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Original Article

Prognostic Factors in Patients with Gemcitabine-Refractory Pancreatic Cancer

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Objective: The purpose of this study was to identify prognostic factors in patients with gemcitabine-refractory pancreatic cancer and to determine criteria for selecting candidates for second-line treatment.
Methods: The records of 74 patients who were treated with gemcitabine (GEM) and followed up until disease progression were reviewed retrospectively. Sixteen clinical variables at the time of disease progression after GEM chemotherapy were chosen for analysis in this study. Univariate and multivariate analyses were conducted to identify prognostic factors associated with survival.
Results: At the time of analysis, 71 patients had died because of tumor progression. The overall median survival time was 5.1 months after first-line chemotherapy with GEM was initiated. Median survival time after disease progression was 2.0 months. Three factors, performance status, peritoneal dissemination and C-reactive protein level, were identified as independent prognostic factors in multivariate analysis. Median survival time in the good prognosis group (patients with performance status 0 or 1, no peritoneal dissemination and C-reactive protein <5.0 mg/dl) was 3.4 months.
Conclusions: Performance status, serum level of C-reactive protein and peritoneal dissemination were identified as important prognostic factors in patients with GEM-refractory pancreatic cancer. These factors should be considered in determining the treatment following first-line chemotherapy in patients with advanced pancreatic cancer.

Key words: pancreatic neoplasms – gemcitabine – prognosis – salvage therapy

INTRODUCTION

Pancreatic cancer (PC) is the fifth leading cause of cancer deaths in Japan, with approximately 19 000 patients dying from this disease every year (1). Unfortunately, the majority of patients present with the disease already in an unresectable state at the time of diagnosis, due to locally advanced or metastatic spread. In recent years, gemcitabine (GEM), which is associated with more clinical benefits and better survival compared with 5-fluorouracil, has been widely used as a standard first-line chemotherapy agent for unresectable PC (2). Molecular targeted agents have also been developed for pancreatic cancer. It has been demonstrated that erlotinib combined with GEM improve survival (3). Moreover, another epidermal growth factor receptor (EGFR)-inhibitor, namely cetuximab, has been tried in phase II study (4). The efficacy of GEM is still unsatisfactory, and therefore the prognosis for patients remains poor, with a median survival time (MST) of around 6 months. In order to improve survival, it is necessary to develop not only a more effective first-line regimen, but also effective agents for second-line chemotherapy.

Generally PC progresses rapidly, and a patient's general condition often deteriorates too rapidly to perform any additional chemotherapy after failure of first-line treatment with GEM. Some patients may suffer from more serious adverse effects during second-line chemotherapy compared

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with first-line chemotherapy. Therefore, second-line chemotherapy is difficult to establish and should be initiated with more care than first-line. It is necessary to clarify the natural prognosis for patients with GEM-refractory PC in order to appropriately treat patients with either additional chemotherapy or best supportive care. Furthermore, identification of prognostic factors after GEM failure can help conducting clinical trials for promising second-line chemotherapy agents in patients with advanced PC. Thus, in the present study we investigated survival and prognostic factors in GEM-refractory PC patients and clarified criteria for selecting appropriate candidates for second-line therapy.

PATIENTS AND METHODS

Patients

In Japan, GEM was approved for the treatment of PC by the Ministry of Health, Labor, and Welfare in April 2001. GEM-refractory pancreatic cancer was defined as PC that progresses after chemotherapy with GEM. A total of 210 patients with histologically or cytologically confirmed unresectable PC who had received no other treatment were admitted to our hospital between April 2001 and March 2004. Forty patients were treated with chemoradiotherapy, 33 received palliative treatment and 137 were treated with systemic chemotherapy. Of the 137 patients who received systemic chemotherapy, 100 patients were treated with GEM alone, and 37 were treated with other regimens as part of clinical trials. Twenty-six of the 100 patients treated with GEM alone were excluded from analysis in this study because they were transferred to other hospitals and could not be followed up until disease progression. Data from the remaining 74 patients were analyzed in the current study. These patients were consistent with the criteria of GEM-refractory pancreatic cancer.

Treatment and Assessment of Efficacy

GEM as the first-line chemotherapy agent was administered weekly at a dose of 1000 mg/m^2 in a 30-min intravenous infusion for three consecutive weeks, followed by a week of rest. Treatment was continued until disease progression, patient refusal, or unacceptable toxicity.

Tumor response was evaluated by enhanced computed tomography (CT) or magnetic resonance imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) at least every 8 weeks. Disease progression was defined as confirmation of progressive disease (PD) on the RECIST or clinical deterioration of the patient's general condition.

Factors Analyzed

Sixteen clinical variables at the time of disease progression after GEM chemotherapy were chosen in this study. Each variable was divided into two categories based on previous investigations (5–11) as follows: age (<65 or ≥65 years), sex (male or female), performance status (PS; 0, 1 or 2–4), white blood cell count (<10,000 or ≥10 000/μl), hemoglobin level (<8.0 or ≥8.0 g/dl), platelet count (<100 000 or ≥100 000/μl), serum total bilirubin level (<2.0 or ≥2.0 mg/dl), serum albumin level (≤2.8 or >2.8 g/dl), serum lactate dehydrogenase level (<400 or ≥400 IU/l), serum C-reactive protein (CRP) level (<5.0 or ≥5.0 mg/dl), serum creatinine level (<1.0 or ≥1.0 mg/dl), size of primary tumor (<50 mm or ≥50 mm), liver metastasis (presence or absence), ascites or peritoneal dissemination (presence or absence), serum carcinoembryonic antigen (CEA) level (<100 or ≥100 ng/ml), and serum carbohydrate antigen 19-9 (CA 19-9) level (<10 000 or ≥10 000 U/ml). PS was evaluated according to the Eastern Cooperative Oncology Group criteria. The size of the primary tumor was measured by enhanced CT. Peritoneal dissemination was defined as recognition of peritoneal nodules in CT scans or accumulation of ascites.

Statistical Methods

Overall survival for first-line GEM treatment was calculated from the day chemotherapy was started to either the day of death or the last day of follow-up. Overall survival after progression was calculated from the day when disease progression was confirmed with imaging examinations to either the day of death or the last day of follow-up. Patients whose disease progression was not evaluated with imaging examinations because of rapid general deterioration were also included in this study and the day GEM chemotherapy was determined to terminate was defined as the day of disease progression. Survival data were analyzed using the Kaplan–Meier method. Differences in survival were evaluated by log-rank tests. The Cox proportional hazards model was used to determine the most significant variables related to survival. Forward and backward stepwise regression procedures based on the partial likelihood ratio were used to determine the major independent predictors of survival. Statistical analyses were performed using the SPSS II 11.0J software package for Windows (SPSS Japan, Tokyo, Japan). All P values presented in this report are of the two-tailed type; $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics are shown in Table 1. Seventy (94.6%) of the 74 patients had distant metastasis. In response to the initial treatment with GEM, three patients showed a partial response, 39 showed a stable disease; 23 patients, however, showed a progressive disease. The remaining nine were not evaluable with imaging examinations because of rapid general deterioration due to disease progression.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Age [median (range)]	61.5 (37–90)
Gender	
Male	44 (59.5)
Female	30 (40.5)
Performance status	
0–1	49 (66.2)
2–4	25 (33.8)
Primary tumor site	
head	23 (31.1)
	51 (68.9)
Distant metastasis	
absent	4 (5.4)
present	70 (94.6)
liver	56
peritoneum	23
lung	8
distant lymph node	15
adrenal gland	2
bone	2
ovary	1
Carbohydrate antigen 19-9 (U/ml)	
[median (25–75 percentile)]	1974.5 (305.8–5886.5)
Carcinoembryonic antigen (ng/ml)	
[median (25–75 percentile)]	15.7 (7.7–40.3)

The overall response rate to first-line chemotherapy with GEM alone was thus 4.1% (95% CI: 0.1–11.4%).

Treatment after Failure of GEM Chemotherapy

Generally, we prioritized using agents on clinical trials (e.g. phase I) for treatment after GEM chemotherapy had failed. However, chemotherapy using GEM alone continued if patients were in good general condition, even after disease progression was evident during imaging examinations. Best supportive care alone was provided for patients who refused to continue chemotherapy or in whom general condition deteriorated.

After disease progression, of the 74 patients, 14 (18.9%) continued GEM chemotherapy, two (2.7%) participated in a phase I study of a new anti-cancer agent, and the remaining 58 (78.4%) patients received best supportive care.

Survival

At the time of analysis, 71 patients had died from tumor progression. Overall MST was 5.1 months after first-line chemotherapy with GEM was initiated (Fig. 1). MST after disease progression was 2.0 months (95% CI: 1.7–2.4 months) (Fig. 2).

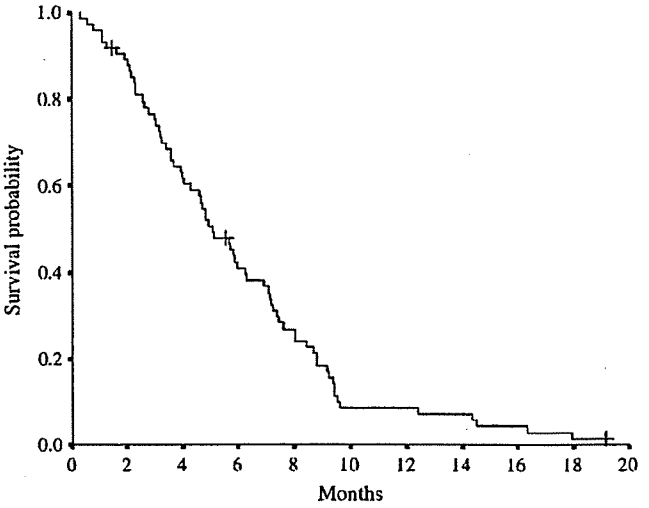

Figure 1. Overall survival curve for 74 pancreatic cancer patients from the day of the start of gemcitabine chemotherapy. The 'plus' sign indicates censored cases. Median survival is 5.1 months.

Univariate Analysis

Among the 16 variables, seven variables were identified as being significantly associated with shorter survival time: PS of 2–4, platelet count of $<100\,000/\mu l$, serum total bilirubin level of ≥ 2.0 mg/dl, serum albumin level of <2.8 g/dl, serum CRP level of ≥ 5.0 mg/dl, presence of peritoneal dissemination and serum CA 19-9 level of $\geq 10\,000$ U/ml (Table 2).

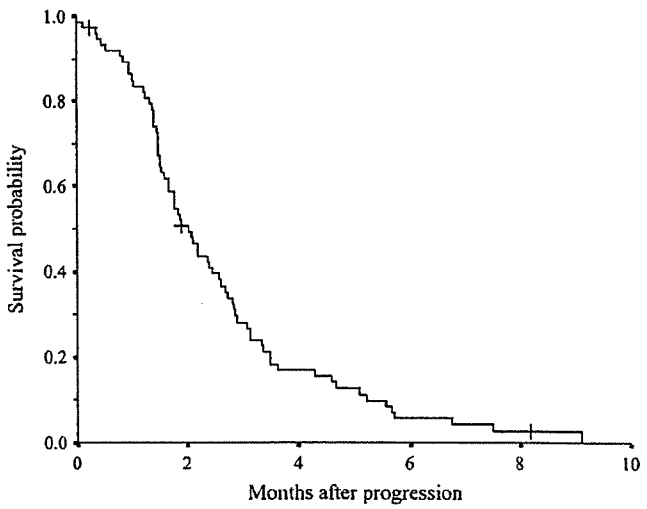

Figure 2. Overall survival curve for 74 pancreatic cancer patients after progression of the first-line of GEM chemotherapy. The 'plus' sign indicates censored cases. Median survival is 2.0 months.

Table 2. Univariate analysis

Variable	*n*	Median survival (months)	*P*-value
Age			
<65	47	1.9	0.9853
≥65	27	2.1	
Sex			
Male	30	2.6	0.2441
Female	44	1.8	
Performance status			
0–1	49	2.6	0.0007
2–4	25	1.5	
White blood ell			
<10 000/mm^3	68	1.9	0.9720
≥10 000/mm^3	6	2.6	
Hemoglobin			
<8.0 g/dl	9	1.6	0.1953
≥8.0 g/dl	65	2.1	
Platelet			
<100 000/μl	7	1.4	0.0498
≥100 000/μl	67	2.1	
Total bilirubin			
<2.0 mg/dl	65	2.0	0.0479
≥2.0 mg/dl			
Albumin			
<2.8 g/dl	15	1.5	0.0023
≥2.8 g/dl	59	2.2	
Lactate dehydrogenase			
<400 IU/l	65	2.1	0.1053
≥400 IU/l	9	1.7	
C-reactive protein			
<5.0 mg/dl	56	2.4	<0.0001
≥5.0 mg/dl	18	1.4	
Serum creatinine			
<1.0 mg/dl	62	2.2	0.5390
≥1.0 mg/dl	12	1.7	
Primary tumor size			
<50 mm	40	2.2	0.1402
≥50 mm	34	1.8	
Liver metastasis			
Absent	18	1.6	0.6471
Present	56	2.1	
Carcinoembryonic antigen			
<100 ng/ml	59	2.2	0.3337
≥100 ng/ml	15	1.7	
Carbohydrate antigen 19-9			
<10 000 U/ml	62	2.1	0.0077
≥10 000 U/ml	12	1.4	

Multivariate Analysis

Multivariate regression analysis was conducted for the seven variables found to have prognostic significance in univariate analysis. Three factors, PS, peritoneal dissemination and CRP, were identified as independent prognostic factors (Table 3). In order to apply these findings to clinical practice, the patients were divided into two groups: the good prognosis group (patients with PS 0 or 1, no peritoneal dissemination and CRP <5.0 mg/dl) and the poor prognosis group (positive for at least one of the three prognostic factors). MST in the good prognosis group was 3.4 months, with the 95% CI ranging from 2.6 to 4.1 months, and MST in the poor prognosis group was 1.5 months, with the 95% CI ranging from 1.4 to 1.6 months (Fig. 3). Twenty-nine patients (39.1%) were included in the good prognosis group.

DISCUSSION

For patients with advanced PC treated with GEM chemotherapy alone, the prognosis is around 6 months. In the present study, median survival was 5.1 months (95% CI: 4.0–6.2 months), which may be worse than that of previous reports. This may be because patients with better conditions were enrolled in clinical trials, such as chemoradiotherapy of new agents. The patients included in this study were treated with GEM as clinical practice, and these patients might have unfavorable factors for survival. For example, PS of these patients were 39 in score 0, 25 in score 1, 10 in score 2. As a result, overall survival of patients included in this study might be worse than that of some previous clinical trials of GEM chemotherapy for patients with advanced PC.

The efficacy of GEM is still poor and it is important not only to develop more effective first-line therapy but to develop effective second-line chemotherapy. No effective second-line chemotherapy has yet been established; however, clinical trials to develop promising second-line chemotherapy are ongoing. In some patients, systemic condition

Table 3. Significant prognostic factors identified by multivariate analysis using Cox proportional hazards model

Variables	*n*	Hazard ratio	95% CI	*P* value
C-reactive protein				
<5.0 mg/dl	56	1		
≥5.0 mg/dl	18	3.291	1.681–6.444	0.001
Performance status				
0–1	49	1		
2–4	25	2.522	1.404–4.529	0.002
Peritoneal dissemination				
Absent	51	1		
Present	23	1.988	1.052–3.757	0.034

CI, confidence interval.

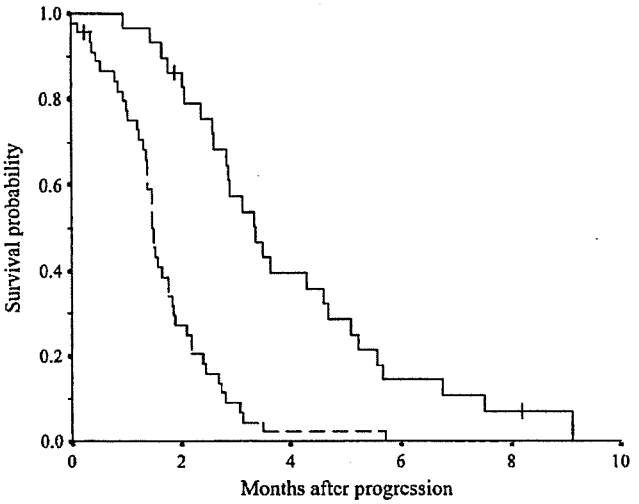

Figure 3. Survival curves for two groups divided: good prognosis group (patients with performance status 0–1, no peritoneal dissemination and C-reactive protein <5.0 mg/dl); and poor prognosis group (positive for at least one among three prognostic factors). Plain line indicates good prognosis group. Dotted line indicates poor prognosis group. There is a significant difference in survival between two groups ($P < 0.0001$). The 'plus' sign indicates censored cases.

rapidly deteriorates after GEM failure and not all patients are suitable candidates for second-line chemotherapy. In the present study, we clarified the prognosis and prognostic factors in patients with GEM-refractory PC, and identified appropriate candidates for second-line chemotherapy.

In this study, three factors, PS, peritoneal dissemination and CRP, were identified as independent prognostic factors in patients with GEM-refractory PC. PS has been widely used to evaluate physical conditions of many cancer patients. It has been recognized as an important prognostic factor in many malignancies. Other studies have similarly found that PS has prognostic value in advanced or metastatic PC after first-line chemotherapy (5–7). Because general conditions of patients with PC often rapidly deteriorate after first-line chemotherapy, the indication of second-line chemotherapy should be limited to good performance patients.

Peritoneal dissemination was also recognized as a prognostic factor in this study. PC spreads easily into the peritoneal cavity, resulting in uncontrollable massive ascites and in deterioration of general condition. In an analysis of prognostic factors in patients with metastatic PC from the start of first-line chemotherapy, it was reported that peritoneal dissemination was not a significant factor associated with shorter survival time. The difference in survival between patients with and without peritoneal dissemination was not found to be significant, but MST was 2.2 months and 3.9 months, respectively (5). The prognostic value of peritoneal dissemination may thus possibly be enhanced after GEM chemotherapy failure.

CRP was found to be the most significant prognostic factor in this study. CRP is a biomarker of infection, inflammation and malignancy. CRP is produced by the liver and is induced by proinflammatory cytokines, such as interleukin-6 or tumor necrosis factor-α (12), which are involved in cachexia. These cytokines are associated with hypermetabolism, weight loss and anorexia and, as a result, may reflect shortened survival (13–15). The prognostic value of CRP has been reported for patients with metastatic PC receiving systemic chemotherapy, and the cut-off value was set at 5.0 mg/dl (5,10,11). We used this reported cut-off value for CRP in analyzing prognosis in the present study. As a result, the same conclusion was reached regarding the prognostic value of CRP in patients with GEM-refractory PC. CRP level has been reported to be a prognostic factor in many malignancies, including hepatocellular carcinoma and colorectal cancer (16–23).

In this study, serum lactate dehydrogenase (LDH) is not identified as a prognostic factor. LDH is an important marker of tumor bulk and tumor load for different solid tumors and lymphoma. Although different cut-off levels other than 400 IU/l were analyzed, there were no significant differences in univariate and multivariate analyses.

MST in patients with a CRP level of <5.0 mg/dl was 2.4 months (95% CI: 1.82–2.98), which is significantly better than the 1.4 months for patients with CRP levels of ≥5.0 mg/dl. CRP level is not included as a variable in most clinical studies of first-line chemotherapy, but it is an important parameter for selecting appropriate patients for clinical studies and selecting candidates for second-line chemotherapy.

To clarify conditions for effective second-line chemotherapy, we divided patients into two groups according to the prognostic factors: the good prognosis group (patients with PS 0 or 1, no peritoneal dissemination and CRP <5.0 mg/dl) and the poor prognosis group (positive for at least one of the three prognostic factors). MST in the good prognosis group was 3.4 months (with the 95% CI ranging from 2.6 to 4.1 months), whereas MST in the poor prognosis group was 1.5 months. Twenty-nine patients (39.1%) were included in the good prognosis group, the members of which could expect at least more than 2 months survival. We consider that those patients with favorable factors (i.e. those that comprise the good prognosis group) are good candidates for second-line chemotherapy. Candidates for clinical trials of new second-line chemotherapy agents should be selected from this group to allow accurate evaluation of survival time. In this study, the number of patients was too small to conduct a Cox proportional hazards model. Therefore, a prospective trial should be conducted to validate these results.

Recently, several trials of salvage chemotherapy regimens have been conducted for GEM-refractory PC, with response rates ranging from 0 to 24% and MST ranging from 3.1 to 10.3 months (24–34). Among these regimens, oxaliplatin combination regimens have shown promising results. Cantore et al. reported oxaliplatin/irinotecan regimen in which objective response was 10% and MST was 5.9 months (24). Jacobs et al. conducted a randomized trial using rubitecan as compared with the physician's choice. This large study comprised 409 patients and found an MST of

3.6 months in rubitecan-treated patients, and 3.1 months in control patients (25). In these studies, survival after failure of GEM treatment was much better than that in the present study. One of the reasons for this may be that only patients with good PS were enrolled in the studies above. It remains urgent to develop promising second-line chemotherapy to prolong survival in patients with advanced PC with poor PS.

Most of the patients in the present study did not receive other chemotherapy after GEM failure, because no other agent was approved for the treatment of PC in Japan. In the present study, GEM treatment was continued in 14 of the 74 patients after confirmation of progression if the patient still had good PS, had clinical benefit, or had decreased tumor marker levels, even after disease progression was confirmed by imaging (e.g. by CT). In Japan, some anti-cancer agents, such as irinotecan and S-1, have been reported to have promising anti-cancer effects in clinical studies when administered as monotherapies (35,36). We expect that these agents will become available as second-line chemotherapy in many patients in near future.

In conclusion, serum levels of CRP, PS and peritoneal dissemination were identified as important prognostic factors in patients with GEM-refractory PC. These factors should be considered in determining the treatment following first-line chemotherapy in patients with advanced PC.

Conflict of interest statement

None declared.

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6. 膵癌薬物応答性に基づく個別化治療

Personalized medicine for pancreatic cancer

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Summary

膵癌における化学療法において，フルオウラシル(5-FU)との無作為比較試験により塩酸ゲムシタビンの有効性が証明され，標準的治療薬として広く用いられるようになった。以降，新規抗癌剤やゲムシタビンを基剤とした併用治療など多くの新しい試みが行われ，最近では分子標的治療薬の併用による臨床試験がすすめられている。また，遺伝子解析による薬剤応答性を調べ，個々の薬物毒性を予測することによる治療の個別化が研究されている。

このように膵癌における化学療法は急速に進歩し，多様化しつつある。今後，より高い治療効果を得るためには，それぞれの治療法の適切な適応を明らかにし，膵癌治療の個別化に向けた試みが必要となってくる。

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Key Words　膵癌，化学療法，分子標的治療薬，遺伝子解析，薬剤応答性

はじめに

膵癌における化学療法は，これまで多くの薬剤や併用治療が試みられてきたが，有効な治療法が証明されないまま探索的に行われてきた。1997年，従来広く用いられてきたフルオロウラシル(5-Fluorouracil：5-FU)と塩酸ゲムシタビン(gemcitabine：GEM)による無作為比較試験が行われ，GEM群で症状緩和効果と生存期間の延長について有効性が明らかとなった[1]。現在，GEMは膵癌における標準的治療薬として用いられ，さらにGEMを基本とした併用化学療法，新規抗癌剤，分子標的治療薬の併用など多くの新しい治療法の開発が試みられている。

一方，有効な治療法が開発され，その効果や副作用などが多様化するに伴い，単純に個々の治療法に優劣がつけられなくなるかもしれない。膵癌にお

◆メモランダム◆

膵癌における主な分子標的とその治療薬

細胞増殖のシグナル伝達の異常が発癌や癌の増殖と関連しており，一連の細胞内シグナル伝達経路のさまざまな部位が分子標的となる。上皮成長因子Epidermal growth factor (EGF)およびそのreceptor (EGFR)は代表的なシグナル伝達系であり，その阻害剤として多くの薬剤が開発されている。EGFRの細胞外側のドメインに対する抗体薬がセタキシマブ(cetuximab)である。EGFRの細胞内部分のチロシンキナーゼに結合するATPと競合し，それ以下の細胞内シグナル伝達を阻害する薬剤がエルロチニブ(erlotinib)である[1)2)]。癌が増殖を続けるためには血管新生が必要であり，血管新生を阻害することにより癌の増殖や転移が抑制される。血管内皮増殖因子Vascular endothelial growth factor (VEGF)およびそのreceptor (VEGFR)が血管新生阻害の分子標的となり，VEGFを中和する抗体がベバシズマブ(bevacizumab)である[2)3)]。

表1　ゲムシタビン単独化学療法の治療成績

	米国のRCT[4]	日本の第Ⅰ相試験[5]	市販後後ろ向き解析[6]
期間	1992～1994年	1999～2000年	2001～2003年
施設	多施設	2施設(NCCH，NCCHE)	NCCHE単施設
患者数	63	11	50
局所進行/転移	18/45	0/11	0/50
奏効率	5.4％	18.2％	10.0％
症状緩和効果	23.8％	28.6％	-
生存期間中央値	5.7ヵ月	6.4ヵ月	5.7ヵ月
1年生存率	18％	-	10％

RCT：無作為化比較試験(Randomized clinical trial)，NCCH：国立がんセンター中央病院(National Cancer Center Hospital)，NCCHE：国立がんセンター東病院(National Cancer Center Hospital East)

表2　膵癌に対する最近の全身化学療法

GEM単独治療	GEM+他抗癌剤	GEM+分子標的治療薬	他の抗癌剤単独治療
大量・隔週投与法[7]	5-FU[9]	マリマスタット[17]	イリノテカン[20]
定速静注法[8]	シスプラチン[10]	ティピファルニブ[3]	S-1[21]
	イリノテカン[11]	セタキシマブ[1]	エキサテカン[22]
	オキザリプラチン[12]	ベバシズマブ[18]	イキサベピロン[23]
	エキサテカン[13]	エルロチニブ[19]	
	ペメトレキセド[14]		
	カペシタビン[15]		
	S-1[16]		

GEM：gemcitabine（ゲムシタビン）

ける分子標的治療薬の有用性も明らかになりつつあり，各々の分子標的の発現に応じた治療適応が必要となるかもしれない。つまり，それぞれの治療法の特徴を十分理解し，個々の患者背景，腫瘍の進行度や性状に応じて，より適切な治療を選択することが必要となってくる。また，ヒトゲノム研究の急速な進歩により，個々の遺伝子解析により薬剤応答性を規定する遺伝子の変異を診断し，薬物治療の効果や副作用の個人差を明らかにする試みも始まっている。本稿は，膵癌における化学療法の現状と膵癌治療の個別化からみた薬物療法について概説する。

全身化学療法の現状

米国で行われた5-FUとGEMとの無作為化比較試験以降，GEMが進行膵癌における標準治療薬である。GEM単独化学療法が標準治療として続いている特長をあげると，①治療成績に再現性がある，②週1回の点滴投与であり，治療法が簡便である，③副作用が比較的軽度で外来治療が可能である，④膵癌に特徴的な疼痛，performance statusの低下，体重減少など症状緩和効果が認められる，である。表1には米国の無作為化比較試験の結果，わが国で行われた臨床第Ⅰ相試験，および国立がんセンター東病院での治療成績を示す[4)-6)]。奏効率，生存期間など治療成績に再現性がみられるが，依然予後不良であることに変わりはない。

この数年，GEM単独治療に勝る治療法の開発がさかんに行われている。新しい化学療法の開発は，GEMの変法やGEMを基本薬剤とした併用療法と新規抗癌剤とに分けられる(表2)。以下，主な治療法について述べる。

GEMはデオキシシチジンキナーゼ

表3　ゲムシタビンと細胞障害性薬剤による無作為化比較試験

	n	RR	MST (mo)	1-year OS %	p-value	Author
Gem	63	5.4 %	5.7	18 %	p=0.0025	Burris (1997)[4]
5-FU	63	0	4.4	2 %		
Gem	162	5.6 %	5.4	20 %	p=0.09	Berlin (2002)[24]
Gem/5-FU	160	6.9 %	6.7	18 %		
Gem	99	8.0 %	6.0	-	p=0.12	Heinemann (2003)[9]
Gem/cisplatin	96	10.2 %	8.3	-		
Gem	173	4.4 %	6.6	20 %	p=0.79	Rocha Lima (2004)[10]
Gem/irinotecan	169	16.1 %	6.3	20 %		
Gem	156	16.7 %	7.1	28 %	p=0.13	Louvet (2005)[11]
Gem/oxaliplatin	157	28.7 %	9.0	38 %		
Gem	174	6.3 %	6.7	23 %	p=0.52	O'Reilly (2004)[12]
Gem/exatecan	175	8.2 %	6.2	21 %		
Gem	282	9.1 %	6.2	20 %	p=0.85	Richards (2004)[13]
Gem/pemetrexed	283	18.3 %	6.3	21 %		
Gem	285	7.9 %	7.3	28 %	p=0.31	Herrmann (2005)[14]
Gem/capecitabine	284	10.1 %	8.4	30 %		

RR：response rate, MST：median survival time, OS：overall survival, Gem：gemcitabine, 5-FU：5-fluorouracil

により三リン酸化物に代謝され，DNA合成を阻害する活性体となる。定速静注法(Fixed-dose rate infusion of gemcitabine：FDR-GEM)は，この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/m²/min が最適な投与速度であるという基礎実験から試みられた治療法である。米国において，1500 mg/m² を 150 分で投与するFDR-GEM と 2200 mg/m² を 30 分で投与する方法との無作為化比較第Ⅱ相試験が行われ，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 ヵ月と 5.0 ヵ月，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[4]。この定速静注は，以下で述べるGEMOX 治療など，併用療法にも用いられている。著者らは日本人における安全性と推奨用量を確認するための第Ⅰ相試験を行ったところ，骨髄抑制から 1200 mg/m²，120 分が適当と考えられた[24]。現在，米国で標準 GEM，FDR-GEM，GEMOX による大規模無作為化比較試験が行われており，今後その位置付けが明らかになるものと期待されている。

GEM と他剤による併用療法は，これまで 5-FU，シスプラチン，イリノテカン，オキザリプラチンなど多くの第Ⅲ相試験が行われてきたが(表 2，3)，GEM 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ていない[9)-15)]。GEM 以外の薬剤として，わが国ではイリノテカンや S-1 などの臨床試験が行われ，高い奏効率が認められている(表 4)[20)21)]。また，S-1 と GEM との併用療法による第Ⅰ相試験が行われ(表 4)[16)]，多数例による臨床試験が行われつつある。

一般に併用療法では全身状態の良好な症例で GEM 単独より生存期間が改善される傾向がある。Performance status がよい場合では奏効率が高い併用治療を行う意義があるかもしれない。またイリノテカンや S-1 など単剤でも GEM より奏効率が高い薬剤では，同時併用よりむしろ交代併用療法でメリットが大きい可能性も考えられる。このように治療法が多様化してくると，大規模な無作為化比較試験(第Ⅲ相試験)が必要となる。その上で適切な治療を適切な症例に行う，いわゆる個別

表4　わが国で行われた最近の臨床試験

	n	RR	MST (mo)	Author
Irinotecan (P-2)	40	27.0％	7.3	Funakoshi (2004)[15]
S-1 (P-2)	40	37.5％	8.8	Furuse (2005)[20]
Gem/S-1 (P-1)	18	33.3％	7.6	Ueno (2005)[21]

RR：response rate, MST：median survival time, OS：overall survival, Gem：gemcitabine, P-2：phase Ⅱ study, P-1：phase Ⅰ study

化治療が可能となる。

分子標的治療薬の併用

癌の分子生物学，分子遺伝学の急速な進歩により，癌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が開発されている。膵癌においてもK-ras遺伝子の異常，epidermal growth factor (EGF)，Vascular endothelial growth factor (VEGF)などさまざまな分子標的が明らかとなっている[25][26]。これまで癌の増殖・転移や腫瘍血管新生に関連するmatrix metalloproteinase (MMP)の阻害剤Marimostatや Ras蛋白の活性化に関する酵素Farnesyl transferaseの阻害剤Tipifarnibなどで臨床試験が行われたが，いずれもネガティブな結果に終わっている(表5)[3][17]。

最近ではGEMとEGFR阻害剤セタキシマブ(cetuximab)やVEGF阻害剤ベバシズマブ(bevacizumab)の分子標的治療薬との併用治療による第Ⅱ相試験が行われ，良好な成績が得られている(表5)[1][18]。現在，米国で第Ⅲ相試験が行われている。2005年ASCO会議では，EGFRを阻害する分子標的治療薬エルロチニブ(erlotinib)とGEMとの併用療法が，GEM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(表5)[19]。生存期間中央値は，GEM単独群で5.9ヵ月，エルロチニブ併用群で6.4ヵ月とその差はわずかであったが，背景因子別の検討では男性，遠隔転移，PS 2，若年，疼痛なしの群で併用効果が認められている。また皮疹が強く発現した例で生存期間の延長がみられており，皮疹の発現と治療効果との関連が注目されている。

このように分子標的治療薬でも均一に併用のメリットが得られるわけではない。分子標的治療薬の適応は，EGFなど目的とする分子標的の発現程度を治療前に正確に評価して考慮されるべきかもしれない。分子標的治療薬はそのコストも大きな問題になりつつある。分子標的治療薬の有効性が期待できる対象を明らかにしていく必要がある。

GEM遺伝子解析

ヒトゲノム研究の急速な進歩により，薬剤応答性の個人差を規定する遺伝子とその変異を診断し，個別に薬剤を選択する客観的な指標を確立する研究が進んでいる。つまり，抗癌剤の薬剤応答性には遺伝子で規定された個人差があり，その違いを診断することによってより有効な化学療法を行う，いわゆる個別化治療の試みである。これまで，5-FUの分解酵素であるdihydropyrimidine dehydrogenase (DPD)やイリノテカンにおけるUDP-glucuronosyltransferase (UGT) 1A1酵素などで酵素欠損あるいは遺伝子多型と抗癌剤における毒性の関連が明らかになっている[2][27]。

国立がんセンターを中心にGEMの投与を受けた膵癌などの患者を対象にGEMを不活性化する酵素cytidine deaminase (CDA)の遺伝子解析が行われた[28]。その結果，3.7％の患者でアミノ酸変異を有することが明らかとなった。その変異をホモ接合体でもつ患者ではGEMのクリアランスが低下し，重篤な骨髄抑制や皮膚粘膜障害が認められた。日本人では頻度は低いもののGEMの代謝に関する遺伝子変異と毒性との関連が明らかとなってきている。

おわりに

現在，ゲムシタビン単独治療が進行膵癌の標準治療という位置付けである。他の抗癌剤や分子標的治療薬の併用では，治療効果の向上がみられる一方，コストや副作用という問題も生じる。新しい治療法の利益と不利益を科学的に検証し，適切な適応を明らかにする必要がある。また切除後補助療法や放射線との併用療法など，薬物療法の役割はさらに多様化し重要となる。薬物

表5　分子標的治療薬による臨床試験

	n	RR	MST (mo)	1-year OS %	p-value	Author
Gem	119	16 %	5.4	17 %	0.95	Bramhall (2002)[17]
Gem/marimostat	120	11 %	5.4	18 %		
Gem	347	8 %	6	24 %	0.75	Cutsem (2004)[3]
Gem/tipifarnib	341	6 %	6.3	27 %		
Gem/cetuximab (P-2)	61	12.2 %	7.1	32 %	-	Xiong (2004)[1]
Gem/bevacizumab (P-2)	52	21.2 %	8.8	29 %	-	Kindler (2005)[18]
Gem	284	6.9 %	5.9	17 %	0.025	Moore (2005)[19]
Gem/Erlotinib	285	8.2 %	6.4	24 %		

RR：response rate, MST：median survival time, OS：overall survival, Gem：gemcitabine, P-2：phase Ⅱ study

療法においては，適切なレジメンや適応症例の選択，そのタイミング，他の治療法との併用，などなど，より複雑になると思われる。すなわち，癌の個別化治療の時代である。適切な薬物療法の確立と実践には，質の高い臨床試験により速やかかつ客観的な評価が重要であるとともに，薬物療法を十分理解した癌化学療法の専門医による実践が必要である。

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第6章 膵・胆道癌に対する化学療法

はじめに

膵・胆道癌は早期診断が難しい難治癌であり，一般に切除率は20～30％と低率である．また根治切除が行われたとしても再発率もきわめて高い．これらの再発例や切除不能例において，化学療法の臨床的役割はきわめて大きい．1997年，進行膵癌において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が進行膵癌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十分満足されるものではなく，新しい治療法の開発に向けて多くの臨床研究が行われている．一方，胆道癌の化学療法においては十分なエビデンスはなく，標準といえるレジメンがないことをよく理解して化学療法を行う必要がある．

Ⅰ．膵・胆道癌における全身化学療法の意義

膵・胆道癌の切除不能進行例を対象に，支持療法と全身化学療法の無作為化比較試験が行われている[1]．それによると膵・胆道癌全体では生存期間中央値は化学療法群6.0カ月に対し，支持療法2.5カ月と有意に化学療法群で良好な生存期間が得られた（$p<0.01$）．疾患別の検討では症例数が少ないためか，統計学的有

意差は認められなかったものの同様の傾向がみられている．

1997年，進行膵癌におけるgemcitabineと5-FUとの無作為化比較試験の結果が報告された[2]．直接抗腫瘍効果を指標とした奏効率はgemcitabine 5.4%，5-FU 0%といずれも低率であったが，疼痛やperformance status（PS）などの症状緩和効果を指標とした有効率はgemcitabine 23.8%，5-FU 4.8%と，gemcitabineで有意に良好な成績が得られた（$p = 0.0022$）．さらに生存期間中央値でも5-FU 4.41カ月に比べgemcitabine 5.65カ月と有意差が認められた（$p = 0.0025$）．これらのエビデンスに基づき，米国National Comprehensive Cancer Network（NCCN）の癌治療ガイドラインでは，gemcitabine単剤の化学療法は転移性膵癌においてcategory 1と高い位置づけがなされている．

一方，胆道癌では，当院において全身化学療法あるいは支持療法が施行された胆嚢癌例の予後を検討したところ，PSの良好な例（PS 0, 1）では支持療法群に比べ化学療法群で有意に予後良好であったが，PSが不良な例（PS 2）では両者で差は認められなかった[3]．現状ではPSが良好な症例でのみ化学療法の利益が得られると理解して，治療に当たる必要がある．

Ⅱ．膵　癌

1．全身化学療法の現状

1）標準治療薬 Gemcitabine

米国で行われたgemcitabineと5-FUとの無作為化比較試験の結果から，gemcitabineが進行膵癌における標準治療薬として広く用いられている[2]．gemcitabineはcytarabineと構造的に類似した代謝拮抗剤に分類される抗癌剤であり，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殺細胞作用を示す．わが国でも第Ⅰ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[4]．現在，gemcitabine 1,000 mg/m^2,

Day	1	8	15	22
Gemcitabine (1,000 mg/m²・div 30min)	↓	↓	↓	休薬

4週ごとに繰り返す

〈休薬規準〉白血球 2,000以上, 好中球 1,000以上, 血小板数 70,000以上

投与例

Day 1，8，15

カイトリル® (1A；3mg)＋ 生食 (100mℓ) ……30分点滴静注

Gemcitabine (1,000mg/m²)＋ 生食 (100mℓ) ……30分点滴静注

図1　Gemcitabineの標準投与法と投与例

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（図）.

2）Gemcitabine投与法の工夫

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/m²/minが最適な投与速度であるという基礎実験から，1,500 mg/m²を150分で投与する定速静注法（10 mg/m²/min）を試みている[5]．2,200 mg/m²を30分で投与する方法との無作為化比較第Ⅱ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予後良好であることが示された[5]．米国のstudy groupであるECOGにおいてgemcitabine 1,000 mg/m²による標準投与法，gemcitabineの定速静注法，gemcitabine 1,000 mg/m²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，その結果が待たれている．

3）Gemcitabineと他剤との併用療法

gemcitabineが標準治療薬として確立したとはいえ，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-FU，cisplatin（ランダ®，ブリプラチン®），irinotecan（カンプト®），oxaliplatinなどとの併用療法による第Ⅲ相臨床試験が報告されている[6)~9)]．しかし，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ていない．

膵癌においてもEGF（epidermal growth factor），VEGF（vascular endothelial growth factor），およびこれらのreceptor，MMP（matrix metalloproteinase），K-*ras*遺伝子の異常などさまざまな分子標的が明らかとなり，分子標的薬の試みが行われてきている．2005年のASCO会議では，EGFR阻害分子標的薬erlotinibとgemcitabineの併用療法とgemcitabine単独との無作為化比較試験において，併用療法で有意に生存期間が改善したと報告され，注目を集めた[10)]．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．そのほかVEGF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[11),12)]．

4）Gemcitabine以外の薬剤

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，比較的高い奏効率が認められている[13),14)]．またS-1とgemcitabineとの併用療法による第Ⅰ相試験では，30～40％と高い奏効率が期待されたことから[15)]，多数例による臨床試験が行われつつある．

2．全身化学療法の適応

切除不能の進行膵癌は，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，局所進行癌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-FU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．欧米ではgemcitabineを中心とした全身化学療法の臨床試験において，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．一方，gemcitabineは強い放射線増感作用も認められ，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[16]．

現在，局所進行膵癌における標準治療はむしろ混乱しているといってもよい状況であり，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．

Ⅲ．胆道癌

多剤併用による化学療法が多く試みられ，最近ではgemcitabine

表　胆道癌に対するおもなgemcitabine-based全身化学療法

抗癌剤	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）[17]
Gemcitabine	36%（9/25）	7.0	17%	Gallardo（2001）[18]
Gemcitabine/Docetaxel	9%（4/43）	11.0	42%	Kuhn（2002）[19]
Gemcitabine/Oxaliplatin	33%（11/33）	15.4	57%	Andre（2004）[20]
*MMC/Gemcitabine	20%（5/25）	6.7	—	Kornek（2004）[21]
MMC/Capecitabine	31%（8/26）	9.3	—	
Gemcitabine/CDDP	28%（11/40）	8.4	—	Thongprasert（2005）[22]
Gemcitabine/Capecitabine	31%（14/45）	14.0	49%	Knox（2005）[23]

MST：median survival time, CDDP：cisplatin, MMC：mitomycin C
*：無作為化比較試験

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（表）[17)~23)]．しかしこれまで標準といえる化学療法は確立していないのが現状である．わが国では，現在胆道癌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®，ただし他の抗腫瘍剤と併用）に限られている．しかしこれらの薬剤では，単独での抗腫瘍効果はほとんど期待できず，胆道癌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[24)]，近い将来保険適応の承認が期待されている．

おわりに

膵・胆道癌においては，切除不能進行癌に対する治療戦略を考えるうえ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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