With this imperative, we surveyed the actual cost of PC treatment especially with respect to the difference after the introduction of a new drug, GEM. To our knowledge, this is the first report of a cost analysis of PC in Japan.

PATIENTS AND METHODS

PATIENTS

Since the day of our hospital opening in July 1992, we have recorded all patients admitted to our division. This database has been updated generally three times a week at our morning conference. We obtained an invasive ductal PC patient list from the database, and surveyed all case records between 1 April 2000 and 30 March 2002 (April 2001 ± 1 year) in the list. The reason we chose this period was to investigate the impact of GEM, which has been introduced to Japanese hospitals since April 2001. We collected each patient's baseline data at the time of diagnosis and their treatment histories. These included gender, age, computed tomography (CT) stage, site of metastasis, performance status according to the Eastern Cooperative Oncology Group criteria, serum level of carcinoembryonic antigen and carbohydrate antigen (CA) 19-9, primary treatment modalities, treatment costs (calculated from patient receipts), and date and cause of death.

TREATMENT

According to the CT stage at presentation, patients with resectable disease underwent resection, and we did not perform any adjuvant therapies until recurrence after surgery. As for locally advanced disease, we performed a combination of intraoperative and external-beam radiotherapy with 5-FU before April 2001 (9). After April 2001, we performed hypofractionated external-beam radiotherapy followed by GEM chemotherapy in selected patients with locally advanced PC (10). We had performed single agent chemotherapy for metastatic or recurrent PC in general by using 5-FU before April 2001, and GEM thereafter (7). Until November 2000, combination therapy of hepatic arterial infusion of 5-FU and external-beam radiation for the primary tumor had been performed in selected patients with no metastases other than in the liver (11).

Patients received a detail explanation about the studies and gave written informed consent after approval of the protocols by the Institutional Review Board of the National Cancer Center.

TREATMENT COST

In Japan, upon joining an organization, the employees and the families of those employed by government offices, and the private sector and public organizations automatically join the health insurance program. People who are not members of the Health Insurance Union have been required to join the National Health Insurance program, which is operated by municipalities throughout the nation, since 1961. The costs for medical services are regulated by the government and are the same throughout Japan, and people can receive medical services with 20–30% of the medical costs as their payment, based on this social security system.

Treatment costs are calculated from patient receipts of our hospital. Other than the uniform treatment costs regulated by the government, the costs in the current study included various actual expenses, such as private room charges, the cost of daily meals during hospitalization and medical certificates for private health insurance. Namely, the total costs meant total payments to the hospital for patients who did not join the Japanese health insurance system.

In the current study, treatment costs were described in terms of United States dollars ($) with the exchange rate at the time of data fixation, 30 June 2004, i.e. $1 = 109 Japanese yen (¥). For example, the cost of pancreaticoduodenectomy is $4825 (¥526 000), and 1 gram of GEM is $255 (¥27 825), in Japan.

ANALYSIS AND STATISTICS

We surveyed the treatment costs and survival data of patients, and examined the relationship among patients' characteristics, treatment costs and survival time. Total treatment cost from the first hospitalization to the death or 30 June 2004 (date of the data fixation), including all costs of every hospital visits and the last hospitalization for terminal care, was defined as the total treatment cost over a lifetime (TCL) in the current study.

Overall survival was measured from the first day of treatment to the date of death or last contact. All patients were censored on 30 June 2004, 14 months after treatment of the last patient. Survival curves were calculated by the Kaplan–Meier method. Differences in survival among subgroups classified by each factor were evaluated by log-rank tests.

Since the treatment costs were not shown to have a normal distribution, the Mann–Whitney test was used to compare the overall differences of them among the subgroups. Frequency analysis was performed with Fisher's exact test for 2×2 tables, and with the χ^2-test for 3×2 tables.

All analyses were performed using the statistical software SPSS 11.0J for Windows. Statistical significance was defined as a two-sided P-value of 0.05 or less.

RESULTS

A total of 113 PC patients were admitted during the 2 years survey. Among the 113 patients, the TCL was calculated in 54 patients, i.e. 49 who died in our hospital and 5 who were alive until 30 June 2004. The TCL was not available in the remaining 59, mainly because they went to other hospitals for terminal care. There was no difference in their backgrounds and the survival between the former 54 and the latter 59 (Table 1) other than the pretreatment CA 19-9 level, which was higher in the former 54.

In the 54 patients, TCL ranged from $4586 to $89 681 and the quartiles at 25, 50 and 75% were $24 046, $35 351 and $48 119, respectively. According to the CT stage, the median of TCL and survival time were $43 865 and 26.5 months for the resectable, $29 255 and 10.0 months for the locally

Table 1. Characteristics of 113 patients who were admitted between 1 April 2000 and 30 March 2002

Total treatment cost over a lifetime	Available (n = 54)	Not available (n = 59)	P-value
Gender			
Man	36	35	0.442†
Woman	18	24	
Age			
Median	59.5	65	0.076‡
CT stage			
Resectable	14	15	0.713§
Locally advanced	21	27	
Metastatic	19	17	
Performance status			
0 or 1	50	55	1.000†
2 or 3	4	4	
Location of the primary tumor			
Head	25	34	0.261†
Body-tail	29	25	
CEA (ng/ml)¶			
Median	7.4	6.8	0.496‡
CA 19-9 (U/ml)#			
Median	510.5	108	0.038‡
Primary treatment			
Surgery	14	15	0.335§
Chemoradiotherapy	20	29	
Chemotherapy or supportive care	20	15	
Survival time (month)			
Median	8.6	8.7	0.603*
95% Confidence interval	6.3–10.9	7.1–10.3	

*Log-rank test; †Fisher's exact test; ‡Mann–Whitney test; §χ^2-test; ¶carcinoembryonic antigen; #carbohydrate antigen 19-9.

Table 2. Characteristics of 54 patients who were completely followed in our hospital

Date of the first admission	Before April 2001 (n = 26)	After April 2001 (n = 28)	P-value
Gender			
Man	17	19	1.000†
Woman	9	9	
Age			
Median	59.5	65	0.206‡
CT stage			
Resectable	9	5	0.017§
Locally advanced	5	16	
Metastatic	12	7	
Performance status			
0 or 1	24	26	1.000†
2 or 3	2	2	
Location of the primary tumor			
Head	11	14	0.597†
Body-tail	15	14	
CEA (ng/ml)			
Median	4.75	9.65	0.063‡
CA 19-9 (U/ml)#			
Median	419	585	0.441‡
Primary treatment			
Surgery	9	5	0.107§
Chemoradiotherapy	11	9	
Chemotherapy or supportive care	6	14	
Gemcitabine chemotherapy over a lifetime			
Present	0	19	0.000†
Absent	26	9	

†Fisher's exact test; ‡Mann–Whitney test; §χ^2-test; ¶carcinoembryonic antigen; #carbohydrate antigen 19-9.

advanced, and \$30 676 and 4.8 months for the metastatic, respectively.

Differences After April 2001

Among the 54 patients available for TCL analysis, 26 were admitted before April 2001 (Group A) and the remaining 28 were admitted thereafter (Group B). The patients' characteristics in each group are shown in Table 2. The frequencies of locally advanced disease and gemcitabine chemotherapy were higher in Group B. As for the patients with locally advanced disease, GEM chemotherapy have been an alternative treatment choice in our hospital since April 2001. Accordingly, there was no significant difference between Groups A and B in the other baseline background factors, including primary treatment.

Table 3 shows several costs and survival times in Groups A and B. The total cost for anticancer agents was significantly higher in Group B than in Group A, whereas there were no significant differences as for overall survival and TCL between the groups. Among the cost of anticancer agents, a fraction of that in the outpatient clinic was the main cause that made the cost in Group B significantly higher than in Group A. Although there was no significant difference in hospital stay in the first admission between the two groups, the cost for the first admission in Group A tended to be high compared to that in Group B. The cost for the first admission included various imaging tests (Table 4). An average number of imaging tests per patient in the first admission was 5.0 in Group A and 3.9 in Group B. In 40 patients with locally advanced or metastatic disease, the median cost and hospital stay in the first admission in Group B (\$11 493 and 37 days, respectively) were lower than those in Group A (\$22 218 and 59 days,

Table 3. Treatment costs and survival of 26 patients who were admitted before gemcitabine introduction (April 2001) and 28 admitted thereafter

Date of the first admission	Before April 2001 (n = 26)	After April 2001 (n = 28)	P-value
Survival time (month)			
Median	7.4	8.8	0.952†
95% Confidence interval	5.5–9.3	4.5–13.2	
Total treatment cost over a lifetime ($)			
Minimum	10 028	4586	0.604‡
25 percentile	27 284	23 768	
Median	35 744	35 226	
75 percentile	47 989	50 680	
Maximum	89 681	61 400	
Total treatment cost/survival time ($/month)			
Minimum	895	331	0.307‡
25 percentile	2016	1654	
Median	3828	3182	
75 percentile	6957	4912	
Maximum	12 366	31 296	
Total cost for anticancer agents ($)			
Minimum	0	0	0.046‡
25 percentile	1603	3326	
Median	3136	5728	
75 percentile	4974	10 163	
Maximum	19 770	43 569	
Percentage of anticancer agents in total cost			
Minimum	0%	0%	0.022‡
25 percentile	5.4%	8.5%	
Median	9.7%	15.5%	
75 percentile	13.7%	25.4%	
Maximum	38.7%	80.3%	
Cost for anticancer agents in admission ($)			
Minimum	0	0	0.216‡
25 percentile	1334	1175	
Median	2596	1951	
75 percentile	4111	3174	
Maximum	11 314	10 759	
Cost for anticancer agents in outpatient clinic ($)			
Minimum	0	0	0.016‡
25 percentile	0	0	
Median	26	2898	
75 percentile	365	6005	
Maximum	14 190	42 426	
Hospital stay in the first admission (days)			
Minimum	10	5	0.232‡
25 percentile	38	25	
Median	59	46	
75 percentile	74	65	
Maximum	134	140	
Cost for the first admission ($)			
Minimum	369	1882	0.097‡
25 percentile	11 379	8663	
Median	22 313	13 217	
75 percentile	29 480	22 135	
Maximum	47 544	47 636	

†Log-rank test; ‡Mann–Whitney test.

Table 4. The frequency of various imaging tests in the first admission before and after introduction of gemcitabine

Date of the first admission	Before April 2001 (n = 26) (%)	After April 2001 (n = 28) (%)
Abdominal ultrasonography	100	100
Computed tomography	100	100
Magnetic resonance imaging	96	100
Upper abdominal fiberscopy	69	29
Colon fiberscopy	12	7
Endoscopic retrograde cholangiopancreatography	54	11
Endoscopic ultrasonography	19	4
Angiography	54	25
Positron emission tomography	23	14

respectively), although the differences were not statistically significant (P = 0.055 and P = 0.156, respectively).

DISCUSSION

As known from previous reports (12,13), the disease stages are correlated with PC treatment costs in Japan. When compared to the total treatment cost of metastatic disease, that of locally advanced and resectable disease was 1.2- to 1.6-fold and 1.6- to 1.9-fold higher, respectively (Table 5). The relative relationship between disease stage and treatment cost was at almost the same proportion in the three countries. As for the absolute treatment costs, however, there were relatively large differences among the three. The average cost of PC treatment in Japan was about twice of that in Sweden, and three quarters of that in the United States. This is probably due to differences of social security and health insurance systems in each country.

Other than the survey of actual PC treatment costs in Japan, economic and medical differences after the introduction of GEM were our main interest in the current study. Before conducting the current study, we hypothesized that the TCL had gone up since the introduction of the expensive new drug, GEM.

However, the TCL did not increase as a result of GEM introduction. Possible reasons were simplification in pretreatment imaging examinations, shorter hospitalization and an early outpatient-based treatment. The frequency of imaging tests before treatment decreased except for ultrasonography, CT and magnetic resonance imaging after the GEM introduction. Because we were aware that the three imaging tests were necessary and sufficient for staging evaluation after the GEM introduction, other invasive examinations, such as endoscopic retrograde cholangiopancreatography or angiography, were optional, especially in advanced cases. Moreover, hospitalization becomes shorter because GEM chemotherapy is feasible for an outpatient treatment. Accordingly, total costs for anticancer agents increased after GEM, especially in the outpatient clinic fraction.

Table 5. International cost comparison of pancreatic cancer treatment

Average	Resectable disease	Locally advanced disease	Metastatic disease	Country, (reference)
$19 499	$27 161	$22 671	$14 277	Sweden (11)
$35 892	$46 250	$34 626	$29 658	Japan (current study)
$48 803	$65 335	$54 717	$35 809	United States (12)

The exchange rate is set to the average in 2000, i.e. $1 = €1.029 = ¥106.

To reduce the costs of cancer treatment, therefore, simplification in examinations and shortening of hospitalization may be effective. However, those efforts may have an apparent limitation, because new expensive agents, such as bevacizumab, will increase the PC chemotherapy costs in the near future, as seen in colorectal cancer chemotherapy costs at present.

In summary, the total cost of PC treatment correlated well with disease staging, and there was no international difference in its proportion. The total costs after GEM did not tend to be high in our hospital, probably because of the simplification in examinations and short hospitalization. We believe it will be necessary to promote cost analysis and to make an effort to reduce treatment costs as well as to develop new effective and expensive agents, because health care resources are becoming scarce in many countries.

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GASTROENTEROLOGY

Impact of gemcitabine on the treatment of metastatic pancreatic cancer

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Abstract

Background and Aim: A previous randomized trial showed gemcitabine was superior to 5-fluorouracil in overall patient survival. However, the incremental improvement in survival was minimal. It is 2.5 years since gemcitabine has become available for the treatment of pancreatic cancer in clinical practice in Japan. The current study was conducted to examine whether treatment outcomes have changed since the introduction of gemcitabine therapy.

Methods: Ninety-one consecutive patients with metastatic pancreatic cancer treated with systemic chemotherapy at the National Cancer Center Hospital East were surveyed. Patients admitted before April 2001 received 5-fluorouracil, and those admitted subsequently received gemcitabine. The patients were divided into the gemcitabine group ($n = 50$) and the non-gemcitabine group ($n = 41$), and these groups were compared for five outcomes, objective response rate, non-progressive disease rate, carbohydrate antigen (CA)19-9 response rate, actual survival time, and difference between estimated and observed survivals. The estimated survival time was determined using the prognostic index reported in the previous study.

Results: Except for the objective response rate, the four other outcomes in the gemcitabine group were significantly superior to those in the non-gemcitabine group. The frequency of non-progressive disease, CA19-9 response, and favorable prognosis compared with the estimated survival, were 58%, 22%, and 60%, respectively, in the gemcitabine group, and 22%, 6%, 30%, respectively, in the non-gemcitabine group. The median survival time in the gemcitabine and non-gemcitabine group was 5.73 and 2.87 months, respectively.

Conclusion: It is suggested that there was a definite improvement in pancreatic cancer treatment after gemcitabine was introduced.

Key words: carbohydrate antigen 19-9, chemotherapy, gemcitabine, pancreatic neoplasm, prognosis.

INTRODUCTION

Pancreatic cancer (PC) is the fifth leading cause of cancer deaths in Japan, and in 1999, there were 18 654 deaths from this malignancy.[1] Although surgical resection is the only curative modality for this malignancy, most patients have unresectable disease at the time of diagnosis. For a long time, chemotherapy for PC had only limited value in clinical practice, and there had been no regimen superior to 5-fluorouracil (5-FU) therapy alone.[2,3] In the late 1990s, however, gemcitabine (GEM) was introduced as a PC chemotherapy. Gemcitabine therapy showed significantly better results in the clinical benefit response rates and survival in the randomized trial compared with 5-FU.[4,5] Accordingly, GEM has been accepted as first-line chemotherapy for advanced PC in many countries. In Japan, GEM was approved by the Government after a phase 1 trial in Japanese patients[6] and was introduced into hospitals as a practical therapy in April 2000.

In this retrospective study, we surveyed all metastatic PC patients treated with systemic chemotherapy at the

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National Cancer Center Hospital East, to examine whether treatment outcomes have changed since the introduction of GEM therapy.

METHODS

Patients

Between July 1992 and April 2003, 91 consecutive patients with metastatic PC received chemotherapy in the Division of Hepatobiliary and Pancreatic Medical Oncology at the National Cancer Center Hospital East. Among them, 74 received single-agent chemotherapy (5-FU or GEM). The remaining 17 received chemotherapy as part of multicenter clinical trials: phase 2 studies of cisplatin and 5-FU[7] in 10, docetaxel[8] in three, and irinotecan in four.

Histological or cytological confirmation of exocrine PC was obtained from all patients before chemotherapy. In addition, clinical trial patients were required to meet the eligibility criteria determined by each protocol. Briefly, they included: no previous chemotherapy; good performance status (PS); adequate bone marrow, renal, and hepatic function; no serious complications; and receipt of written informed consent.

Chemotherapy

In clinical practice, patients admitted before April 2001 received 5-FU, and those admitted subsequently received GEM. The 5-FU 600 mg/m^2 was administered over 2 h once weekly, or GEM 1000 mg/m^2 was administered over 30 min weekly, three times every 4 weeks. In clinical trials, details of the regimen are shown in the references. In brief: 5-FU 500 mg/m^2 for 5 days and cisplatin 80 mg/m^2 on the first day every 4 weeks;[7] docetaxel 60 mg/m^2 every 3–4 weeks;[8] and irinotecan 100 mg/m^2 weekly, three times every 4 weeks. In each regimen, chemotherapy was continued until evidence of disease progression. Follow-up computed tomography (CT) was performed after every course to objectively assess tumor response according to World Health Organization criteria.[9]

Data collection

We surveyed all case records of the 91 patients and collected each patient's baseline data including potential prognostic value[10–12] and their treatment outcomes. These were: regimen of chemotherapy; age; gender; PS according to the Eastern Cooperative Oncology Group criteria; presence or absence of prior surgery; location of the primary tumor; site of distant metastasis; presence or absence of measurable lesion; serum levels of carcinoembryonic antigen (CEA)[10] and C-reactive protein (CRP)[11] before chemotherapy; serial serum levels of carbohydrate antigen 19–9 (CA19-9) before and after chemotherapy;[12] serial CT reports; the first day of chemotherapy; and the date of death or last contact.

Treatment responses were evaluated using CT and serial change of serum CA19-9.

The CT response criteria were as follows: a complete response (CR) required the disappearance of all measurable disease for more than 28 days, during which time no new lesions could appear; a partial response (PR) required reduction of greater than 50% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for more than 28 days, during which time no new lesions could appear; stable disease (SD) required reduction of less than 50% or an increase of less than 25% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for more than 28 days, during which time no new lesions could appear; and progressive disease (PD) was defined as an increase of more than 25% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions or the development of any new lesions. In the current study, we evaluated the primary pancreatic tumor by CT, but did not regard it as the measurable lesion.

When patients had an abnormal serum CA19-9 level of 100 U/mL or greater before chemotherapy, we defined a CA19-9 responder as a patient whose serum CA19-9 level was reduced by greater than 50% within 2 months after the initiation of chemotherapy.[12]

Statistics and analysis

We divided patients into the GEM or non-GEM group according to their regimen, and compared patient backgrounds, treatment responses and survival time between the two groups.

The frequency of each variable of the patient's background was analyzed using the chi-squared test. Continuous variables were grouped by a convenient value near the median value (age) or potential prognostic values (CEA, CA19-9, and CRP).

In the current study, an objective response was reported as a rate of patients with CR + PR divided by all patients in each group. The non-PD rate was also reported as a rate of patients with CR + PR + SD divided by all patients in each group. The CA19-9 response rate was defined as responders divided by all patients with a CA19-9 level of 100 U/mL or greater before chemotherapy in each group. The frequency of each response was analyzed by the chi-squared test.

Overall survival was measured from the first day of chemotherapy to the day of death or the last day of follow up. Survival curves were calculated by the Kaplan–Meier method.[13] Differences in survival were evaluated by log–rank tests. We calculated the prognostic index in each patient using to an equation reported previously.[12] The equation for the index was as follows: 1.144 × (0 for CRP less than 5 mg/dL and 1 for CRP of 5 mg/dL or greater) + 1.029 × (0 for a PS of 0–1 and 1 for a PS of 2–3) + 0.538 × (0 for CA19-9 <10 000 U/mL and 1 for CA19-9 of ≥10 000 U/mL). The pretreatment CA19-9 was not available in one patient so calculations were performed for the remaining 90. We estimated each patient's median survival time in months using this

index: 5.2, 2.6, and 1.4 in the good, intermediate, and poor prognosis groups, respectively, and compared this with his or her observed survival time., When an observed survival time was longer than the estimated one, we regarded it as a favorable prognosis. Censored cases within the estimated median survival time were not regarded as evaluable cases. The frequency of patients with favorable prognosis in each group was analyzed by the chi-squared test.

All analyses were performed using the statistical software SPSS 11.0 J for Windows. Statistical significance was defined as a two-sided *P*-value of 0.05 or less.

RESULTS

Among the 91 patients, 41 were from the non-GEM group and 50 were from the GEM group. Patient characteristics in each group were very similar to each other and are shown in Table 1. Of the nine patients with no measurable lesion, four had ascites with malignant cells other than the primary pancreatic tumor. The remaining five had minute liver metastasis (two patients) and/or peritoneal dissemination (four patients) at the time of laparotomy. Five had recurrent cancer after resection of the primary tumor with curative intent. Of these five, four had distant metastasis with no evidence of local recurrence.

Treatment responses are summarized in Table 2. There was no significant difference in the objective response between the two groups. The non-PD rate in the GEM group (58%) was significantly higher ($P = 0.011$) than that in the non-GEM group (22%). The CA19-9 response rate was evaluated in 72 patients, because pretreatment CA19-9 was not 100 U/mL or greater in the remaining 19. Serial CA19-9 changes after chemotherapy was not available in 17 patients mainly due to their early deterioration. These 17 patients were regarded as non-responders. The CA19-9 response rate in the GEM group was also significantly higher than that in non-GEM group.

Of the 91 patients studied, 81 died and 10 were still alive at the time of writing (December 2003). Six patients (7%) were lost to follow up after observation with a median of 4.3 months. Median survival time in

Table 1 Baseline characteristics of patients in the gemcitabine (GEM) and non-GEM groups

	Non-GEM ($n = 41$)	GEM ($n = 50$)	*P*-value
Age (years)			
Median (range)	60 (28–76)	59 (34–78)	
>60	21 (51%)	29 (58%)	0.534
Sex			
Male	27 (66%)	34 (68%)	1.000
Female	14	16	
Primary tumor			
Head	14 (34%)	10 (20%)	0.153
Body-tail	25	37	
Post-resection	2	3	
Eastern Cooperative Oncology Group performance status			
0, 1	36 (88%)	45 (90%)	0.750
2, 3	5	5	
Site of metastasis			
Liver	36 (88%)	42 (84%)	0.766
Peritoneum	5	10	
Lymph node	5	3	
Lung	5	2	
Bone	1	1	
Soft tissue	1	1	
Measurable lesion			
Present	39 (95%)	43 (86%)	0.177
Absent	2	7	
Carcinoembryonic antigen (ng/mL)			
Median (range)	7.9 (1.5–9082)	12 (1.5–238)	
>10 ng/mL	17 (41%)	32 (64%)	0.056
Carbohydrate antigen 19-9 (U/mL)			
Median (range)	2046 (1–314 070)	1737 (1–38 712)	
>10 000 U/mL	9 (22%)	7 (14%)	0.406
C-reactive protein (mg/dL)			
Median (range)	0.8 (0–13.2)	0.7 (0–29.2)	
>5 mg/dL	5 (12%)	9 (18%)	0.564

Table 2 Treatment responses of patients in the gemcitabine (GEM) and non-GEM groups

	Non-GEM ($n = 41$)	GEM ($n = 50$)	P value
Computed tomography response			
Partial response	1 (2%)	5 (10%)	0.217
Stable disease	8	24	
Progressive disease	18	8	
Not evaluable	14	13	
Serial carbohydrate antigen 19-9			
Pretreatment level >100 U/mL	33	39	
Responder	2 (6%)	11 (22%)	0.029
Non-responder	31	28	

GEM group was 5.73 months with 95% confidence interval (CI) between 3.95 and 7.51. It was significantly longer ($P = 0.0004$) than that in non-GEM group (median; 2.87, 95% CI; 1.72–4.02) (Fig. 1).

According to the calculating prognostic index,[12] we divided the 90 patients into three groups: good ($n = 61$), intermediate ($n = 24$), and poor prognosis groups ($n = 5$). Survival curves in the three prognostic groups showed the index had a good validity ($P = 0.0069$). Because there were three censored cases within the estimated median survival time, we compared each patient's estimated and observed survival time in the remaining 87 (Table 3). Of 47 patients in the GEM group, 28 (60%) showed favorable prognosis, and the frequency was significantly higher than that (12 of 40 patients, 30%) in the non-GEM group ($P = 0.009$).

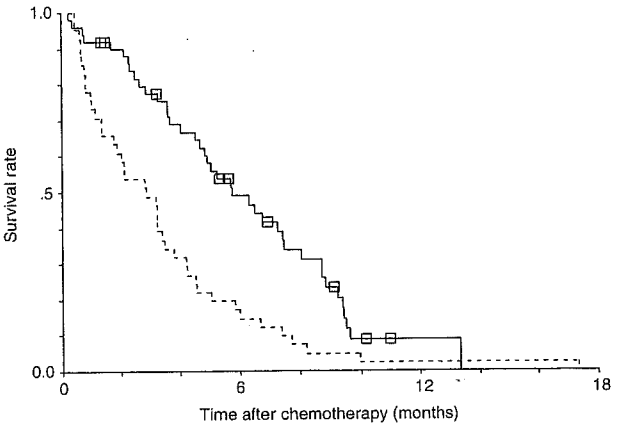

Figure 1 Survival curves of patients in the (—) gemcitabine (GEM) group ($n = 50$) and the (---) non-GEM group ($n = 41$). (□) Censored cases.

DISCUSSION

Gemcitabine was shown to be superior to 5-FU both in the clinical benefit response and in overall patient survival.[5] However, the incremental improvement in overall survival seen with GEM was minimal. In Japan, GEM had been available for the treatment of PC in clinical practice 2.5 years. In the current study, we surveyed PC treatment outcomes to focus on the change before and after the introduction of GEM.

We studied five outcomes: the objective response rate, non-PD rate, CA19-9 response rate, actual survival time, and difference between estimated and observed survivals. The advantage of GEM was demonstrated for four of these outcomes, but was not demonstrated for the objective response rate. The objective response of 8% in the current study was similar to previous findings of GEM monotherapy.[4,5] Despite this poor activity for tumor shrinkage, we favored GEM because of its clinical benefit and manageable toxicity, which were difficult to evaluate in a retrospective analysis. There was a definite antitumor effect in the GEM group, which was indicated by non-PD and CA19-9 response rates, but it was not strong enough to cause evident tumor shrinkage.

We had to make survival comparison analyses carefully because various biases could not be excluded completely in a retrospective study. Although this single institution study warranted all patients to have the same initial staging examinations, monitoring, and approach to supportive care, historical changes of treatment strategy might cause some biases. At first, we compared survival of all (locally advanced and metastatic) patients who received chemotherapy alone. Before the introduction of GEM, we had treated locally advanced patients by intraoperative radiotherapy trials.[14,15] These trials revealed that occult metastases were found in one-third of the patients with CT-staging locally advanced disease at the time of laparotomy. We thereafter selected only good candidates for chemoradiotherapy, whereas 5-FU based concurrent chemoradiotherapy was the standard treatment for locally advanced PC.[16–18] As a result, we treated more CT-staging locally advanced patients with GEM compared with non-GEM chemotherapy. Accordingly, we focused on metastatic PC patients in the current final analysis. The introduction of the prognostic model proposed previously[12] was also used to avoid the biases. The advantage of GEM was significant in the two comparisons. At the initiation of analysis we expected that there would be a subtle difference because the survival advantage of GEM over 5-FU was reported to be only 1 month in a previous randomized trial.[5]

Table 3 Difference between estimated and observed survival time of patients in the gemcitabine (GEM) and non-GEM groups

Prognostic index	Estimated survival time (months)	Non-GEM ($n = 40$) Observed survival time <EST	>EST	GEM ($n = 47$) Observed survival time <EST	>EST
0	5.2	17	7	15	20
0.538	2.6	4	3	1	2
1.029		2	1	0	0
1.144		3	1	1	2
1.567		1	0	0	1
1.682		0	0	1	0
2.173	1.4	0	0	1	2
2.711		1	0	0	1
		28	12 (30%)	19	28 (60%)

EST, estimated survival time.

There is an evident limitation in the comparison of treatments in such a retrospective study. Various historical changes, such as technical improvement of diagnostic modalities, staging methods, supportive treatments and so on, usually result in better patient survival in addition to anticancer treatment; however, we observed some good responses since the introduction of GEM treatment. From the current analysis, we suggest that there was a definitive improvement of PC treatment following the introduction GEM.

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臨床腫瘍学の現状と展望

V．がん薬物療法の実際

5．肝胆膵癌

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はじめに

1997年，進行膵がんにおいてgemcitabine（ジェムザール®）と5-fluorouracil（5-FU®）との無作為化比較試験によりgemcitabineの有効性が証明され，以降gemcitabineが進行膵がんに対する標準化学療法として広く用いられている．しかし，その治療成績は満足のいくものではなく，多くの新しい治療法の開発が行われている．一方，肝・胆道がんにおいては依然標準といえる化学療法はなく，その確立が急務である．

肝がんにおける化学療法

原発性肝がんは，肝細胞がんや肝内胆管がんなど多くの組織型がみられ，極めて多彩である[1]．ここでは，原発性肝がんの約90%を占める肝細胞がんについて述べる．

1．化学療法の適応

肝細胞がんにおいては，がんの進行度と肝障害度に応じて治療法が選択され，肝切除，ラジオ波やエタノール注入による局所壊死療法，動脈化学塞栓療法（TACE）が標準治療として行われている．化学療法は，高度の門脈腫瘍塞栓を伴う例，上記の標準治療が適応困難な例，および遠隔転移例が適応となる．

肝細胞がんに対する化学療法は，肝動脈から注入する経動脈性化学療法（動注化学療法）と，経静脈あるいは経口による全身化学療法に分けられる．肝細胞がんでは，肝硬変など慢性肝障害を背景にもつ例が多いことから，肝障害を助長するリスクも大きく，その適応は慎重に考慮する必要がある．肝障害度評価としてChild-Pugh分類が汎用されているが[2]，Child-Pugh Cの肝機能不良例では化学療法は原則として禁忌である．

2．動注化学療法

TACE無効例やTACEの適応とならない巨大腫瘍，高度門脈腫瘍塞栓例が適応となる．ここではリピオドールを併用しない抗がん剤のみを注入する治療を，動注化学療法として取り上げる．わが国では動注化学療法剤としてepirubicin（ファルモルビシン®），5-fluorouracilが主に用いられてきたが，2004年7月，cisplatin（アイエーコール®）の保険適応が承認された．表1に主な薬剤の治療成績を示す．

Epirubicinは一般に奏効率15%程度と報告されている[3]．門脈1次分枝以上に及ぶ高度門脈腫瘍塞栓例を対象に，同治療の有効性を検討したところ，19%の奏効率が得られ，2年以上の長期生存例も認めている[9]．Cisplatinはepirubicinより高い抗腫瘍効果が認められ，動注化学療法でも有効性が期待されているが，骨髄毒性や肝障害の増悪など，重篤な有害事象も少なくないことから，適応は慎重に行うべきである[10]．5-fluorouracilの動注化学療法は，原則的にリザーバーシステムの留置が必要である．最近では5-fluorouracilを基本薬剤とした併用治療が試みられ，5-fluorouracil＋cisplatinや5-fluorouracil＋interferon（IFN）で高い奏効率が報告されている[7,8]．しかし，これらの動注化学療法の有効性や位置づけは確立しておらず，比較試験など多数例での検討が必要である．

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表1　肝細胞がんに対する主な動注化学療法

抗がん剤	奏効率	MST(月)	1年生存率	報告者(報告年)
Epirubicin	15%(8/53)	6.8	28%	Epirubicin Study Group in Japan(1987)[3]
Floxuridine/LV/DXR/CDDP	41%(12/29)	15.0	54%	Patt(1994)[4]
MTX/5-FU/CDDP/IFN	47%(7/15)*	7.0	27%	Urabe(1998)[5]
CDDP/IFN	33%(6/18)	4.9	27%	Chung(2000)[6]
CDDP/5-FU	48%(23/48)*	10.2	45%	Ando(2002)[7]
5-FU/IFN	52%(12/23)*	—	—	左近(2003)[8]
Epirubicin	19%(3/16)*	6.0	21%	光永(2004)[9]

MST：median survival time, LV：leucovorin, DXR：doxorubicin, CDDP：cisplatin, MTX：methotrexate, 5-FU：5-fluorouracil, IFN：interferon. *：門脈腫瘍塞栓例のみが対象.

表2　肝細胞がんに対する主な全身化学療法

抗がん剤	奏効率	MST(月)	1年生存率		報告者(報告年)
Mitoxantrone	23%(4/17)	5.0	—		Colleoni(1992)[11]
CDDP	15%(4/26)	—	—		Okada(1993)[12]
Gemcitabine	18%(5/28)	4.4	20%		Yang(2000)[13]
Gemcitabine	0 %(0/30)	6.9	40%		Fuchs(2002)[14]
Epirubicin/etoposide	39%(14/36)	10.0	28%		Bobbio-Pallavicini(1997)[15]
CDDP/DXR/5-FU/IFN	26%(13/50)	8.9	36%		Leung(1999)[16]
5-FU/Mit/CDDP(FMP)	27%(14/51)	11.6	44%		Ikeda(2005)[17]
EPI/CDDP/5-FU(ECF)	14%(3/21)	10.0	70%		Boucher(2002)[18]
5-FU/IFN-α-2b	14%(4/28)	15.5	62%		Patt(2003)[19]
*Doxorubicin	3 %(2/60)	2.5	5 %	p=0.036	Lai(1988)[20]
BSC	n=46	1.8	5 %		
*IFN-α	31%(11/35)	2.6	18%	p=0.047	Lai(1993)[21]
BSC	n=36	1.8	3 %		
*Tamoxifen	0 %(0/58)	14.3	51%	p=0.75	Castells(1995)[22]
Placebo	n=62	6.0	43%		
*IFN-α	7 %(2/30)	15.2	58%	p=0.19	Llovet(2000)[23]
BSC	n=30	7.2	38%		

MST：median survival time, CDDP：cisplatin, DXR：doxorubicin, 5-FU：5-fluorouracil, IFN：interferon, Mit：mitoxantrone, EPI：epirubicin, BSC：best supportive care. *：無作為化比較試験.

3．全身化学療法

動注化学療法と同様，標準治療の適応とならない例，TACEの無効例，および遠隔転移例に適応される．門脈腫瘍塞栓例は極めて予後が不良であり，現在のところ全身化学療法では有効例は極めて少なく，適応は難しい．

単剤で15%以上の奏効率が報告されている薬剤は，cisplatin，mitoxantrone(ノバントロン®)など，わずかである．多剤併用療法では，5-fluorouracil/mitoxantrone/cisplatin(FMP)，cisplatin/doxorubicin/5-fluorouracil/IFN-αで25%を超える高い奏効率が報告されている(表2)．これまで肝細胞がん患者を対象とした無作為化比較試験がいくつか行われている．Doxorubicinでは，無治療群に比べ有意に生存期間の延長が得られているが[20]，tamoxifenやIFN-αでは生存期間の改善は明らかではない[21-23]．これまで肝細胞がんでは，有効な全身化学療法は確立しておらず，生存期間を評価項目とした大規模試験が必要である．また，肝細胞がんは血管新生が豊富な腫瘍であり，VEGFR阻害薬などの分子標的薬の開発が期待されている．

胆道がん

1．全身化学療法の適応

胆道がんにおける化学療法は，奏効例は認めるもの

表3　胆道がんに対する主な全身化学療法

抗がん剤	奏効率	MST(月)	1年生存率	報告者(報告年)
Gemcitabine	22%(7/32)	11.5	44%	Penz(2001)[25]
Gemcitabine	36%(9/25)	7.0	17%	Gallardo(2001)[26]
LV/5-FU/CDDP	34%(10/29)	9.5	50%	Taieb(2002)[27]
5-FU/LV/oxaliplatin	19%(3/16)	9.5	−	Nehls(2002)[28]
Gemcitabine/docetaxel	9%(4/43)	11.0	42%	Kuhn(2002)[29]
CDDP/EPI/5-FU	19%(7/37)	5.9	24%	Morizane(2003)[30]
Gemcitabine/oxaliplatin	33%(11/33)	15.4	57%	Andre(2004)[31]
Gemcitabine/5-FU/LV	12%(5/42)	9.7	36%	Alberts(2005)[32]
EPI/CDDP/UFT/LV	23%(9/40)	7.9	32%	Park(2005)[33]
Gemcitabine/CDDP	28%(11/40)	8.4	−	Thongprasert(2005)[34]
Gemcitabine/capecitabine	31%(14/45)	14.0	49%	Knox(2005)[35]
*MMC/gemcitabine	20%(5/25)	6.7	−	Kornek(2004)[36]
MMC/capecitabine	31%(8/26)	9.3	−	

MST：median survival time, LV：leucovorin, 5-FU：5-fluorouracil, CDDP：cisplatin, EPI：epirubicin, UFT：tegafur-uracil, MMC：mitomycin C. *：無作為化比較試験.

の根治例はなく，切除不能の進行例が治療対象となる．また，胆嚢がんの化学療法の治療成績を検討したところ，全身化学療法は全身状態が不良な例(PS 2)に比べ，良好な例(PS 0 または 1)で予後の改善に寄与することが確認されており[24]，現状では全身状態を十分考慮した上で適応を考慮すべきである．

2．全身化学療法の現状

表3に最近の主な化学療法の治療成績を示す．多剤併用による化学療法が多く試みられ，最近ではgemcitabineを基本薬剤とした多剤併用療法により，比較的高い奏効率が報告されつつある．わが国では現在，胆道がんに保険適応が承認されている薬剤は，tegafur-uracil(UFT®)，doxorubicin(アドリアシン®)，cytarabine(キロサイド®；ただし他の抗腫瘍薬と併用)に限られている．しかし，これらの薬剤では有効性は期待できず，胆道がんに有効な薬剤の開発と標準治療の確立が急務である．最近，わが国ではgemcitabineやS-1による臨床試験が行われ，保険適応の承認が期待されている．

膵　が　ん

1．全身化学療法の現状

1997年，5-fluorouracilとの無作為化比較試験によりgemcitabineの有用性が明らかとなり，gemcitabineが進行膵がんにおける新たな標準治療薬として各国に広がった[37]．Gemcitabineはcytarabineと構造的に類似した代謝拮抗薬に分類される抗がん剤であり，細胞内で三リン酸化物に代謝され，DNA合成を阻害することにより，強い殺細胞作用を示す．米国で行われた5-fluorouracilとの無作為化比較試験では，gemcitabine群において疼痛，performance status，体重減少など症状緩和効果が高率に認められ，生存期間においても有意差がみられた．わが国でも第1相試験が行われ，同様の投与法が可能であることが確認され，治療効果においても同等以上の成績が得られたことから，保険適応が承認された[38]．現在，gemcitabine 1,000 mg/m^2，週1回，3週投与，1週休薬を1コースとして繰り返す投与が推奨投与法として行われている．

一方，gemcitabineの投与法を変えることにより，その治療効果を高める試みが行われている．Temperoらは，gemcitabineの活性体である三リン酸化物の形成が投与量と投与時間に依存しており，10 mg/m^2/minが最適な投与速度であるという基礎実験から，1,500 mg/m^{2}を150分で投与する定速静注法(10 mg/m^2/min)を試みている．2,200 mg/m^{2}を30分で投与する方法との無作為化比較第2相試験では，奏効率は両者で差がみられなかったものの，生存期間中央値(MST)は8.0カ月と5.0カ月，1年生存率は28.8%と9.0%と，定速静注法で有意に良好であることが示された[39]．現在，米国のstudy groupであるECOGにおいて，gemcitabine 1,000 mg/m^{2}による標準投与法，gemcitabine定速静注法，gemcitabine 1,000 mg/m^{2}の定速静注投与とoxaliplatin(エルプラット®)の併用療法(GEMOX)の3群による大規模な無作為化比較試験が行われている．

Gemcitabineが標準治療薬として確立したとはいえ，

表4　進行膵がんにおけるgemcitabine単独と他レジメンの無作為化比較試験

抗がん剤	n	奏効率	MST(月)	1年生存率		報告者(報告年)
Gemcitabine	63	5.4%	5.7	18%	p=0.0025	Burris(1997)[37]
5-FU	63	0%	4.4	2%		
Gemcitabine	162	5.6%	5.4	20%	p=0.09	Berlin(2002)[40]
Gem/5-FU	160	6.9%	6.7	18%		
Gemcitabine	99	8.0%	6.0	—	p=0.12	Heinemann(2003)[41]
Gem/CDDP	96	10.2%	8.3	—		
Gemcitabine	173	4.4%	6.6	20%	p=0.79	Rocha Lima(2004)[42]
Gem/irinotecan	169	16.1%	6.3	20%		
Gemcitabine	156	16.7%	7.1	28%	p=0.13	Louvet(2005)[43]
Gem/oxaliplatin	157	28.7%	9.0	38%		
Gemcitabine	174	6.3%	6.7	23%	p=0.52	O'Reilly(2004)[44]
Gem/exatecan	175	8.2%	6.2	21%		
Gemcitabine	282	9.1%	6.2	20%	p=0.85	Richards(2004)[45]
Gem/pemetrexed	283	18.3%	6.3	21%		
Gemcitabine	159	8.0%	5.9	17%	p=0.025	Moore(2005)[46]
Gem/erlotinib	160	8.6%	6.4	24%		
Gemcitabine	285	7.9%	7.3	28%	p=0.31	Herrmann(2005)[47]
Gem/capecitabine	284	10.1%	8.4	30%		

MST：median survival time, 5-FU：5-fluorouracil, Gem：gemcitabine, CDDP：cisplatin.

その治療成績は依然満足できるものではない．現在，gemcitabineと他の薬剤との併用治療が盛んに試みられている．これまで5-fluorouracil, cisplatin, irinotecan(カンプト®)，oxaliplatinなどとの併用療法による第3相臨床試験が報告されている(表4)[40-47]．多くの併用療法においてgemcitabine単独に比べ高い奏効率が得られるものの，明らかな生存期間の延長は認められなかった．2005年ASCO会議では，EGFRを阻害する分子標的薬erlotinibとgemcitabineの併用療法が，gemcitabine単独との無作為化比較試験において，有意に生存期間を改善したと報告され，注目を集めた．しかし，その差はわずかであり，同併用療法で得られる利点をさらに詳細に検討する必要がある．

Gemcitabine以外の薬剤として，わが国ではirinotecanやS-1(ティーエスワン®)などの臨床試験が行われ，高い奏効率が認められている[48,49]．また，S-1とgemcitabineとの併用療法による第1相試験が行われ，30～40%と高い奏効率が期待されることから[50]，多数例による臨床試験が行われつつある．

2．分子標的薬

がんの分子生物学，分子遺伝学の急速な進歩により，がん細胞に特徴的な遺伝子発現が明らかになり，その変異した分子を標的にした治療薬，いわゆる分子標的治療(molecular targeting therapy)が開発されている．膵がんにおいても，EGFR(epidermal growth factor receptor)，VEGFR(vascular endothelial growth factor receptor)，MMP(matrix metalloproteinase)，K-ras遺伝子の異常など，様々な分子標的が明らかとなっている．膵がんにおける分子標的薬としては，先に述べたerlotinibのほかにもVEGFR阻害薬bevacizumab，EGFR阻害薬cetuximabなどが注目され，gemcitabineとの併用治療による臨床試験が行われている[51,52]．

3．全身化学療法の適応

切除不能の進行膵がんは，遠隔転移を認めない局所進行例と遠隔転移を有する例に分けられる．UICC第6版による進行度分類では，局所進行がんは腹腔動脈，あるいは上腸間膜動脈浸潤を認めるT4NxM0(StageⅢ)に当たり，遠隔転移はTxNxM1(StageⅣ)になる．遠隔転移例では，現在gemcitabineによる全身化学療法が標準治療として行われている．局所進行例においては，5-fluorouracilによる同時併用放射線化学療法が標準治療として位置づけられているが，消化管毒性などが少なくないことから，gemcitabineによる全身化学療法も多く行われている．Gemcitabineを中心とした全

身化学療法の臨床試験では，遠隔転移例とともに局所進行例も対象に含めたものが少なくない．Gemcitabineは強い放射線増感作用も認めており，gemcitabineによる放射線化学療法も試みられているが，際立った治療成績は得られていない[53]．現在，局所進行膵がんにおける標準治療は，むしろ混乱しているといってもいい状況であり，より有効な治療法の開発とともに，放射線化学療法とgemcitabineを用いた全身化学療法による大規模な比較試験も必要である．

おわりに

肝・胆道・膵がんにおいては，切除不能進行がんに対する治療戦略を考える上で，化学療法は重要な役割を果たしている．今後，より良好な抗腫瘍効果を有する治療法の開発が期待されるとともに，質の高い臨床試験の実施が必要である．

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Current Status of Systemic Chemotherapy for Hepatobiliary and Pancreatic Cancer

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Gemcitabine has shown promise in advanced pancreatic cancer in a randomized trial comparing it with 5-FU. Gemcitabine is more effective than 5-FU in alleviating some disease-related symptoms, and it also offers an advantage in terms of survival rate. Gemcitabine has been accepted as the standard agent for the treatment of advanced pancreatic cancer, and despite numerous trials comparing gemcitabine-based combination chemotherapy and gemcitabine alone, no regimen has been found to have a definite survival advantage over gemcitabine alone. Molecular targeting agents, such as erlotinib, bevacizumab, and cetuximab, have recently been used in gemcitabine-based combination chemotherapy for pancreatic cancer. No regimen of systemic chemotherapy has shown a definite clinical benefit for hepatobiliary cancer. Most chemotherapy regimens have been performed as clinical trials, and although no usefulness of systemic chemotherapy for hepatocellular carcinoma or biliary tract cancer has been demonstrated in any of them, some promising agents are being developed, e.g., hepatic arterial infusion chemotherapy with 5-FU and CDDP or 5-FU and interferon for hepatocellular carcinoma, and gemcitabine or S-1 for biliary tract cancer. Well-designed clinical trials are needed to establish a standard regimen for advanced hepatobiliary cancer.

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Phase I trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer

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The objective of this study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of S-1, an oral fluorouracil derivative, combined with gemcitabine, the current standard treatment for advanced pancreatic cancer (APC). The subjects were histopathologically proven APC patients with distant metastasis. S-1 was administered orally twice daily each day for 14 days and gemcitabine on days 8 and 15 of each cycle, and this was repeated every 21 days. Doses of each drug were planned as follows: level 1: 800/60, level 2a: 800/80, level 2b: 1000/60, level 3: 1000/80 (gemcitabine ($mg\,m^{-2}$)/S-1 ($mg\,m^{-2}\,day^{-1}$)). In all, 21 patients with APC were enrolled. The main grade 3–4 toxicities observed during first cycle were neutropenia (33%), anaemia (10%), thrombocytopenia (14%) and anorexia (10%). There were no DLT observed in level 1. Three of six patients in level 2a had DLT and this level was considered the MTD. In all, 12 patients in level 2b had no DLT and this level was selected as the recommended dose. Applicable responses were one complete response and nine partial responses (48%). As toxicities were well tolerated and antitumour activities seem to be promising, this combination can be recommended for further phase II studies with APC.
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The incidence and mortality of pancreatic cancer has increased so rapidly over the past 20 years in Japan that it is now the fifth leading cause of cancer mortality in the country (Matsuno *et al*, 2004). The 5-year survival rate is still poor, at less than 10%, commonly considered to be linked to the high incidence of distant metastasis even at initial diagnosis, as well as the tumour's resistance to anticancer agents. Innovation in systemic chemotherapy is thus urgently needed to improve the survival of patients with pancreatic cancer (Glimelius *et al*, 1996; Evans *et al*, 1997).

Since 1997, gemcitabine has been the most widely used chemotherapeutic agent in advanced pancreatic cancer (APC) and was reported to have significantly better symptom control in APC compared with 5-FU in a randomised phase III clinical study (Burris *et al*, 1997). Even with gemcitabine, however, monotherapy has obvious limitations in APC and various combinations with other agents have been investigated. The combination of gemcitabine and 5-FU is shown to have a marked synergistic cytotoxic effect against pancreatic cancer cells in *in vitro* assay (Bruckner *et al*, 1998). Phase I and II studies of combined therapy of gemcitabine with 5-FU demonstrated superior results (Berlin *et al*, 1998, 2000; Cascinu *et al*, 1999; Hidalgo *et al*, 1999; Matano *et al*, 2000). However, adding weekly intravenous bolus 5-FU to weekly gemcitabine did not confer a significant survival benefit in a randomised trial (Berlin *et al*, 2002). There are no randomised data on the combination of infusional 5-FU with gemcitabine in APC.

S-1 is a new oral fluorinated pyrimidine developed by Taiho Pharmaceutical Co. Ltd (Tokyo, Japan). The agent contains tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of FT : CDHP : Oxo = 1 : 0.4 : 1, based on a biochemical modulation of 5-FU (Shirasaka *et al*, 1996a, b). Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU and is rapidly catabolised by dihydropyridine dehydrogenase (DPD) in the liver. 5-Chloro-2,4-dihydroxypyridine is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting DPD (Tatsumi *et al*, 1987). When tegafur is combined with CDHP, the resulting high 5-FU levels are maintained in both plasma and tumour. In addition, it has been suggested that CDHP has the potential to enhance the antitumour activity of 5-FU against subcutaneous tumour in nude mice, using human pancreas carcinoma cells with a high tumoral DPD activity (Takechi *et al*, 2002). Oxo inhibits the enzyme orotate phosphoribosyltransferase, the major enzyme responsible for 5-FU activation in colon cancer (Peters *et al*, 1991). Oxo preferentially localises in the gut rather than in the tumour and has a potential biochemical effect on the enzyme orotate phosphoribosyltransferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects (Takechi *et al*, 1997). In phase II studies for advanced gastric cancer conducted in Japan, S-1 showed high response rates of 44–49% (Sakata *et al*, 1998; Koizumi *et al*, 2000), and the usefulness of S-1 was also reported in head and neck (Inuyama

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et al, 2001), breast (Saeki et al, 2004) and colorectal cancer patients (Ohtsu et al, 2000). In studies outside Japan, the phase II studies of S-1 against gastric (Chollet et al, 2003) and colorectal cancer (Van den Brande et al, 2003) in Europe by the EORTC-Early Clinical Study Group revealed moderate activity. The antitumour activity of S-1 in patients with pancreatic cancer has not yet been investigated outside Japan, but preliminary favourable results of S-1 have been reported in Japanese early phase II study of patients with APC (Okada et al, 2002).

The administration of oral S-1 is more convenient and simulates the effect of continuous infusion of 5-FU. We anticipated that combination chemotherapy of gemcitabine and S-1 would be effective through the additive and synergistic activity of gemcitabine and 5-FU derived from S-1. As yet, the combination regimen of gemcitabine and S-1 for patients with APC has not been investigated. Therefore, the author performed a phase I study to evaluate the safety of treatment combined gemcitabine with S-1 and to determine the maximum tolerated dose (MTD) of each drug for patients with APC.

PATIENTS AND METHODS

Patient selection

Patients with histopathologically proven APC with distant metastasis were eligible for the study. Other eligibility criteria included: 20–74 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (ambulatory and capable of self-care), estimated life expectancy of more than 2 months, adequate renal function (normal serum creatinine and blood urea nitrogen levels), liver function (total bilirubin level $\leqslant$2.5 times upper normal limit (UNL) or $\leqslant$3 times UNL after biliary drainage if the patient had obstructive jaundice and serum transaminases (GOT, GPT) levels $\leqslant$2.5 times UNL or $\leqslant$3 times UNL), bone marrow reserve (white blood cell count between 4000 and 12 000 mm^{-3}, neutrophil count $\geqslant$2000 mm^{-3}, platelet count $\geqslant$100 000 mm^{-3} and haemoglobin level $\geqslant$9.5 g dl^{-1}) and pulmonary function ($PaO_2 \geqslant 70$ mmHg). If the patients had a previous history of cancer treatment, that treatment (tumour resection, chemotherapy, immunotherapy, or radiotherapy) had to have been discontinued for at least 4 weeks before entry into the study. All subjects provided written informed consent.

The exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia, marked pleural or pericardial effusion or marked peripheral oedema, severe heart disease, difficult to control diabetes mellitus, active infection, pregnant or lactating females, women of childbearing age unless using effective contraception, severe drug hypersensitivity, metastases to the central nervous system, severe neurological impairment or mental disorder, active concomitant malignancy and other serious medical conditions.

This study was approved by the institutional review board of Chiba University Graduate School of Medicine.

Study design

This was an open-label, single-centre, nonrandomised, dose-escalating phase I study. All laboratory tests required to assess eligibility had to be completed within 7 days prior to the start of treatment. S-1 was administered orally twice daily after a meal for 14 consecutive days (from the evening of day 1 to the morning of day 15), followed by a 1-week break. Each capsule of S-1 contained 20 or 25 mg of tegafur. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. Gemcitabine was administered as a 30-min intravenous infusion on days 8 and 15 of each cycle. The cycle was repeated every 21 days. This schedule was based on an *in vitro* study which showed maximum synergy when fluoropyrimidine precedes exposure to gemcitabine (Rauchwerger et al, 2000). The dose of each drug in this study was planned as follows: level 1 was S-1 60 mg m^{-2} day^{-1} and gemcitabine 800 mg m^{-2}, level 2a was S-1 80 mg m^{-2} day^{-1} and gemcitabine 800 mg m^{-2}, level 2b was S-1 60 mg m^{-2} day^{-1} and gemcitabine 1000 mg m^{-2}, level 3 was S-1 80 mg m^{-2} day^{-1} and gemcitabine 1000 mg m^{-2}. However, only when neither level 2a nor level 2b reached the MTD would patients be assigned to dose level 3.

Definition of dose-limiting toxicities (DLTs) and MTD

Dose-limiting toxicities (DLTs) were determined during the first treatment cycle. Dose-limiting toxicity was defined, using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0), as one or more of the following effects attributable to study drug: (a) grade 3 or 4 neutropenia complicated by fever; (b) grade 4 neutropenia lasting longer than 4 days; (c) grade 4 thrombocytopenia; (d) any other grade 3–4 nonhaematologic toxicity except anorexia, nausea and vomiting in the absence of appropriate antiemetics and (e) delay of recovery from treatment-related toxicity for more than 2 weeks. At least three patients were enrolled at each dose level. If DLT was observed after the first cycle in one or two patients, three additional patients were placed on that dose level. If only one or two of six patients experienced DLT, dose escalation would continue. There was no dose escalation in individual patients. The MTD of the combination was defined as the dose level that produced DLT in $\geqslant$3 of six patients or in all of the initial three patients. The recommended dose (RD) was defined as the dose level that is one level under MTD considering the toxicity and tolerability in outpatient setting.

Pretreatment and follow-up studies

Before entry into the study, all patients gave a full history and underwent a physical examination. A complete blood count (CBC) with differential, electrolyte levels, and creatinine levels were measured. Routine chemistry tests, urinalyses and 24-h urine collections were performed to detect proteinuria. Electrocardiograms, chest X-rays and computed tomographic scans of the chest and abdomen were performed at baseline in all patients. Additional imaging investigations were performed if clinically indicated or for disease measurement. A complete blood count with differential, serum chemistry, creatinine level, and electrolyte level were measured weekly. Computed tomographic scanning and imaging of the measurable disease to assess tumour response were performed every two cycles. At the completion of the study, all clinical, laboratory, radiologic imaging and other evaluations were repeated. After completion of the study, patients underwent follow-up examinations every 2 months until death. Additional treatment after disease progression was left to the discretion of the treating physician.

Assessment of efficacy

All patients were included in efficacy measurements on an intent-to-treat basis. Tumour responses were evaluated according to the World Health Organization's criteria (World Health Organization, 1979). A complete response (CR) was defined as the disappearance of all evidence of cancer for 4 weeks or longer. A partial response (PR) was defined as a 50% or more reduction in the sum of the product of the longest perpendicular dimensions of all lesions for 4 weeks or longer without any evidence of new lesions or the progression of any lesions. Stable disease (SD) was defined as less than a 50% reduction or less than a 25% increase in the sum of the product of the longest perpendicular dimensions of all lesions without any evidence of new lesions. Progressive disease (PD) was

defined as a greater than 25% increase in one or more lesions or the appearance of any new lesion. To assess objective response, patients were evaluated every 6 weeks (two cycles) by three independent radiologists.

Serum CA19-9 levels were measured every 4 weeks during the chemotherapy using a commercially available chemiluminescent enzyme immunoassay based on the two-step sandwich method (CL-EIA). A value of 37 U ml^{-1} was defined as the upper limit of the normal.

Overall survival was estimated from the date of first treatment to death or last follow-up visit, calculated using the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.

RESULTS

All 21 patients with APC registered between January 2003 and March 2004 had primary sites. Out of 21, 18 patients had liver metastasis except one who had lung metastasis, and two who presented with peritoneal carcinomatosis only (Table 1). Although the eligibility criteria included patients who had a previous history of cancer treatment (tumour resection, chemotherapy, immunotherapy, or radiotherapy) before entry into the study, in actuality no patients had previously received such treatment.

Table 1 Patient characteristics

Patients enrolled	21
Men	10
Women	11
Age, years	
Median	61
Range	48–73
ECOG status	
0	8
1	11
2	2
Sites of metastatic disease	
Liver	18
Lung	3
Peritoneum	2

Table 2 Dose levels

Dose level	S-1 (mg m^{-2} day^{-1}: 2 weeks)	Gemcitabine (mg m^{-2}: on days 8, 15)	No. of patients
1	60	800	3
2a	80	800	6
2b	60	1000	12

The numbers of patients at each level are shown in Table 2. Three patients were assigned to dose level 1 without DLT. At dose level 2a, DLT was observed in two of the first three patients; thus three additional patients were assigned to this level. Dose-limiting toxicity was observed in three of six patients, and level 2a reached MTD. Thus, three patients were assigned to level 2b and no DLT was observed in the first three patients. However, nine additional patients were assigned to this level to explore the responses to and continuity of the treatment.

Toxicity and treatment cycles

The most common toxicities observed during the first cycle of chemotherapy are listed in Tables 3 and 4. Of three patients in level 1, one had thrombocytopenia of grade 3, but no DLT leading to MTD was observed in any patient. Of six patients in level 2a, grade 3–4 neutropenia occurred in four patients, grade 3 anaemia in one patient and grade 3 thrombocytopenia in two patients. In terms of nonhaematological toxicities, grade 4 anorexia, grade 3 nausea and grade 3 rash occurred in one patient, each. Three of six patients at level 2a showed DLT; one patient developed sepsis with grade 4 leukopenia and neutropenia, a second patient developed a grade 3 rash and a third patient developed grade 2 leukopenia, not recovering within the planned period. Thus, DLT was observed in three of six patients, and level 2a reached MTD. Of 12 patients at level 2b, grade 3 to 4 neutropenia occurred in three patients and grade 3 anaemia in one patient, while grade 3 anorexia occurred in one patient, and DLT leading to MTD was not observed. Based on these results, level 2b was selected as the RD for the phase II study we are to conduct.

The median and range of the treatment cycles and the number of patients who received a dose reduction were shown in Table 5. The median number of cycles delivered at dose level 2b, which was selected as the RD, was four, and only six of 61 cycles at this dose level needed to reduce their dose of gemcitabine.

Efficacy

Although assessment of tumour response was not a primary objective of this study, patients were evaluated for tumour response every two cycles (6 weeks) of the treatment. All 21 patients were assessed for response during this treatment. Responses in the 21 assessable patients were: one CR (dose level 2a), nine PRs (one at dose level 1, three at dose level 2a and five at dose level 2b), six stable disease (two at dose level 1, one at dose level 2a, and three at dose level 2b) and progression in only five patients (one at dose level 2a and four at dose level 2b). As a result, 10 of the 21 patients (48%) showed complete or PRs (Table 6). The value of CA 19-9 before treatment was elevated (>37 U l^{-1}) in 15 of 21 patients. Of those 15 patients, CA 19-9 decreased 50% or more compared with the level prior to treatment in seven (47%) and showed a normal value in three (20%). In contrast, an increase of CA 19-9 was observed in only four patients (27%). At present, seven patients are still alive. After a median follow-up of 8.9

Table 3 Haematological toxicity during first cycle (in all cycles)

		No. of patients (cycles) with grade of toxicity						
		Neutropenia		Anaemia		Thrombocytopenia		
Dose level	Total no. of patients (cycles)	1–2	3–4	1–2	3–4	1–2	3–4	DLT
1	3 (27)	2 (13)	0 (5)	3 (5)	0 (1)	2 (6)	1 (5)	
2a	6 (66)	2 (34)	4 (22)	5 (15)	1 (5)	4 (13)	2 (13)	2
2b	12 (61)	7 (25)	3 (6)	5 (8)	1 (2)	11 (13)	0 (0)	

Table 4 Nonhaematological toxicity during first cycle (in all cycles)

		No. of patients (cycles) with grade of toxicity						
		Anorexia		Nausea and vomiting		Rash		
Dose level	Total no. of patients (cycles)	1–2	3–4	1–2	3–4	1–2	3–4	DLT
1	3 (27)	1 (2)	0 (0)	1 (1)	0 (0)	3 (6)	0 (0)	
2a	6 (66)	1 (4)	1 (2)	1 (5)	1 (2)	3 (7)	1 (1)	1
2b	12 (61)	2 (5)	1 (1)	5 (8)	0 (0)	11 (12)	0 (0)	

Table 5 Duration of administration and dose intensity

			No. of cycles		Cycles with dose reduction in gemcitabine	
Dose level	S-1/gemcitabine (mg m^{-2})	No. of patients	Total	Median (range)	No.	%
1	60/800	3	27	10 (3–14)	5	19
2a	80/800	6	66	7 (2–20)	31	47
2b	60/1000	12	61	4 (2–10)	6	10

Table 6 Objective tumour response

		Response				
Dose level	No. of patients	CR	PR	SD	PD	Response rate (%)
Level 1	3	0	1	2	0	33
Level 2a	6	1	3	1	1	67
Level 2b	12	0	5	3	4	42
Total	21	1	9	6	5	48

months (range, 2.2–16.1 months), the median survival time was 9.3 months (95% CI, 6.3–12.3%) and the 1-year survival rate was 35% (95% CI, 12–58%).

DISCUSSION

The primary end point of this trial was to define a chemotherapy regimen with an acceptable toxicity profile that could potentially improve the therapeutic efficacy of gemcitabine in patients with pancreatic cancer. S-1 has been selected as a candidate to be investigated in combination with gemcitabine in patients with pancreatic cancer because of its consistent activity as a single agent in this disease and because of the lack of cross-resistance between gemcitabine and 5-FU derived from S-1, as suggested by the observed activity of gemcitabine in patients refractory to 5-FU (Rothenberg *et al*, 1996). Also, gemcitabine combined with infusional 5-FU has been noted to possess synergy in *in vitro* cytotoxicity in a variety of malignant cell lines, including pancreatic cancer (Bruckner *et al*, 1998). Therefore, we expected additive and synergistic efficacy by combining gemcitabine with S-1, hoping that it would mimic the continuous infusion of 5-FU and also have DPD inhibition, leading to enhancement of antitumour activity (Takechi *et al*, 2002).

When considering this study regimen, the authors considered the possibility that this combination of gemcitabine with S-1 might produce more severe toxicities than those generated by gemcitabine alone. Thus, we tried to lessen the frequency of gemcitabine in this regimen, administering it twice every 3 weeks. S-1 has already undergone phase I and II testing in several solid tumours in Japan and western countries. The DLT was myelosuppression in a Japanese phase I study (Taguchi *et al*, 1997), and diarrhoea in a European and a North-American phase I study (van Groeningen *et al*, 2000; Hoff *et al*, 2003). In Japan, the standard single-agent dose is 80 mg m^{-2} day^{-1} for 28 consecutive days, every 5–6 weeks, although the RD of S-1 was 70–80 mg m^{-2} for 28 consecutive days, every 5 weeks in Europe, and 60 mg m^{-2} for 28 consecutive days, every 5 weeks in the US, divided into twice-daily doses. Consequently, we conducted this study in an attempt to maintain the same dose intensity as that used in the standard S-1 administration, but in combination with gemcitabine. Both of the phase II trials in Japan revealed that low grades of gastrointestinal toxicities, including nausea, vomiting and anorexia, and of myelotoxocities such as neutropenia, occurred frequently during the third week of S-1 administration. Therefore, we adopted the regimen of S-1 administration for 14 consecutive days repeated every 3 weeks to avoid severe toxicity. The dose intensity of S-1 in this regimen amounts to almost the same level as that in Japanese standard regimen: S-1 for 28 consecutive days, every 5–6 weeks. Also, given that an *in vitro* study of pancreatic cancer cells has also demonstrated maximum synergy for gemcitabine when exposure to a thymidylate synthase inhibitor such as 5-FU precedes exposure to gemcitabine (Rauchwerger *et al*, 2000), we adopted the regimen of gemcitabine administration on days 8 and 15 after S-1 administration of each cycle.

Myelosuppression, especially neutropenia, frequently seen in the combination of continuous infusion 5-FU and gemcitabine, was predicted as the main toxicity of this study. In this study, the incidence of grade 3 or 4 neutropenia during the first cycle was higher than that of other toxicities, with four of six patients at dose