only one patient at Level 3, and MTD was not reached in this study. However, all six patients displayed Grade 3 or 4 neutropenia during the first course at Level 3, and no patient received all three doses of gemcitabine during the first course. In contrast, three patients at Level 2 experienced Grade 3 neutropenia, and only one patient had to skip the dose of gemcitabine on Day 15. Based on these results, the recommended dose should be 1200 mg/m^2 in further studies of FDR infusion of gemcitabine in Japan from the perspective of dose intensity for gemcitabine.

Preclinical data, using primary human tumor cell lines including pancreatic carcinoma, have suggested a possible dose–response relationship, and exposure to high concentrations of gemcitabine, independent of infusion duration, might correlate with improved cytoxicity and enhanced clinical effectiveness (12). Thus, a randomized trial of gemcitabine comparing high-dose gemcitabine (2200 mg/m^2) administered using a standard 30 min infusion to FDR infusion of 1500 mg/m^2 over 150 min was conducted in patients with locally advanced or metastatic pancreatic cancer according to the results of two Phase I studies in the United States (10–12). Although no difference in tumor response was noted between the 30 min infusion and FDR arms, MST was reported as 5.0 months in the 30 min infusion arm and 8.0 months in the FDR arm (P = 0.013), and 1 and 2 year survival rates were 9.0 and 2.2%, respectively, in the 30 min infusion arm, and 28.8 and 18.3%, respectively, in the FDR arm. In the study conducted by Burris et al. (8), MST for gemcitabine using the standard 30 min infusion of 1000 mg/m^2 was 5.7 months, and 1 and 2 year survival rates were 18 and 0%, respectively. A retrospective analysis reported that the MST of patients in Japan treated with gemcitabine by standard infusion of 1000 mg/m^2 was 5.7 months (14). In comparison, survival outcomes of patients treated using the standard 30 min infusion are similar, and MST is <6 months. In contrast, in a study with a limited number of patients using FDR infusion, MST was 7.3 months and similar to MST in the FDR arm of the randomized trial in the United States (12).

The most common toxicity for FDR infusion was myelosuppression, particularly neutropenia, as noted in a randomized trial by Tempero et al. (12). In our study, Grade 3 or 4 neutropenia developed in 81.3% of patients, and Grade 3 or 4 leukopenia and thrombocytopenia were observed in 62.5 and 18.8%, respectively. By contrast, a Phase I study for the standard infusion of gemcitabine in Japan reported rates of Grade 3 or 4 neutropenia, leukopenia and thrombocytopenia of 36.4, 27.3 and 0%, respectively (15). The FDR infusion schedule thus seems more hematologically toxic. Conversely, the non-hematological toxicity of FDR infusion was relatively mild. Grade 3 nausea and vomiting that occurred in 12.5% of patients on FDR infusion resembled the results obtained with standard infusion in the Japanese Phase I study, in which 9.1% of patients developed Grade 3 nausea and vomiting. Skin rashes were more frequent with FDR infusion, with 50% of patients developing Grade 1 or 2 skin rashes, than with standard infusion, in which 27.3% of patients developed Grade 1 or 2 skin rashes.

Various regimens of gemcitabine in combination with potentially synergistic drugs have been trialed to improve prognosis in patients with unresectable pancreatic cancer (16–22), and FDR infusion of gemcitabine has also been applied to combination chemotherapy with other anticancer drugs (20–22). A Phase III study comparing standard infusion of gemcitabine, FDR infusion of gemcitabine and combined FDR infusion of gemcitabine and oxaliplatin is under way as an ECOG study in the United States. The results of that study should be awaited before deciding whether FDR infusion of gemcitabine alone can be used as the standard treatment for unresectable pancreatic cancer. However, data from the present study confirm that FDR infusion of gemcitabine is tolerated by Japanese patients, and continued evaluation of FDR infusion, alone or in combination with other agents, is warranted in Japan.

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A Phase I/II Study of Combination Chemotherapy with Gemcitabine and 5-Fluorouracil for Advanced Pancreatic Cancer

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Background: In an effort to improve efficacy of single-agent gemcitabine in pancreatic cancer, several studies have examined the effects of 5-FU combined with gemcitabine. However, no studies to date have been performed in Japanese patients. We thus conducted a phase I/II study of gemcitabine and infusional 5-FU in Japanese patients to determine a recommended dosage for this combination and clarify efficacy and toxicity.
Methods: Phase I evaluated the frequency of dose limiting toxicity of two 5-FU dosages (400 and 500 mg/m^2/day) infused continuously over 5 days combined with gemcitabine 1000 mg/m^2 × 3 every 4 weeks. Results from phase I determined the recommended dosage to be examined in phase II for effect on survival period, clinical benefit response (CBR), tumor response and safety.
Results: A total of 34 chemo-naive patients were entered into the study. All had a Karnofsky performance of ≥50 points and distant metastases. Dose limiting toxicities in phase I determined the recommended 5-FU dosage at 400 mg/m^2/day. Grade 3–4 hematological toxicities (neutropenia, leukopenia and thrombocytopenia) were the most common severe toxicities. For the 28 patients administered the recommended dosage, 1-year survival rate was 14.3%, median survival time 7.1 months and progression free survival 3.2 months. Seven patients achieved a 25% overall response rate and three showed 27.3% improvement in CBR.
Conclusion: Although a meaningful survival benefit over single-agent gemcitabine was not demonstrated, 5-FU 400 mg/m^2/day infused continuously over 5 days in combination with gemcitabine 1000 mg/m^2 × 3 every 4 weeks appeared to be a moderately effective palliative treatment with low toxicity in Japanese patients with metastatic pancreatic cancer.

Key words: pancreatic cancer – phase I/II study – chemotherapy – gemcitabine – 5-FU

INTRODUCTION

Pancreatic cancer is a virulent disease with an extremely poor prognosis. Of all the treatment modalities for pancreatic cancer, only surgical resection offers the opportunity for a cure. However, because of local extension and/or metastatic disease, only a small minority of pancreatic cancer patients are candidates for curative resection. Moreover, even for these selected patients, prognosis remains unsatisfactory because of the postoperative recurrence, indicating that surgery alone has only limited value in the treatment of pancreatic cancer. Accordingly, to improve the overall survival of patients with pancreatic cancer, there is an urgent need to develop an effective non-surgical treatment for this disease.

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Previously a randomized controlled study demonstrated that gemcitabine, a nucleoside analogue, was effective in palliating symptoms and prolonging survival in patients with advanced pancreatic cancer (1). In the present study, gemcitabine showed a statistically significant advantage in both clinical benefit response (CBR) (23.8% versus 4.8%, $P = 0.0022$) and median survival (5.65 versus 4.41 months, $P = 0.0025$) compared with weekly bolus 5-fluorouracil (5-FU). Although single-agent gemcitabine has been accepted worldwide as the first-line therapy for advanced pancreatic cancer, there is substantial room for improvement in chemotherapy for pancreatic cancer because single-agent gemcitabine provides only limited benefit with a median survival of 4–6 months (1–3).

One approach has been to look for possible agents to use in combination with gemcitabine. A promising candidate has been the fluoropyrimidine, 5-FU, a key chemotherapeutic agent for pancreatic cancer before introduction of gemcitabine. Initially two *in vitro* studies in HT-29 colon cancer cells

obstructive jaundice or liver metastasis, the 5-FU dosage could be reduced to a lower dosage level in subsequent courses or 5-FU could be omitted in subsequent courses when the lowest dosage (400 mg/m^2/day) of 5-FU was given. When patients had leukocytopenia (<2000/mm^2) or thrombocytopenia (70 000/mm^2) on day 7–8 or day 14–15, gemcitabine administration was omitted on that day and postponed to the next scheduled treatment day (12).

Step 2 (Phase II)

Step 2 began once the recommended dosage was determined in Step 1. Administration proceeded with the recommended dosage using the same dosing schedule as in Step 1.

Study Assessments

The objectives of Step 1 were to evaluate DLT frequency and to determine a recommended 5-FU dosage to be used with the standard dosage of gemcitabine in Step 2. The criteria of DLT included Grade 4 leukopenia or neutropenia, Grade 3 or higher neutropenia accompanied by fever (≥38°C) or infection (clinically or biologically confirmed), thrombocytopenia (<25 000/mm^3) or transfusion given to patient, Grade 3 non-hematological toxicity (except nausea/vomiting, anorexia, fatigue, hyperglycemia), AST and ALT > 10 times UNL, total bilirubin > 5 times UNL (patients with obstructive jaundice or liver metastasis) or gemcitabine administration omitted twice in succession. The primary endpoint of Step 2 was to evaluate the 1-year survival rate with the recommended dosage since statistically significant improvement was not recognized in objective tumor response (5% versus 0%), but was observed in survival period in a randomized phase III study comparing gemcitabine and 5-FU (1). The secondary endpoint was to evaluate CBR and objective tumor response, as well as the frequency and severity of adverse events.

CBR was evaluated by KPS and pain, as described elsewhere (13–15). KPS was recorded weekly by the physician. Pain was evaluated by measuring changes from baseline in pain intensity and morphine consumption (analgesic use other than morphine was converted to an equivalent morphine dosage). Each patient recorded pain intensity on a pain assessment card everyday. Patients who met at least one of the following criteria were defined as eligible for evaluation of CBR: (i) baseline KPS of 50–70 points, (ii) baseline pain intensity ≥ 20 (out of 100) as measured by the pain assessment card, (iii) baseline morphine consumption ≥ 10 mg/day.

Objective tumor response was assessed every 4 weeks. In the present study, the sizes of metastatic lesions were measured to evaluate tumor response, although pancreatic masses were not considered to be measurable because of the difficulty of accurately determining pancreatic tumor size with current imaging technology (16).

The Japan Society for Cancer Therapy criteria, which are fundamentally similar to the World Health Organization criteria and NCI Common Toxicity Criteria, were used to evaluate tumor responses and adverse events (17,18). The duration of tumor response was calculated from the first day of treatment. Duration of survival was also calculated from the first day of treatment using the Kaplan–Meier method.

Statistical Analysis

The sample size for the recommended dosage was determined as follows. The 1-year survival rate of existing treatments was assumed to be 5% in view of the 1-year survival rate observed in the Ueno et al. (19) study. To demonstrate that the true 1-year survival rate of the recommended dosage exceeded 5% at a one-sided significance level of 10% with a power of 80% when a normal approximation test was used the sample size for the recommended dosage needed to be at least 28 patients.

RESULTS

Patients and Treatments

Of the 36 patients who registered for the present study 34 patients were administered the study drugs: 12 patients completed Step 1 (phase I) and an additional 22 patients completed Step 2 (phase II). Table 1 shows the baseline characteristics for patients in Step 1 (Level 1: 6 patients and Level 0: 6 patients), Step 2 and the total number of patients (20) who received the recommended 5-FU dosage in combination with standard gemcitabine (Level 0). There were 20 males and 8 females (median age: 59) who completed at least one administration course at Level 0. All patients showed a good KPS of ≥80 points. The major metastatic lesions for patients who received the recommended dosage were liver (21 patients: 75.0%), lymph node (6 patients: 21.4%) and lung (5 patients: 17.9%).

In Step 1 the dosing criteria, as defined by observed DLT events, assigned patients to the starting (Level 1: 6 patients) and lower (Level 0: 6 patients) dosage levels. No patients were administered the study drugs at Level 2. The recommended dosage (Level 0) was determined by the DLT frequency observed for each level: Level 1 (3/6 patients), Level 0 (2/6 patients).

At Level 1 (Step 1), a total of 22 administration courses were given with a median of three courses for each patient. A total of 89 administration courses were administered at Level 0 (Steps 1 and 2) with a median of two courses for each patient. At the recommended dosage level (Level 0), 23 (8.7%) of 265 scheduled gemcitabine administrations and 1 (0.2%) of 445 scheduled 5-FU administrations were omitted. The dosage was reduced for two (0.8%) gemcitabine administrations, but no dosage reductions of 5-FU were needed. The actual weekly mean dosages administered were 653.4 mg/m^2 (87.1% of planned dosage) for gemcitabine and 478.7 mg/m^2 (95.7% of planned dosage) for 5-FU.

Table 1. Profile of pancreatic cancer patient population

Characteristics	Step 1		Step 2	Total at recommended dose (Level 0)
	Level 0	Level 1	Level 0	
No. of patients	6	6	22	28
Gender, *n* (%)				
Male	5 (83.3)	3 (50.0)	15 (68.2)	20 (71.4)
Female	1 (16.7)	3 (50.0)	7 (31.8)	8 (28.6)
Age, years				
Median	61	58	58	59
Range	50–69	50–63	43–72	43–72
KPS, *n* (%)				
100	1 (16.7)	1 (16.7)	4 (18.2)	5 (17.9)
90	5 (83.3)	5 (83.3)	13 (59.1)	18 (64.3)
80	0 (0.0)	0 (0.0)	5 (22.7)	5 (17.9)
Metastatic sites, *n* (%)				
Liver	5 (83.3)	5 (83.3)	16 (72.7)	21 (75.0)
Lung	1 (16.7)	1 (16.7)	4 (18.2)	5 (17.9)
Depth lymph node	1 (16.7)	0 (0.0)	5 (22.7)	6 (21.4)
Bone	0 (0.0)	0 (0.0)	1 (4.5)	1 (3.6)

KPS, Karnofsky performance status.

The reasons for treatment discontinuation in Steps 1 and 2 were disease progression (27 patients), Grade 3 hepatic dysfunction (2 patients), Grade 3 appetite loss and Grade 3 infection (1 patient), patient refusal due to Grade 3 gastric ulcer (1 patient), Grade 4 stomatitis (1 patient), patient refusal to be admitted to hospital (1 patient) and patient refusal to follow the study protocol (1 patient). All patients who discontinued the treatment due to adverse events recovered from these toxicities after treatment discontinuation.

Toxicity

All patients in Steps 1 and 2 were evaluated for toxicity. DLT in Step 1 was observed in three out of six patients at Level 1 and in two out of six patients at Level 0. At Level 1, neutropenia (Grade 4) occurred in two patients, and a combination of stomatitis (Grade 4), esophagitis (Grade 4) and increased gamma-glutamyltransferase (Grade 3) in one patient. Less severe DLT events were observed at Level 0: one patient had a gastric ulcer hemorrhage (Grade 3) and one patient a combination of infection (Grade 3) and neutropenia (Grade 3).

Table 2 summarizes the toxicities of all patients (20) who received the recommended dosage (Level 0). This combination therapy at the recommended dosage was generally well tolerated and no treatment-related toxic deaths were reported. Hematological toxicities, notably neutropenia and leukopenia, were the most common severe toxicities. The main Grade 3–4 hematological toxicities were neutropenia (53.6%), leukopenia (25.0%) and thrombocytopenia (10.7%). Hepatic dysfunction (elevated alanine aminotransferase: 17.9%), anorexia (7.2%) and nausea (25.0%) were also commonly observed as Grade 3–4 toxicities. However, the above reactions were all predictable since they are known to be associated with gemcitabine and/or 5-FU, and were well managed during the study.

Table 2. Adverse drug reactions at recommended dose

	Grade 1–4		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%
Hematologic toxicities						
Neutropenia	19	67.9	14	50.0	1	3.6
Leukopenia	22	78.6	7	25.0	0	0.0
Thrombocytopenia	18	64.3	3	10.7	0	0.0
Anemia	19	67.9	2	7.1	0	0.0
Non-hematologic toxicities						
Elevated ALT	13	46.4	5	17.9	0	0.0
Elevated γ-GTP	5	17.9	2	7.1	0	0.0
Increased serum ALP	4	14.3	2	7.1	0	0.0
Elevated AST	11	39.3	1	3.6	0	0.0
Increased serum bilirubin	5	17.9	1	3.6	0	0.0
Increased serum uric acid	1	3.6	0	0.0	1	3.6
Nausea	17	60.7	7	25.0	0	0.0
Vomiting	11	39.3	2	7.1	0	0.0
Gastric ulcer hemorrhage	1	3.6	1	3.6	0	0.0
Fatigue	14	50.0	1	3.6	0	0.0
Malaise	3	10.7	1	3.6	0	0.0
Infection	1	3.6	1	3.6	0	0.0
Anorexia/appetite impaired	19	67.9	7	25.0	2	7.2
Rash	12	42.9	1	3.6	0	0.0

ALT, alanine aminotransferase; γ-GTP, γ-glutamyltransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

Efficacy

Table 3 summarizes efficacy at the recommended dosage. Of the 28 patients who were administered the recommended dosage, 26 had died by completion of the study follow-up period. Four of these were classified as early deaths, which were defined as deaths within 91 days after beginning the first administration or within 29 days after the last administration, but all deaths were due to disease progression and not related to treatment. The 1-year survival rate was 14.3% [95% Confidence Interval (CI): 1.3–27.2%], median survival time 7.1 months (95% CI: 6.1–8.6 months) and progression free survival 3.2 months (95% CI: 1.7–4.6 months: Figure 1).

All of the 28 patients administered the recommended dosage were evaluable for tumor response; of these, 7 patients achieved a partial response for an overall response rate of 25.0% (95% CI, 10.7–44.9%). The median duration of the response was 4.8 months (range, 1.9–6.3 months), and

Table 3. Efficacy at recommended dose

Therapeutic outcome		
Median survival time	7.1 months	(95% CI, 6.1–8.6)
1 year survival rate	14.3%	(95% CI, 1.3–27.2)
Progression free survival	3.2 months	(95% CI, 1.7–4.6)
Tumor response		
Response rate	25.0%	(95% CI, 10.7–44.9)
Complete response (*n*)	0	
Partial response (*n*)	7	
Minor response (*n*)	0	
No change (*n*)	10	
Progressive disease (*n*)	10	
Not evaluable (*n*)	1[a]	
Clinical benefit response[b]	27.3%	(95% CI, 6.0–61.0)

CI, confidence interval.
[a]One patient discontinued due to early death and could not be evaluated for antitumor effects.
[b]Eleven patients were evaluable.

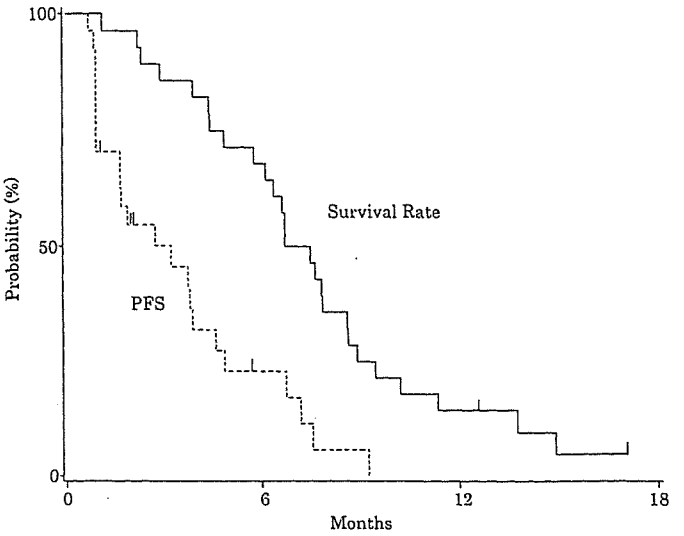

Figure 1. Survival rate and progression free survival (PFS) at recommended dose.

10 patients (35.7%) had stable disease and 10 patients (35.7%) had progressive disease. Tumor response was not determined in one patient due to a serious adverse event (hepatic dysfunction), which made it necessary for this patient to discontinue the study early.

Three of the 11 patients who met the CBR analysis criteria showed improvement in CBR for an overall improvement rate of 27.3% (95% CI: 6.0–61.0%). In all 3 patients, KPS was unchanged but pain intensity was reduced. Of the remaining eight patients, CBR was unchanged in three patients and aggravated in five patients.

DISCUSSION

Despite worldwide agreement about the role of gemcitabine as a first-line agent in advanced pancreatic cancer, therapies that can achieve more significant survival advantage are needed because the prognosis of patients with this disease remains very poor. Several phase II clinical trials combining gemcitabine with 5-FU have been performed using different sequences and schedules of administration (6–9,20–31). A review of the various combination regimens of gemcitabine and 5-FU used in these studies for the treatment of advanced pancreatic cancer found them to be well tolerated (32), although adding weekly intravenous bolus 5-FU to weekly gemcitabine did not confer a significant survival benefit in a randomized trial (10). This finding may be related to the power of the study or the mode of administration of 5-FU rather than to a lack of activity of 5-FU, and it may be possible that giving continuous infusional 5-FU would increase the efficacy of the regimen sufficiently to reach both clinical and statistical significance.

The primary objective of this trial was to find a recommended dosage of infusional 5-FU for use in combination with gemcitabine and to evaluate its efficacy and toxicity in Japanese patients with metastatic pancreatic cancer. Based on the results of our trial (Step 1), we found the recommended dosage to be 5-day continuous infusional 5-FU at 400 mg/m^2/day (Level 0). DLT findings seen in three of the six patients given 5-FU at 500 mg/m^2/day (Level 1) ruled this out as a recommended dosage. Neutropenia, which was observed as DLT in two patients at Level 1, was common in this combination. However, stomatitis and esophagitis in the remaining one patient, both of which were considered DLT and were also consistent with the toxicity profiles of 5-FU, might have been aggravated by Sjogren syndrome in this patient.

In 28 patients at the recommended dosage level, the most common toxicities were myelosuppression, liver dysfunction, appetite loss and nausea, all of which are well known as toxicities of these two agents. Four patients discontinued the treatment due to Grade 4 appetite loss, Grade 3 infection, and Grade 3 hepatic dysfunction, although most of these adverse reactions were transient and the overall toxicity profile in this regimen was acceptable. There appears to be no cumulative toxicity.

At the recommended dosage level, there was a 25% objective response rate with a 1-year survival rate of 14.3% and a median survival of 7.1 months. With respect to CBR, 3 of 11 evaluable patients (27.3%) showed a quality of life improvement. Compared with other reports of single-agent studies of gemcitabine or 5-FU, these results imply an additional benefit for the use of this scheme. Although the activity of this regimen seems to be consistent with results reported from previous studies that used infusional 5-FU in combination regimens (20–31), most of these have been associated with only a modest increase in response rate and/or survival. However, a definitive judgment of the superiority of this

combination is difficult because the majority of the data, including our results, represent only phase I or II trial outcomes.

Recently, Costanzo et al. (33) randomized patients with advanced pancreatic cancer to infusional 5-FU plus gemcitabine versus gemcitabine alone in a randomized phase II study. The results did not support better activity of the combination over gemcitabine alone. The overall response rate was 8% for gemcitabine alone and 11% for the combination, and the median survival time was 31 weeks and 30 weeks, respectively. Riess et al. (34) conducted a phase III study to compare the combination of gemcitabine and 5-FU administered as a continuous 24-h infusion, modulated by folinic acid, with gemcitabine monotherapy. This study also failed to demonstrate any benefit of the combination in terms of overall survival or time to tumor progression despite a manageable safety profile.

The concept of continuous 5-FU administration is evolving with the introduction of oral fluoropyrimidines. Herrmann et al. (35) compared the combination of gemcitabine plus capecitabine with gemcitabine alone in a randomized phase III study. However, no differences were observed with regard to response rate, progression free survival or overall survival. Recently, Cunningham reported a statistically significant survival benefit of capecitabine and gemcitabine combination over gemcitabine, although the role of fluoropyrimidines in the combination with gemcitabine remains controversial because the difference in the median survival time was only 1.4 months (36).

In conclusion, the regimen in the present study appears to be a moderately effective palliative treatment with a low toxicity profile for Japanese patients with metastatic pancreatic cancer. Since randomized trials failed to demonstrate a meaningful survival benefit for combinations of gemcitabine with fluoropyrimidine, including bolus 5-FU, infusional 5-FU and oral fluoropyrimidines such as capecitabine, caution should be taken before planning phase III studies until more promising regimens have been confirmed in phase II studies.

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Evaluation of Acute Intestinal Toxicity in Relation to the Volume of Irradiated Small Bowel in Patients Treated with Concurrent Weekly Gemcitabine and Radiotherapy for Locally Advanced Pancreatic Cancer

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Abstract. *Background: Treatment of concurrent gemcitabine and radiotherapy for pancreatic cancer was reported to have a higher rate of severe acute intestinal toxicity. This study evaluated the acute intestinal toxicity in relation to the volume of irradiated small bowel and other factors using dosimetric analyses in pancreatic cancer patients treated with gemcitabine-based chemoradiotherapy. Materials and Methods: The patient population was derived from a phase II trial of concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. Gemcitabine was administered weekly at a dose of 250 mg/m^2. The total dose was 50.4 Gy in 28 fractions using a four-field conformal technique. A dose-volume histogram was generated for the small bowel, colon and planning target volume (PTV) and dosimetric parameters were recorded. Correlations between the acute intestinal toxicity and the volume of irradiated small bowel and other factors were evaluated. Results: Forty-two patients enrolled between July 2001 and July 2002 were analyzed. Grade 3+ acute intestinal toxicities were observed in twenty-four (62%) patients. There was no correlation between the acute intestinal toxicity and the volume of irradiated small bowel. However, the total volume of PTV was shown to be significantly correlated with the development of Grade 3+ acute intestinal toxicity ($p=0.021$). Conclusion: The volume of irradiated small bowel did not directly influence the acute intestinal toxicity, but only the volume of PTV significantly correlated with severe acute intestinal toxicity.*

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Key Words: Pancreatic cancer, chemoradiotherapy, gemcitabine, intestinal toxicity.

Pancreatic cancer is usually diagnosed as an unresectable locally advanced or metastatic disease in most patients. In patients with locally advanced pancreatic cancer, chemoradiotherapy has been commonly used as a standard treatment since it was recognized that radiotherapy with concurrent 5-fluorouracil (5-FU) prolonged survival when compared to radiotherapy or chemotherapy alone (1-3). Various novel agents and radiation schedules have been examined in clinical trials to improve the efficacy of the treatment (4).

Gemcitabine is a novel deoxycitidine analog with a broad spectrum of antitumor activity against a variety of solid tumors, including pancreatic cancer, which has demonstrated greater clinical benefit and survival compared with 5-FU in patients with advanced pancreatic cancer (5). Gemcitabine has also been shown to be a potent radiosensitizer in human pancreatic cancer (6-8). Therefore, concurrent gemcitabine and radiotherapy are currently being examined in clinical trials, suggesting that the combination of radiotherapy and gemcitabine may improve survival in patients with locally advanced pancreatic cancer (9-13).

However, significant acute intestinal toxicity (AIT) in the treatment of concurrent gemcitabine and radiotherapy was reported compared with concurrent 5-FU and radiotherapy (9, 10, 14). In rectal cancer treated with concurrent chemoradiotherapy, a significant relationship between the intestinal toxicity and the volume of irradiated small bowel is well recognized from the results of examinations using small bowel contrast and orthogonal radiographs to calculate the volume of small bowel in the high-dose volume (15-17) and more accurately three-dimensional (3D) treatment-planning tools (18). However, it has not been reported whether the volume of irradiated small intestine is related to the degree of AIT in patients treated with concurrent chemoradiotherapy for pancreatic cancer. The purpose of this study was to evaluate the AIT in relation to

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the volume of irradiated small bowel and to other factors using dosimetric analyses in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer.

Materials and Methods

Patient population. The patient population for this study was derived from a phase II trial of concurrent weekly gemcitabine and radiotherapy for unresectable locally advanced pancreatic cancer at the National Cancer Center Hospital (19). Eligibility criteria for this phase II trial included histologically or cytologically confirmed nonresectable adenocarcinoma, 20-74 years of age, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, no evidence of distant metastasis, adequate hematological function (hemoglobin ≥10 g/dl, leukocytes ≥4000 mm^3, neutrophils >2000 mm^3, and platelets ≥100000 mm^3), adequate hepatic function (serum total bilirubin ≤2.0 mg/dl, and serum transaminase (aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) < 2.5 times the upper normal limit (UNL), adequate renal function (serum creatinine within normal limit) and written informed consent.

Treatment details and dosimetric analysis. Gemcitabine was administered intravenously over 30 min starting 2 h before radiotherapy, weekly for 6 weeks, at a dose of 250 mg/m^2, which had been previously determined in a phase I trial in our hospital (20). When grade 3 hematological toxicity, serum creatinine of 1.5-2.0 times UNL, total bilirubin level of 3.0-5.0 times UNL, serum AST/APT of 5.0-10 times UNL and/or grade 2 non-hematological toxicity (excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and dehydration) were observed, gemcitabine administration was omitted and postponed to the next scheduled treatment days.

Radiotherapy was delivered *via* a racetrack microtron (MM50, Scanditronix, Uppsala, Sweden) with a 25 MV X-rays. All patients had treatment planning computed tomography (CT) scans (X-vision, Toshiba, Tokyo, Japan), 5 mm thickness with a 5 mm slice interval, with oral small bowel contrast. The clinical target volume (CTV) included the primary tumor, nodal involvement detected by CT scan, and draining and para-aortic lymph nodes. The planning target volume (PTV) was defined as CTV plus a 10 mm margin in the lateral direction and a 10-20 mm margin in the cranio-caudal direction. Four-field techniques (anterior, posterior and opposed lateral fields) were used. The spinal cord dose was maintained below 45 Gy and ≥50% of the liver was limited to ≤30 Gy, ≥50% of both kidneys were limited to ≤20 Gy. The prescription dose was 50.4 Gy, delivered in 1.8 Gy daily fractions. FOCUS (version 3.2.1, CMS, St. Louis, MO, USA) was used as a radiotherapy treatment planning system. The individual loops of small bowel and colon were delineated on each slice of the planning CT scan from the upper end level of the liver to the lower end level of the kidneys. The volumes of small bowel receiving doses between 5 and 45 Gy were recorded from DVH at 5-Gy intervals.

Toxicity assessment. Patients were evaluated at least weekly during radiotherapy, prospectively. National Cancer Institute common toxicity criteria, version 2.0, were used for toxicity assessment. AIT was defined as any toxicity that could be related to the small bowel, which included nausea, vomiting, anorexia and diarrhea, according to the previous report for rectal cancer (17) and ≥grade 3 was considered severe toxicity.

Table I. *Patient characteristics.*

Characteristic	No. of patients (N=42)
Gender	
male	19
female	23
Age, years	
range	43-73
median	59
Performance status	
0	12
1	30
Tumor size, cm	
range	2.0-10.0
median	4.0
Tumor site	
head	20
body-tail	22

Statistical analysis. For each 5-Gy dose level from 5 to 45 Gy, an association between the volume of small bowel irradiated and grade 3+ AIT was analyzed. The differences in mean small bowel volume irradiated to each 5-Gy dose level from 5 to 45 Gy were assessed using the *t*-test for the equality of means. Univariate analysis comparing the clinical and treatment factors and grade 3+ AIT was performed using the Fisher's exact test. *P*-values less than 0.05 were considered to be statistically significant.

Results

Forty-two patients were enrolled in a phase II trial between July 2001 and July 2002, and all patients were entered in this study. The patient characteristics are shown in Table I. Forty patients completed the planned radiotherapy (50.4 Gy). Two patients discontinued radiotherapy. One patient stopped at 30.6 Gy because of duodenal bleeding and another patient stopped at 45.0 Gy because of refusal due to general fatigue. The number of times gemcitabine was administered was 6 times in 17 patients, 5 times in 15 patients, 4 times in 6 patients, 3 times in 2 patients and 2 times in 2 patients. Grade 3 and grade 4 non-hematological toxicities were observed in 31% and 33% of patients, respectively. Overall, the maximum AIT encountered during radiotherapy was grade 0 in 4 patients (9.5%), grade 1 in 9 patients (21.4%), grade 2 in 3 patients (7.2%), grade 3 in 12 patients (28.6%) and grade 4 in 14 patients (33.3%). Median and range values of the dosimetric parameters of small bowel, colon and PTV are shown in Table II. The volume of irradiated small bowel ranged from 43 cm^3 to 552 cm^3, with a median value of 251 cm^3 and the volume of

Table II. *Median and range values of dosimetric parameters.*

Parameter	Median	Range
Small bowel		
total volume, cm^3	274	47-663
irradiated volume, cm^3	251	43-552
max dose, cGy	5072	3079-5229
mean dose, cGy	1485	376-2915
Colon		
total volume, cm^3	403	120-714
irradiated volume, cm^3	397	117-686
max dose, cGy	5028	1975-5221
mean dose, cGy	1516	633-2848
Planning target volume		
total volume, cm^3	555	357-1215
max dose, cGy	5120	3106-5275
mean dose, cGy	4948	3002-5045

Table III. *Volume of irradiated small intestine at each 5-Gy dose level between 5 and 45 Gy vs. the degree of acute intestinal toxicity (mean±SE, cm^3).*

RT dose level (Gy)	Grade 0-2 toxicity	Grade 3-4 toxicity	*p*-value
5	169±99	182±99	0.669
10	150±94	161±92	0.707
15	140±90	148±90	0.787
20	64±41	66±50	0.873
25	53±36	55±42	0.879
30	49±33	50±40	0.910
35	43±27	45±36	0.864
40	38±23	41±32	0.786
45	32±20	35±28	0.715

PTV ranged from 357 cm^3 to 1215 cm^3, with a median value of 555 cm^3, corresponding to a cube of 8.2 cm on a side. The average volume of small bowel irradiated at each 5-Gy dose level between 5 and 45 Gy are shown in Table III.

The average volume of small bowel irradiated at each dose level was not significantly different between the group of grade 3+ AIT and the group of grade 0-2 AIT by the *t*-test for equality of means. The relationships between grade 3+ AIT and clinical factors are shown in Table IVa. No significant correlation was seen between grade 3+ AIT and clinical factors, including age, performance status, tumor size, tumor site, and number of times gemcitabine was administered. The relationships between grade 3+ AIT and the calculated parameters are shown in Table IVb. No significant correlation was seen between grade 3+ AIT and the volume of small bowel irradiated or other parameters regarding the small bowel and the colon. However, the total volume of PTV was shown to be significantly

Table IVa. *Univariate analysis of clinical and treatment factors related to the development of ≥ grade 3 acute intestinal toxicity.*

Characteristic	n	% toxicity	*p*-value*
Gender			
male	19	63.2%	
female	23	60.9%	>0.999
Age, years			
<60	22	54.5%	
≥60	20	70.0%	0.355
PS			
0	12	41.7%	
1	30	70.0%	0.158
Tumor size, cm			
≤4	22	54.5%	
>4	20	70.0%	0.355
Tumor Site			
head	20	65.0%	
body-tail	22	59.1%	0.758
Number of times gemcitabine was administered			
<5	10	80.0%	
≥5	32	56.3%	0.270

*Fisher's exact test.

Table IVb. *Univariate analysis of calculated parameters related to the development of ≥ grade 3 acute intestinal toxicity.*

Characteristic	n	% toxicity	*p*-value*
Small bowel			
irradiated volume, cm^3			
<250	18	66.7%	
≥250	24	58.3%	0.750
max dose, cGy			
<5100	30	60.0%	
≥5100	12	66.7%	0.740
mean dose, cGy			
<1500	22	63.6%	
≥1500	20	60.0%	>0.999
Colon			
irradiated volume, cm^3			
<400	22	59.1%	
≥400	20	65.0%	0.758
max dose, cGy			
<5000	16	68.8%	
≥5000	26	57.7%	0.530
mean dose, cGy			
<1500	21	66.7%	
≥1500	21	57.1%	0.751
Planning target volume			
total volume, cm^3			
<500	16	37.5%	
≥500	26	76.9%	0.021

*Fisher's exact test.

correlated with the development of grade 3+ AIT (p=0.021). The highest incidence of grade 3+ AIT was in patients with the volume of PTV ≥500 cm^3, corresponding to a cube of 7.9 cm on a side.

Discussion

We evaluated the relationship between the AIT and the volume of irradiated small bowel in patients treated with concurrent gemcitabine and radiotherapy for pancreatic cancer and univariate analysis revealed that the volume of irradiated small bowel, which was significantly related to AIT in the treatment of rectal cancer, did not correlate to the AIT here. Minsky *et al.* reported a significant relationship between AIT and the volume of irradiated small bowel in patients with rectal cancer treated with concurrent 5-FU-based chemotherapy and pelvic radiotherapy (17). Orthogonal radiographs were used to calculate the volume of small bowel within the treated volume, using the sum of the anterior-posterior film volume and the lateral film volume. The volume of small bowel in the pelvic radiation field was greater for patients who experienced grade 3+ AIT (441±153 cm^3) compared with those who experienced grade 0-2 acute intestinal toxicity (230±43 cm^3). Baglan *et al.* reported a strong dose-relationship for the development of grade 3+ AIT in patients treated with concurrent 5-FU based chemoradiotherapy for rectal cancer using three-dimensional (3D) treatment planning tools, the same as our method (18). A highly significant association was found between the development of grade 3+ AIT and the average volume of small bowel irradiated to each 5-Gy dose level between 5 and 40 Gy (p<0.001). The volume of small bowel that received at least 15 Gy (V15) was strongly associated with the degree of AIT.

The present report represents the first analysis of AIT using dosimetric analysis in pancreatic cancer treated with chemoradiotherapy. In this study, the patient population and treatment schedule was more homogeneous compared with previous reports for rectal cancer and toxicities were evaluated prospectively, because all patients entered in this analysis were previously enrolled in a clinical trial. The reasons for the different results regarding AIT and the volume of irradiated small bowel between rectal cancer and pancreatic cancer could be several. First, the agent of chemotherapy in the combination of radiotherapy was different between the two groups. In previous reports for rectal cancer, 5-FU based chemotherapy was used, while in our study for pancreatic cancer, gemcitabine was used. An *in vivo* study showed that there was markedly increased normal tissue toxicity, such as jejunal mucosa, when gemcitabine was given more than once a week in combination with radiotherapy (21). Second, the volume of irradiated stomach and duodenum may be related to the AIT in part, since in the treatment of pancreatic cancer the upper abdomen is irradiated and the stomach and duodenum are usually included in the treated volume. However, in this study we did not evaluate the volume of irradiated stomach since it was difficult to evaluate the volume of stomach, exactly, due to the great variation in volume depending on the time of day compared with the small bowel and colon. We also did not evaluate the volume of irradiated duodenum. Because most of the duodenum was included in the radiation field with prophylactic regional lymph node area, the volume of irradiated duodenum was considered similar among the patients.

We found that the PTV was significantly associated with severe AIT. This result indicates that a larger treated volume affects a large volume of normal tissue, not just the small bowel. Recently, in an attempt to decrease the toxicity in the treatment of gemcitabine-based chemoradiotherapy, researchers at the University of Michigan and M.D. Anderson Cancer Center performed and recommended radiation treatment planning, which set only the gross tumor in the target volume without a prophylactic regional lymph node area (11, 14, 22). These authors reported that the PTV ranged from 134 cm^3 to 465 cm^3, with a median value of 255 cm^3, corresponding to a cube of only 6.3 cm on a side, which was much smaller compared with conventional radiotherapy and patients were able to tolerate the treatment (22). Our result that the smaller PTV (<500 cm^3, corresponding to a cube of 7.9 cm on a side) had less acute intestinal toxicity supports their recommendation. However, the efficacy of treatment without prophylactic regional lymph node irradiation should be evaluated in clinical trials and a longer follow-up is needed.

In conclusion, the volume of irradiated small bowel did not directly influence the AIT in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. However, only the PTV significantly correlated with severe AIT. Reducing the treated volume, *e.g.*, by omitting prophylactic regional lymph node irradiation, seemed to result in decreased AIT when patients were treated concurrently with gemcitabine-based chemoradiotherapy.

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特集

化学放射線療法の現況ならびに対象症例の選択
(第41回日本癌治療学会総会より)

膵がんに対する放射線化学療法の現況と展望

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Chemoradiotherapy for Pancreatic Cancer－Current Status and Perspective－: Okusaka T[*1] and Ito Y[*2] ([*1]Hepatobiliary and Pancreatic Oncology Division, [*2]Radiation Oncology Division, National Cancer Center Hospital)

Chemoradiotherapy has been used in the management of pancreatic cancer both for treatment of locally advanced pancreatic cancer and as adjuvant therapy after resection. Postoperative chemoradiotherapy appeared to improve median survival in the GITSG trial, although recent European randomized studies did not confirm this result. In patients with locally advanced unresectable disease, three randomized trials have proved that chemoradiotherapy is slightly superior to either radiotherapy or chemotherapy alone. However, there is an urgent need to develop more effective nonsurgical treatment, because the survival for both resectable and unresectable pancreatic cancer patients remains unfavorable even after receiving chemoradiotherapy.

Key words: Pancreatic cancer, Chemoradiotherapy, Adjuvant therapy

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はじめに

わが国における膵がんの死亡数は年々増加傾向にあり，現在，年間約2万人が膵がんにより死亡し，がんによる死亡原因の第5位を占めている．膵がん患者の多くは切除が困難な状態で発見されており，日本膵臓学会膵癌全国登録調査報告によると，切除例は膵がん全体の42.6%（2000年）にとどまっている．切除は根治の期待できる唯一の治療法ではあるが，切除例の多くは術後早期に再発し，切除例の5年生存率はわずか12.2%となっている[1]．このような膵がん患者の予後を改善するためには手術療法のみでは限界があり，化学療法や放射線療法などの非手術療法の発展が必要である．本稿では，膵がん（浸潤性膵管がん）に対する放射線化学療法の成績を国内外の臨床試験の結果を基に解説し，現在進行中の試験や今後の展望についても述べる．

1. 膵がんの病態と治療の選択

膵がんの治療は，病態により選択され，一般にUICC（国際対がん連合，International Union Against Cancer）分類[2]のStage ⅡBまでが切除可能例，Stage Ⅲ以上が非切除例とされている（図1）．非切除例のうち，遠隔転移は認めないが腹腔動脈あるいは上腸間膜動脈に浸潤したUICC-Stage Ⅲ（局所進行例）には，後に述べる無作為化比較試験の結果，放射線療法と化学療法との併用療法（放射線化学療法）が標準的治療法と位置づけられ繁用されてきた．遠隔転移を認めるUICC-Stage Ⅳに対しては，化学療法を中心に様々な臨床試験が行われてきており，治療法の開発が進められてきている．

2. 切除例に対する補助放射線化学療法

膵がん切除後の患者の多くは術後早期に再発し，その予後は未だ不良である．これらの患者の

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Stage 0	Tis	N0	M0
Stage Ⅰa	T1	N0	M0
Stage Ⅰb	T2	N0	M0
Stage Ⅱa	T3	N0	M0
Stage Ⅱb	T1, T2, T3	N1	M0
Stage Ⅲ	T4	Any N	M0
Stage Ⅳ	Any T	Any N	M1

Tis	上皮内癌
T1	膵内に限局する最大径2 cm以下の腫瘍
T2	膵内に限局する最大径2 cmを超える腫瘍
T3	膵外進展あり
T4	腹腔動脈または上腸管膜動脈浸潤あり
N1	所属リンパ節転移あり
M1	遠隔転移あり

図1　UICC進行度分類（第6版）[2]

表1　術後補助療法に関する無作為化比較試験

報告者	報告年	症例数	補助療法	コントロール	50%生存期間（月）	P値	
GITSG[3]	1985	43	放射線化学療法	補助療法なし	20 vs 11	0.03	
Bakkevold[4]	1993	61	化学療法（AMF）	補助療法なし	23 vs 11	0.02	乳頭部癌を含む
EORTC[5]	1999	218	放射線化学療法	補助療法なし	24.5 vs 19	n.s.	乳頭部領域癌を含む
ESPAC[6]	2001	826	放射線化学療法*	*	15.5 vs 16.1	n.s.	
			化学療法（5-FU/LV）**	**	19.7 vs 14	0.0005	

AMF: doxorubicin, mitomicin C, 5-FU
LV: leucovorin
n.s.: 有意差なし
*：両群とも化学療法施行例を含む
**：両群とも放射線化学療法施行例を含む

予後の改善をめざして様々な補助療法が試みられており，欧米においては術後補助療法に関する無作為化比較試験が行われてきた（表1）．1985年，米国のGastrointestinal Tumor Study Group（GITSG）は補助療法として放射線化学療法を施行した群が無治療群に比べ，生存期間が有意に良好であることを報告している[3]．しかし，その後のEuropean Organisation for Research and Treatment of Cancer（EORTC）による無作為化比較試験では，放射線化学療法群と無治療群との間には有意差が得られていない[5]．さらに近年European Study Group for Pancreatic Cancer（ESPAC）により実施された比較試験では，化学療法（5-FU, leucovorin）群において有意な延命効果を認めたが，放射線化学療法群では延命効果が得られなかったことを報告している[6]．このように，米国においては術後補助放射線化学療法が標準的治療法として実地臨床でも用いられている一方，欧州で行われた臨床試験はこれを支持する成績が得られておらず，未だ一定の結論が得られていない．

3. 切除可能例に対する放射線化学療法と切除術の比較試験

わが国においては，切除可能例のうち比較的進行した症例を対象に放射線化学療法と切除術の比較試験が実施されている．膵癌取扱い規約第4版に基づき，1）S2, RP2, PV2のいずれか1つ