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

K Nakamura[1], T Yamaguchi*[,1], T Ishihara[1], K Sudo[1], H Kato[2] and H Saisho[1]

[1]*Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan;* [2]*Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan*

We conducted a phase II trial of gemcitabine with S-1, oral fluorouracil (5-FU) prodrug tegafur combined with two modulators, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate, to evaluate the activity and toxicity of such a combination in metastatic pancreatic cancer (MPC) patients. Patients who had pathologically proven pancreatic cancer with metastatic lesions were eligible candidates for entry into the study. S-1 was given orally (30 mg m^{-2}) b.i.d. for 14 consecutive days and gemcitabine (1000 mg m^{-2}) was given on days 8 and 15. The cycle was repeated every 21 days. We enrolled 33 MPC patients. The median number of cycles was eight (range 1–20). Grade 3–4 toxicities were leucopenia (33%), neutropenia (55%), anaemia (9%), thrombocytopenia (15%), anorexia (6%), fever (9%), and interstitial pneumonia (6%). Objective responses were obtained in 16 patients (one complete response and 15 partial responses; response rate, 48%; 95% confidence interval (CI), 33–65). Median survival and 1-year survival rate were 12.5 months (95% CI, 5.9–19.1) and 54% (95% CI, 36–72), respectively. Combination chemotherapy with GEM and S-1 was well tolerated and yielded a significantly high response rate.
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Pancreatic cancer is one of the most frequently observed gastrointestinal cancers and its prognosis remains extremely dismal. It is the fifth leading cause of cancer death in Japan, as well as in the US and European countries (Matsuno *et al*, 2004). The 5-year survival rate is still poor, at less than 10%, which is commonly considered to be linked to the high incidence of metastatic disease even on initial diagnosis, as well as the relative chemoresistance of this tumour. Therefore, innovations in systemic chemotherapy are needed to improve the survival of patients with advanced pancreatic cancer (APC) (Glimelius *et al*, 1996; Evans *et al*, 1997).

Over the past few years, gemcitabine has been the most widely used chemotherapeutic agent in APC and was reported to yield significantly better symptom control of APC than 5-FU in a randomised phase III clinical study (Burris *et al*, 1997). However, the activity of gemcitabine in pancreatic cancer remains modest and there is a clear need to improve its efficacy by combining it with other anticancer drugs.

Chemotherapy combinations for the treatment of pancreatic cancer could involve prolonged or continuous infusion of 5-FU, because 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). Oral administration of 5-FU is not effective, owing to the inability to achieve plasma concentration of sufficient magnitude. An interesting way to increase the efficacy of 5-FU is through the inhibition of the degrading enzyme, dihydropyrimidine dehydrogenase (DPD).

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 the 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 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 combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations, both in plasma and in tumours. In addition, it has been suggested that CDHP has the potential to enhance the antitumour activity of 5-FU against subcutaneous tumours in nude mice, using human pancreas carcinoma cells with a high tumoural DPD activity (Takechi *et al*, 2002). Oxo is an agent that decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase. Oxo preferentially localises in the gut rather than in the tumour and has a potential biochemical effect on the enzyme pyrimidine phosphoribosyl transferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects (Takechi *et al*, 1997).

S-1 has undergone phase I evaluation in Japan, as well as extensive phase II studies in gastric, colon, head and neck and breast cancers, leading to registration in this country for gastric

*Correspondence: Dr T Yamaguchi; E-mail: yama.take@faculty.chiba-u.jp
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cancer. 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). In studies outside of 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 favourable results of S-1 monotherapy have been reported in Japanese early phase II and late phase II studies of patients with APC (Furuse *et al*, 2005; Ueno *et al*, 2005).

The administration of oral S-1 is more convenient and simulates the effect of continuous infusion of 5-FU. 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). We anticipated that combination chemotherapy of gemcitabine and S-1 would be effective through the synergistic activity of gemcitabine and 5-FU derived from S-1. Thus, we performed a phase I study to evaluate the safety of treatment combining GEM with S-1 and to determine the MTD of each drug in patients with APC (Nakamura *et al*, 2005). This combination chemotherapy was well tolerated and showed outstanding antitumour activity.

Therefore we conducted a phase II study of this combination chemotherapy in patients with metastatic pancreatic cancer (MPC) and assessed the efficacy and toxicity of this regimen.

PATIENTS AND METHODS

End point

The primary end point of this study was to determine the efficacy of a combination of gemcitabine and S-1 in MPC. The secondary end points were to assess toxicity, time to progression, and survival.

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 pericardial effusion, severe heart disease, difficult to control diabetes mellitus, active infection, pregnant or lactating women, 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. The patients that have pancreatic cancer with neuroendocrine characteristics were excluded.

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

Treatment plan

We gave orally 30 $mg\,m^{-2}$ S-1 twice daily, after breakfast and dinner 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 FT. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. We administered 1000 $mg\,m^{-2}$ gemcitabine in a 30-min intravenous infusion on days 8 and 15 of each cycle. The cycle was repeated every 21 days.

The dose of S-1 was not adjusted for toxicity, because reducing dose of 30 $mg\,m^{-2}$ twice daily S-1 could not maintain effective blood concentration as 5-FU and the synergistic activity of gemcitabine and 5-FU derived from S-1 was weakened. Similarly, the dose of infusional 5-FU was fixed, and the dose of gemcitabine was adjusted for toxicity in the report of phase I/II study of gemcitabine combined infusional 5-FU (Hidalgo *et al*, 1999).

Full doses of both drugs were given in cases with grade 0–1 toxicity. If grade 2 toxicity was observed the gemcitabine dose was reduced to 800 $mg\,m^{-2}$ on days 8 or 15. In cases of grade 3 toxicity, gemcitabine administration was omitted. In cases of grade 4 toxicity, both drugs were stopped and adjourned for 1 week.

When grade 3 toxicity was observed in two consecutive cycles, or when grade 4 toxicity was observed even once, 800 $mg\,m^{-2}$ gemcitabine and 30 $mg\,m^{-2}$ twice daily S-1 were administered for subsequent cycles. When grade 3 or 4 toxicity was observed even at those doses, further reduction to 600 $mg\,m^{-2}$ gemcitabine and 30 $mg\,m^{-2}$ twice daily S-1 were administered for subsequent cycles. We abandoned this treatment when grade 3 or 4 toxicity was observed at that dose.

Pretreatment and follow-up studies

Pretreatment evaluation consisted of baseline studies including medical history, physical examination, WHO performance status assessment, blood chemistries, urine analysis, electrocardiograms, CA19-9 serum levels. Chest X-ray and abdominal computed tomography (CT) were performed within the period of 2 weeks before starting chemotherapy in order to accurately define the extent of the disease and the target lesions. Measurable disease was defined as a bidimensionally measurable lesion 10 mm or more in size on spiral CT scan. Patients were re-evaluated every two cycles (i.e. every 6 weeks) and then every 2 months after the withdrawal of the protocol. Blood cell counts were performed weekly during treatment and serum chemistry before every new cycle.

The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0) was used to evaluate treatment-related side effects.

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 clinical evidence of the tumour for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for 4 weeks or longer without any evidence of new lesions. Stable disease (SD) was defined as less than a 50% reduction or less than a 25% increase in the sum of the products of the two perpendicular diameters of all lesions for 4 weeks or longer without any evidence of new lesions. Progressive disease (PD) was defined as an increase of 25% or more in the sum of the products of two perpendicular diameters of all lesions, the appearance of any new lesion, or deterioration in clinical status that was consistent with disease progression. To assess objective response,

patients were evaluated every two cycles (i.e. every 6 weeks) by three independent radiologists

The time to progression was measured from entry into the trial up to the time when progression or death without evidence of progression was observed.

Overall survival was estimated from the date of first treatment to death or last follow-up visit.

Statistics

The number of patients required for the study was determined according to the optimal two-stage design. Threshold response rate and expected response rate were 10 and 30%, respectively. The sample size of this trial was 29 patients (α- and β-error probabilities 0.05 and 0.2, respectively). Time-related parameters were analysed using Kaplan–Meier on an intention-to-treat analysis.

RESULTS

All 33 patients with APC were registered between September 2003 and February 2005. Of 33 patients, 28 had liver metastasis, six had lung metastasis and one presented with peritoneal carcinomatosis and massive ascites only (Table 1). Although 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.

A total of 278 cycles (median 8, range 1–20) were administered. Eleven patients (33%) received full dose intensity (Table 2).

A total of 22 patients (67%) observed grade 2 or more toxicity needed dose reductions of administration of gemcitabine at least once. However, 13 out of these patients could continue this combination regimen at preplanned dose of 1000 mg m^{-2} of gemcitabine from the subsequent cycles. The other nine (27%) patients still continued at reduced dose of gemcitabine for the subsequent cycles. Thus, 24 (73%) of all 33 patients did not require one or more step of dose reduction of administration of gemcitabine for all cycles.

Table 1 Patient characteristics

Median age (range)	**61 (45–73)**
Gender	No. of patients (%)
Male	21 (64)
Female	12 (36)
ECOG PS	
0	11 (33)
1	20 (61)
2	2 (6)
Stage	
Locally advanced	0
Metastatic	33 (100)
Prior therapy	
Tumour resection	0
Radiotherapy	0
Chemotherapy	0
Sites of metastatic disease[a]	
Liver	28 (85)
Lung	6 (18)
Peritoneum	1 (3)

[a]Some were overlapping. ECOG = Eastern Cooperative Oncology Group.

Table 2 Duration of administration and dose intensity of gemcitabine

No. of patients	**33**
No. of cycles	
Total	278
Median	8
Range	1–20
Relative dose intensity of gemcitabine	
Average	0.81
Median	0.90
Range	0.43–1.0

Table 3 Tumour response

	Response				
No. of patients	**CR**	**PR**	**SD**	**PD**	**Response rate (%)**
33	1	15	9	8	48 (95% CI: 33–65%)

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

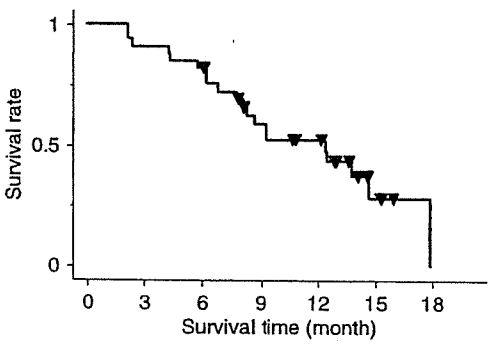

Figure 1 Overall survival curve for all 33 patients. Of 33 patients, 13 are still alive. Median survival time was 12.5 months (95% CI, 5.9–19.1 months). One-year survival rate was 54% (95% CI, 36–72%).

Efficacy and survival

Results are shown in Table 3. An overall objective response was observed in 16: one CR and 15 PR, and the overall response rate was thus 48% (95% confidence interval (CI), 33–65%). Although early discontinuation of treatment before the first evaluation was caused by early progression in two patients, all responses were confirmed 1 month later. Progressive disease was observed in eight patients (24%) including the two patients.

Median time to progression was 5.4 months (95% CI, 2.5–8.4 months). Overall survival was 12.5 months (95% CI, 5.9–19.1 months). The Kaplan–Meier estimate of survival is shown in Figure 1. The 1-year survival rate was 54% (95% CI, 36–72%). Overall, at the time of the last analysis, 20 patients had died, all of them due to progression of disease.

Toxicity

Maximum toxicity data for the 33 patients during all cycles of this chemotherapy are listed in Table 4. The National Cancer Institute/Common Toxicity Criteria grade 3 or 4 neutropenia, thrombocytopenia and anaemia were observed in 55, 15 and 9% of the patients, respectively, including two cases of febrile neutropenia; relevant grade 3 or 4 nonhaematological toxicities consisted of anorexia, nausea, vomiting and diarrhoea but were very limited.

Table 4 Maximum toxicity per patient during all cycles

	Grade 1		Grade 2		Grade 3		Grade 4	
	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)
Leucopenia	5 (15)	78 (28)	14 (42)	66 (24)	11 (33)	16 (5.8)	0	0
Neutropenia	4 (12)	61 (22)	7 (21)	48 (17)	12 (36)	37 (13)	6 (18)	14 (5.1)
Anaemia	5 (15)	24 (8.7)	13 (39)	38 (14)	3 (9.1)	4 (1.5)	0	0
Thrombocytopenia	10 (30)	38 (14)	13 (39)	22 (8.0)	5 (15)	8 (2.9)	0	0
Anorexia	12 (36)	30 (11)	2 (6.1)	5 (1.8)	2 (6.1)	2 (0.7)	0	0
Nausea	14 (42)	26 (9.5)	2 (6.1)	4 (1.5)	0	0	0	0
Vomiting	4 (12)	6 (2.2)	0	0	0	0	0	0
Diarrhoea	1 (3.0)	2 (0.7)	0	0	0	0	0	0
Rash	14 (42)	15 (5.5)	12 (36)	12 (4.4)	0	0	0	0
Fever	5 (15)	10 (3.6)	0	0	3 (9.1)	3 (1.1)	0	0
Stomatitis	4 (12)	4 (1.5)	1 (3.0)	1 (0.4)	0	0	0	0
Interstitial pneumonia	0	0	0	0	2 (6.1)	2 (0.7)	0	0

The total number of cycles was 278, in a total of 33 patients.

Although a reduction of administration of gemcitabine was needed in two-thirds of the patients in this study because of grade 3 or 4 neutropenia, it was possible to limit grade 3 or 4 neutropenia during all cycles to 18% by reducing the quantity of administration of gemcitabine in subsequent cycles. There was no patient who gave up treatment because of neutropenia. There were two patients who stopped treatment because of interstitial pneumonia. Although grade 1 or 2 rash was observed in 79% of the patients for the first cycle, it had improved by the preventive administration of 4 or 8 mg dexamethasone before administration of gemcitabine for subsequent cycles.

DISCUSSION

Although the current standard regimen for patients with APC consists of single-agent gemcitabine, the objective responses are low and the median survival benefit is modest in comparison with 5-FU alone. Owing to the activity of gemcitabine, a variety of studies have now assessed its activity in combination with other chemotherapy or novel agents. These studies have shown varying degrees of success, with no combination showing clear evidence of significantly superior activity.

Preliminary favourable results of S-1 in patients with APC have been reported in Japanese early phase II study and late phase II study (Furuse *et al*, 2005; Ueno *et al*, 2005). As yet, the combination regimen of S-1 and gemcitabine for patients with APC has not been investigated. We previously performed a phase I study to evaluate the safety of treatment combining gemcitabine with S-1 to determine the MTD of each drug in patients with APC (Nakamura *et al*, 2005). That study indicated that the recommended dose was 30 mg m^{-2} twice daily of S-1 given orally for 14 consecutive days and 1000 mg m^{-2} gemcitabine given on day 8 and 15, and that the cycle should be repeated every 21 days. The main grade 3–4 toxicities observed during first cycle were neutropenia (33%), anaemia (10%), thrombocytopenia (14%) and anorexia (10%). Responses were one CR (5%) and nine PR (43%) among 21 patients. This combination was well tolerated and showed outstanding antitumuor activity. Therefore, we chose to use this regimen in a phase II study in patients with MPC.

This treatment administration as well as the tolerance profile can be considered as satisfactory regarding the toxicities observed although a reduction of administration of gemcitabine was required in two-thirds of the patients. Myelosuppression, especially neutropenia, frequently seen in the combination of continuous infusion 5-FU and gemcitabine, was predicted as the main toxicity of this study. The incidence of grade 3 or 4 neutropenia was greater than that of other toxicities, but, the incidence of gastrointestinal toxicity during all cycles was low.

Our efficacy results compare well with the other combination regimen in pancreatic cancer although it is difficult to compare phase II studies. Our response rate (48%) was much higher than that observed in gemcitabine combined with infusional 5-FU (19%) (Hidalgo *et al*, 1999) and in gemcitabine combined with capecitabine (19%) (Hess *et al*, 2003) or UFT (16%) (Feliu *et al*, 2000), which is also an oral prodrug of 5-FU, like S-1. Moreover, the median survival (12.5 months) and 1-year survival rate (54%) were favourable notwithstanding all patients in this study having distant metastatic disease.

Moreover, oral administration of S-1, which eliminates the cost and inconvenience of continuous infusion of 5-FU, requiring special pumps and catheters, with their potential risks of infection and thrombosis, also contributes to fewer hospital visits during this outpatient treatment. In fact, 31 of all 33 patients were treated at outpatient clinics. These results indicated that the combination at the recommended doses selected in this study is quite feasible in the outpatient treatment setting.

In conclusion, the results of this study demonstrate the tolerability and effectiveness of gemcitabine combined with oral S-1 in patients with APC. The toxicities observed in this study were mainly haematologic, with mild nonhaematologic toxicity. An encouragingly high response rate was observed. This result is very promising, but the survival benefit in comparison with gemcitabine monotherapy needs to be confirmed in a future randomised clinical trial.

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2. 膵 癌

千葉大学大学院医学研究院腫瘍内科学　須藤研太郎
同　腫瘍内科学講師　山口　武人

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動　向

膵癌は最も予後不良な悪性疾患の1つであり，5年生存率はわずか5～10%に過ぎない．しかも近年，膵癌死亡者数は漸増傾向にあり有効な診断法および治療法の確立は21世紀における重要な課題である．

近年，検査機器や手技の発達に伴い，膵癌の発癌過程に対する分子生物学的な知見が多数報告される．またPanIN分類が提唱され，通常型膵管癌の発育，進展モデルとして遺伝子異常や蛋白発現の解析が行われている．さらに，従来の遺伝子レベルの解析に加え，新たにプロテオミクス技術を用いた蛋白質レベルの解析も始まっている．これら基礎的研究によって得られた新たな知見は，診断・治療の両面において徐々に臨床へフィードバックされつつある．

一方，高率に遠隔転移を認める膵癌の治療において，有効なsystemic therapyの確立が急務である．これまで全生存期間においてgemcitabine (GEM) を凌ぐ治療法はみられなかったが，ASCO (American Society of Clinical Oncology) において，GEMと上皮増殖因子受容体 (EGFR) チロシンキナーゼ阻害剤であるerlotinibの併用療法の治療成績が初めてGEM単独の成績を上回ったことは2005年の大きなトピックスである．標準的治療としてGEM + erlotinibが認知されるかについては議論の余地があるが，分子標的治療薬の有用性を示した研究としてその意義は大きい．

膵癌の予後改善にはさらなる病態解明が不可欠であり，それに基づいた新しい診断法や治療法の開発，治療の個別化などが求められていく．

A. 疫　学

現在，膵癌は米国における癌死の第4位を占める．また罹患者数 (32,180人) と死亡者数 (31,800人) の比率は近接しており，その差は約1.2%とあらゆる固形癌の中で最も予後不良である[1]．根治手術例における5年生存率は10～20%程度と報告されるが，いわゆる通常型膵管癌において長期生存例はまれである．Carpelan-Holmstromらは1990～1996年にフィンランドにおけるcancer registry and statisticsに膵癌として登録された4,922人のうち，5年生存例89人 (1.8%) の診断を病理学的に再検討したところ，実際に膵管癌であることが確認できたのはわずか10人のみであった[2]．この89人の中には内分泌腫瘍，乳頭部癌，intraductal papillary mucinous neoplasm,

膵炎，solid pseudopapillary neoplasm，serous cystadenomaなどが含まれていた．この報告において筆者らは膵管癌における長期生存の最も多い原因は誤った診断であると結論している．

これまでの疫学的研究により，喫煙が主たる膵癌発症の危険因子として認知されており，そのodds ratioは1.6～5.4と報告される[3]．この他にも糖尿病，慢性膵炎，家族歴，遺伝因子，性別(男性)，人種（黒人），胃切除，職業，食生活，肥満などの因子が検討されている[3]．

糖尿病を膵癌のリスクファクターとする疫学的研究は多くみられるが，膵癌のスクリーニング対象としての意義は確立されていない．糖尿病の罹患期間と膵癌の相対危険度の相関を指摘する報告があるが，罹患期間の長い高齢の糖尿病患者の絶対数は多く，膵癌診断のスクリーニング対象としての意義は限られる．一方，Chariらは新規発症の糖尿病が膵癌診断のマーカーになる可能性について報告している[4]．彼らは50歳以上で初めて糖尿病と診断された2,122人を対象とし，3年以内に膵癌を発症した患者の割合について検討した．全対象中，18人（0.85%）が膵癌を発症し，リスク比は7.94であった．なお，この18人中10人（56%）が糖尿病診断から6カ月未満に膵癌と診断されている．本研究の結果は50歳以上の新規発症の糖尿病患者100人につき約1人の割合で3年以内に膵癌が発症するということを意味しており，膵癌のスクリーニングという観点から興味深い検討である．

食事と膵癌の関係についても多くの疫学研究が実施されているが，一致した見解が得られていない[5]．主として症例対照研究により野菜や果物の摂取は膵癌発症と逆相関の関係にあると報告されるが，一方，過去に行われた前向きコホート研究ではこれらの関連について否定的な見解も示されている．また肉食と膵癌の関係についても研究者により異なった見解が示されている．近年，Michaudらは果物や野菜中心の食生活と，肉や脂肪中心の食生活について，膵癌発症の相対危険度を検討した結果，食事パターンと膵癌には相関はみられなかった[5]．

膵癌の家族歴は膵癌発症の危険因子の1つであり，遺伝性膵炎，Peutz-Jugher症候群，末梢血管拡張性運動失調症，家族性黒色腫，家族性乳癌，遺伝性非腺腫症性大腸癌などの遺伝性疾患と膵癌の関連も報告される[3]．Kleinらは一親等間で膵癌を有する家族性膵癌370家系を含む838家系5,179人につき検討を行い，家族性膵癌の家系では膵癌発症のリスクが9.0［95% confidence interval (CI) 4.5～16.1］と有意に高いことを示した．また，一親等の膵癌罹患数が増加するに従い膵癌発症のリスクは増加した[6]．

以前よりアスピリンが膵癌リスクを低下させる可能性について報告されているが，最近2つの大規模な前向き研究により否定的な見解が示された．Jacobsらは987,590人のコホートを対象として1982年から2000年の期間経過観察を行い，4,577人が膵癌にて死亡したがアスピリン30回/月以上の投与例と未投与例の膵癌死亡のrate ratioは0.97［95%CI 0.86～1.09］と両者に差を認めなかった[7]．また，Schernhammerらは88,378人を対象として18年間経過観察し161人に膵癌発症を認めたが，アスピリン投与歴と膵癌死亡と関連はみられなかった（rate ratio 1.20［95%CI 0.87～1.65］)[8]．

B. 分子生物学

近年，検査機器や手技の発達に伴い，膵癌の発癌過程に対する分子生物学的な知見が多数報告される．また，膵管上皮内腫瘍性病変をpancreatic intraepithelial neoplasia（PanIN）とよび，通常型膵管癌の発育，進展モデルとして遺伝子異常や蛋白発現の解析が行われている[9]．膵癌の発生に

はK-rasなどの癌遺伝子およびp16, p53, Smad4などの癌抑制遺伝子の異常に加え，プロモーター領域の異常メチル化などepigeneticな変化の関与が指摘される．また，これら遺伝子の異常に加え，低酸素やアシドーシス，フリーラジカルなど腫瘍細胞を取り巻く環境的因子やインターロイキン8, VEGFなどの細胞増殖，血管新生をつかさどる種々のgrowth factorの統制機構の破綻などが関連する．新たな診断および治療法の開発に膵癌発生の分子生物学的メカニズムの解明は不可欠であり，現在精力的に研究が行われている[3,10-12]．

K-rasの点突然変異は膵管腫瘍化の早期に起こり，膵癌の約90%以上にみられる．しかし，K-ras遺伝子変異は膵癌に特異的なものではなく，膵液や便中のK-ras遺伝子変異の検討では慢性膵炎や喫煙者などでも認められる．また，血液中のK-ras遺伝子変異の検討では，進行癌での陽性率は高いものの早期診断における有用性は否定的である[10]．近年，血液や膵液中のK-ras遺伝子変異を従来よりも高精度に定量可能なLigAmp法が報告され，今後の展開に期待される．本法ではK-ras遺伝子の変異型，野生型を同時に測定可能であり，膵癌と他疾患の鑑別に有用となる可能性がある[13]．

膵癌の発癌過程において多くの遺伝子メチル化異常の関与が報告されるが，これらの変化は正常膵組織において認められることはまれであり，膵癌診断への応用が期待される．現在，P16, ppENK, SPARC, Cyclin D2, SOCS1, TSLC1などの遺伝子において異常メチル化の関与が知られるが，プロモーター領域の異常メチル化は癌関連遺伝子の不活化の一因と考えられ重要な意義を有する[10]．最近ではBNIP3, CDH13, TFPI2などの異常メチル化による不活化が報告される[14-16]．BNIP3は低酸素状態で細胞にアポトーシスを誘導するregulatorであり，膵癌ではBNIP3の不活化によって低酸素環境においても細胞死に至らない可能性が示唆される[14]．また，TFPI2は広いspectrumを有するセリンプロテアーゼ阻害作用を有し，TFPI2の不活化と膵癌の発育，浸潤性の関連が指摘されている[16]．

現在，これら遺伝子レベルの解析に加え膵液や血液を利用した蛋白質レベルでの検討も始まっている．遺伝子のコードする最終産物は蛋白質であり，膵癌に特異的な蛋白質や蛋白発現のパターンを発見できれば診断に有用となる可能性がある．最近の報告では膵液や血液を対象としてSELDI (surface enhanced laser desorption ionization) やMALDI (matrix associated laser desorption ionization) などの新しいプロテオミクスの技法を用いた研究が試みられており，今後の展開に期待される[17-19]．

また，膵癌診断の新たなマーカーとして血清中のMIC-1やosteopontinなどの有用性が報告される[20-22]．Koopmannらは膵癌切除群，慢性膵炎群，健常コントロール群のおのおの50人につきMIC-1とCA19-9の比較検討を行ったが，膵癌切除群と健常コントロール群の鑑別においてMIC-1が有意に良好な成績であった (area under the curve 0.99 vs 0.78, $p = 0.003$)[21]．

C. 治　療

1. 局所進行膵癌に対する治療

明らかな遠隔転移はないが膵周囲への強い浸潤により切除不能と判断される場合，これを局所進行膵癌とよぶ．しかし，この定義は非常に曖昧であり施設により異なるのが現状である．従来，欧米では上腸管膜静脈や門脈への浸潤，または，上腸管膜動脈，腹腔動脈への浸潤などを有する場合，切除不能とされてきた[23]．しかし最近は手術手技の進歩により，門脈や上腸管膜静脈への浸潤については切除可能とする施設もみられる．局所進展により切除不能と判断された場合，5FUを使

用した放射線化学療法が主として行われる．

近年，本邦より膵被膜外浸潤を有する膵癌に対する外科切除と5FU併用放射線化学療法の無作為化比較試験が報告された[24]．本試験での対象は膵前方浸潤（S＋），膵後方浸潤（RP＋）または門脈浸潤のいずれかを認めるものとし，門脈閉塞，側副血行を有する門脈狭窄，上腸管膜動脈浸潤，総肝動脈浸潤，膵周囲神経叢浸潤（PL）を認める症例は除外している．本試験は同一の病期において外科切除と非切除療法を比較した点でその意義は大きい．手術群に20例，放射線化学療法群に22例が登録され，平均生存期間は16.9カ月 vs 11カ月と手術群で有意に良好であった（$p = 0.03$）．しかし，生存期間中央値（MST）および1年生存率については手術群で良好な傾向があるものの有意差が得られておらず，より大規模な症例数での検討が必要と考えられる．また本試験の結果の解釈にはその対象に充分留意する必要がある．本試験の対象はS（＋），RP（＋），PV（＋）のいずれか1つ以上を満たすものとしており，これは膵癌取り扱い規約第5版におけるstage IIIまたはIV Aの一部に相当する．A（＋），PL（＋）などが除外されている点で第5版stage IV Aとは一致しない．またいわゆる局所進行膵癌との比較でも，より早期のstageと考えられる．

従来，切除不能局所進行膵癌に対する治療は過去の複数の無作為化比較試験に基づき5FU併用放射線療法が主たる治療法と位置づけられてきた[23,43]．しかしそのMSTは7～10カ月と充分でなく，現在種々の治療法が試みられている．

Gemcitabine（GEM）は膵癌全身化学療法の標準的治療薬であると同時に強力な放射線増感作用を有する．しかし，GEMは正常組織の放射線感受性も増強する可能性が示され，これまで行われたGEM併用放射線療法の第I相試験によれば従来の照射野で50～60Gyの放射線と併用する場合，GEMの投与量は大きく制限される．また，full doseのGEM（1g/m^2/week）と放射線を併用する場合，照射野および線量を絞る必要がある．OkusakaらはGEM 250mg/m^{2}週1回投与とfull doseのradiationの併用療法第II相試験を行い，grade3以上の白血球減少を全体の52%に，grade 3/4のanorexiaを24/33%に認め，また1例十二指腸出血，sepsisによる死亡例を認めた[25]．この報告での毒性は従来の5FU併用放射線療法に比して強く，また生存期間についてもMST9.5カ月と優位性は示されなかった．小規模のRCTにおいてGEM併用放射線療法を支持する報告もみられるが[26]，否定的な見解もあり評価は一定していない[27]．

Paclitaxelは放射線増感作用を有し，局所進行膵癌に対する放射線化学療法においても期待される薬剤の1つである．Radiation Therapy Oncology Group（RTOG）はpaclitaxel併用放射線療法第II相試験を行いMST11.2カ月と良好な成績を示している[28]．現在，RTOGではGEM＋paclitaxelを併用した放射線化学療法について検討を行っている[29]．

また，分子標的薬を併用した放射線化学療法についても検討が行われている．血管内皮細胞増殖因子（VEGF）に対するモノクローナル抗体であるbevacizumabや，後述する上皮増殖因子受容体（EGFR）チロシンキナーゼ阻害剤であるerlotinibを使用した放射線化学療法などが試みられている[30,31]．

この他，新たな照射法としてintensity modulate radiotherapy（IMRT）の有用性についても報告される．IMRTは照射野内のビーム強度を変化させることで腫瘍の三次元形状への線量集中度を格段に向上させる放射線治療法であり，原体照射に代わる照射法として高い注目を集めている[32,33]．

一方，局所進行膵癌において放射線化学療法後の再発は多くが遠隔転移であることから，放

射線治療の必要性について疑問を呈する意見もある[23]．実際，最近の膵癌全身化学療法に関する第III相試験の多くが遠隔転移例と局所進行例を分けずに試験対象としている．現在，ECOGにおいて局所進行膵癌に対するGEM併用放射線療法 vs GEMの比較試験が進行中であり，結果が待たれる．

2. 遠隔転移を有する進行膵癌に対する治療

1997年Burrisらの報告以後，遠隔転移を有する進行膵癌に対する標準的治療はgemcitabineによる全身化学療法とされる[34]．しかし，そのMSTは5～7カ月といまだ不良であり現在新たな治療法が多数検討されている．これまでGEM + 5FU[35]，GEM + cisplain (CDDP)[36]，GEM + irinotecan[37]，GEM + oxaliplatine[38] などGEMと他の抗癌剤との併用療法や，marimastat + GEM[39]，BAY (12-9566)[40]，tipifarnib + GEM[41] など分子標的薬を用いた治療法などが検討されてきたが，いずれも全生存期間においてGEM単独の治療成績を凌駕することはできなかった．

このような状況のなか，2005年のAmerican Society of Clinical Oncology（ASCO）においてerlotinibとGEMの併用療法の有用性を示す報告が行われた[42]．erlotinibは上皮増殖因子受容体（EGFR）チロシンキナーゼ阻害作用を有する分子標的薬である．MooreらはGEM + erlotinib vs GEM + placebo の二重盲検下無作為化比較試験を行い，erlotinib群285人のMSTは6.37カ月，placebo群284人では5.91カ月（p = 0.025）と有意差を認めた．無増悪生存期間についてもerlotinib群3.75カ月，placebo群3.55カ月（p = 003）とerlotinib群で良好であった．今回報告されたGEM + erlotinib療法はGEM単独療法に対し初めて全生存期間において優位性の示された治療法である．また，膵癌において分子標的薬の臨床的な有用性が示された点についてもその意義は大きい．しかし，臨床的に2群間のMSTの差は2週間程度とわずかであり，対費用効果などを考慮した場合，GEM単独療法に代わる標準的治療になりうるかについては議論の余地がある．

分子標的薬は膵癌治療において最も注目される薬剤の1つであり，現在もerlotinibの他，抗VEGFモノクローナル抗体であるbevacizumab + GEM vs GEMや，cetuximab + GEM vs GEMなどの第III相試験が進行中である[43-45]．なかでもbevacizumabは種々の癌腫でpositiveなdataが報告されており，今後期待される薬剤である．

この他，2005年ASCOではGEM + 5FU + 葉酸 vs GEM[46]，GEM + capecitabine vs GEM[47]，の2つの大規模無作為化比較試験の結果が報告された．葉酸は5FUの効果を増強するmodulatorとしての働きを有し，GEM + 5FUを上回る効果が期待されたが，GEM + 5FU + 葉酸 vs GEMの比較試験では併用群のMST5.85カ月，GEM群6.2カ月（p = 0.68）と併用療法の有用性は示されなかった．また，capecitabineは新しい経口5FU系製剤であり，膵癌に対する有用性も期待される薬剤だが，GEM + capecitabine vs GEMの比較試験では併用群のMST8.4カ月，GEM群7.3カ月（p = 0.314）と差はみられなかった．これら2つの試験はいずれもGEMと5FU系薬剤の併用療法という点で共通しており，過去に行われたGEM + 5FU vs GEMの比較試験の結果とあわせ[35]，今回のASCOではGEM + 5FU系薬剤の併用は生存期間を延長しないという考えが示された．

一方，本邦より進行膵癌に対するS-1の有用性を示す報告が散見される．S-1は経口フッ化ピリミジン製剤であり，強力なDPD阻害作用を有するgimeracilを配合し，種々の固形癌において良好な抗腫瘍効果が報告される．最近報告された遠隔転移を有する進行膵癌に対するS-1化学療法第II相試験では，奏効率21.1%～37.5%，MST5.6カ月～8.8カ月と良好な成績が示されており今後の

展開に期待される[48-49].

また近年，GEM無効膵癌に対する2nd line therapyの検討が報告される．OettleらはGEMによる治療中，増悪が確認された患者を対象としてoxaliplatine＋葉酸＋5FU＋支持療法（OFF群）vs 支持療法（BSC群）の無作為化比較試験を行った[50]．46例が登録された段階で2nd line治療開始後のMSTはOFF群21週，BSC群10週（p＝0.0077）と有意差がみられたため登録は中止された．本試験はGEM治療後の2nd line therapyの有用性を示すものとして興味深い．この他にも2nd line therapyとして5FU＋celecoxib，oxaliplatine，oxaliplatine＋irinotecan，raltitrexed＋irinotecanなどが試みられているが，確立されたものはなく有効な治療法の確立が急務である[51-54].

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A. 膵　癌　VII. 膵癌の治療
進行・再発膵癌の治療／化学療法

Gemcitabine

大川伸一

Key words　gemcitabine，膵癌，化学療法

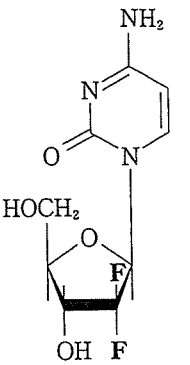
はじめに

各画像診断が進歩し続ける現在においてもなお，膵癌は早期診断が困難であり病院を訪れる膵癌患者の約80％は初診時に既に切除不能な進行膵癌である．したがって膵癌の治療において過去も現在も化学療法は極めて重要であるが，過去長きにわたって5-FU系の薬剤がその主流であった[1-3]．5-FUの進行膵癌に対する奏効率は6-26％であり，他剤と組み合わせてもこれを上回る奏効率は得られなかった．しかし1997年にBurrisら[4]が進行膵癌に対してgemcitabineと5-FUの成績を比較した研究を発表して以来，欧米ではgemcitabineが膵癌化学療法における標準薬となり，遅れて日本でも2001年から膵癌に認可された．

本稿ではgemcitabineについてその作用機序，膵癌に対する治療成績，最近の知見および今後の展望などについて述べる．

1. 作用機序[5]

gemcitabine(塩酸ゲムシタビン：dFdC)はデオキシシチジン(dCyd)の糖鎖の2′の水素をフッ素に置換したヌクレオシド誘導体で，DNA合成が主に行われているS期に特異的な作用を示す(**図1**)．gemcitabineは，細胞内で三リン酸化物(dFdCTP)に代謝された後，デオキシシチジン三リン酸(dCTP)と競合してDNA鎖に取り込まれ，DNAの合成を阻害する．



2′,2′-ジフルオロデオキシシチジン，
dFdC

図1　Gemcitabineの構造

通常，DNA鎖に誤って取り込まれたヌクレオチドはDNAポリメラーゼにより除去されてDNA鎖が修復されるが，gemcitabineによるDNA鎖の伸長停止は，dFdCTPがDNA鎖に取り込まれた後，別のヌクレオチドが1つ付加されたときに起こる．そのため，DNAポリメラーゼにより除去されず，DNA鎖の修復が阻止され('マスクされたDNA鎖修復')，DNA合成が不可逆的に阻害される．

更にgemcitabineは，'自己増強'と呼ばれる

Shinichi Ohkawa: Division of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center　神奈川県立がんセンター 消化器内科肝胆膵

0047-1852/06/¥40/頁/JCLS

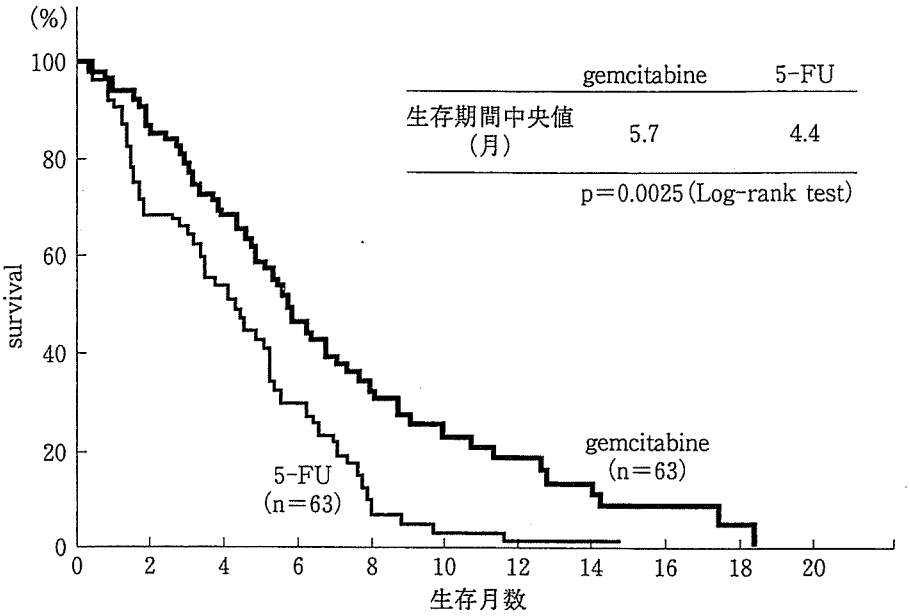


図2 生存期間の比較(gemcitabine対5-FU) (Burris HA ら[4]より引用)

代謝特性を有し，活性代謝物が効果的に作用して自己のリン酸化を促進し，gemcitabineの活性代謝物(dFdCTP)が正常なDNA合成経路のdCTP産生にかかわるリボヌクレオチドリダクターゼを抑制し，細胞内のdCTP濃度を低下させる．またデオキシシチジンキナーゼはdCTPによる負の制御を受けているため，細胞内のdCTP濃度が低下するとデオキシシチジンキナーゼが活性化されてgemcitabineのリン酸化が促進され，かつ不活性化酵素を阻害するため，細胞内濃度が高濃度に維持され，dFCTPとの競合過程において，DNA鎖に有利に取り込まれ，強い抗腫瘍効果を示すと考えられている．

2. 治療成績

1997年にBurris ら[4]は，切除不能の進行膵癌患者を無作為に2群に分け，一方にgemcitabineを，もう一方に5-FUを投与し成績を比較し報告した．生存期間中央値(median survival time: MST)は5-FUが約4.4カ月に対してgemcitabineが約5.7カ月と有意に延長していた(図2)．更に1年生存率は5-FUの2%に対してgemcitabineは18%であった．この研究の優れた点は症状緩和効果(clinical benefit response: CBR)を評価項目としたことである(図3)．すなわち，化学療法によりperformance status(PS)と疼痛の改善を有意に認めたものをCBR陽性とし評価したところ，5-FUでは4.8%の改善しか認めなかったがgemcitabineでは23.8%の症状緩和効果を認めた．有害事象もgemcitabineには生命を脅かすものはほとんど認められず，十分忍容性があった．また5-FUに抵抗性の膵癌に対してもgemcitabineはCBRを27%に認めた[6]．膵癌は疼痛や食欲低下など多くの症状を有する疾患であり，抗癌剤によりこの点が改善でき患者のQOLの向上を可能にしたことはそれまでの薬剤には認められなかったため画期的なものとして評価された．gemcitabineはこのようにそれまでの標準的薬剤であった5-FUとの比較試験を経た初めての薬として評価され膵癌に対する第一選択薬となっている．

3. 投与方法と注意点

最も標準的な投与方法は，体表面積を算出し100 m*l*の生理食塩水に1,000 mg/m^{2}を溶解し，30分以内の時間で点滴にて投与する．30分以上時間をかけると毒性が強くなるため投与時間には注意が必要である．このとき制吐剤として5-HT$_3$製剤を同時に投与してもよい．また皮疹が出現した患者にはステロイド剤を併用するこ

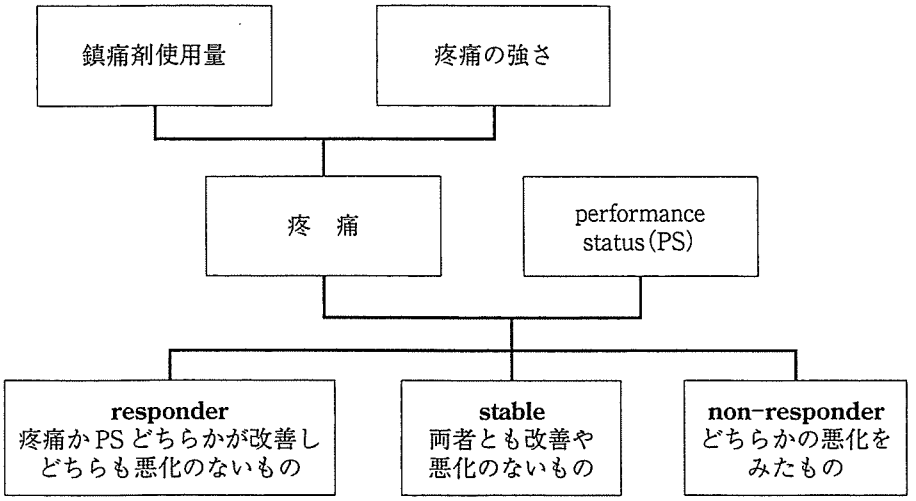


図3 症状緩和効果(clinical benefit response: CBR)アルゴリズム
(Rothenberg ML ら[6]より引用)

ともある．このようにしてgemcitabineをday 1, 8, 15に投与しday 22は休薬，28日間を1コースとし，これを繰り返す．有害事象は主として骨髄抑制，嘔気などであるが，骨髄抑制は投与日または前日に採血して白血球数や血小板数をチェックし，減量や休薬規準を厳守することにより危険は避けられる．嘔気なども制吐剤などにてコントロールが可能である．このような標準的な投与方法は外来治療が十分可能であり，外来にて治療を開始するcaseも増加している．

4. Gemcitabineの投与法変法および他剤との併用療法

a. 投与法の変法

gemcitabineの1回の投与に時間をかけることにより治療効果の改善をはかった研究が幾つか報告されている[7,8]．毒性は増強するが抗腫瘍効果も増強する場合がある．

b. 併用療法

様々な薬剤とgemcitabineの併用療法が試みられている(表1)．

1) Cytotoxicな薬剤

cisplatin, irinotecan, exatecan, oxaliplatinなどが報告されている．cisplatinについては早くから研究報告があり抗腫瘍効果がある程度増すことは認められている[9]．gemcitabineとこれらの薬剤との併用療法がgemcitabine単独療法に比べて優れているか否かを調べる比較試験が行われている．irinotecan[10]やexatecan[11]については米国にて比較試験が行われた．またcisplatin[9]やoxaliplatin[12]については欧州にて比較試験が行われ効果が期待された．しかしこれらの主立った薬剤については現在までのところgemcitabine単独療法に比べて抗腫瘍効果の改善はみられることがあるものの，生存期間の有意な延長は認められていない．

2) 分子標的薬

欧米では種々試みられている．metalloprotease inhibitorであるmarimastat[13]，farnesyl transferase inhibitorであるtipifarnib[14]，epidermal growth factor receptor inhibitorであるerlotinib[15]などについてgemcitabineとの併用療法がgemcitabine単独療法より優れているかどうかの比較試験が行われた．marimastatおよびtipifarnibはgemcitabineと併用しても単独療法に比べて抗腫瘍効果やMSTの有意な延長は認められなかった．またerlotinibとの併用試験については生存期間の有意な延長は認めたが，その差はごくわずかであり(6.37カ月対5.91カ月)，gemcitabineの単独療法に代わる標準治療とは成り得ていない(表1)．以上の結果，現段階では欧米にてもgemcitabineの単独療法がいまだに標準治療とされている．

表1 Gemcitabineの併用療法と単独療法の比較試験

drug	例数	奏効率	MST(月)	1年生存率
Gem+cisplatin	53	26%	6.9	—
Gem	54	9%	4.6	—
Gem+irinotecan	180	16%	6.3	～20%
Gem	180	4%	6.4	～20%
Gem+exatecan	175	8%	6.7	23%
Gem	174	7%	6.2	21%
Gem+oxaliplatin	157	26%	9.0	34.7%
Gem	156	16%	7.1	27.8%
Gem+marimastat	120	11%	5.4	18%
Gem	119	16%	5.4	17%
Gem+tipifarnib	341	6%	6.3	27%
Gem	347	8%	5.98	24%
Gem+erlotinib	285	8.6%	6.37	24%
Gem	284	8%	5.91	17%

5. Gemcitabineによる治療の問題点と将来の展望

gemcitabineは膵癌治療に初めて明確なevidenceとして有効性が示された薬剤であり，様々な苦痛を伴う膵癌に対して症状緩和効果を発揮する優れた薬剤である．しかし，gemcitabine治療後のsecond line therapyについてはほとんど選択すべき有効な薬剤がなく，実際の臨床上大きな問題である．またgemcitabineは抗腫瘍効果の点ではそれまでの薬剤と同等であり，他の薬剤との併用療法にて更に治療効果の改善が切に望まれるところである．現段階では単独療法を明らかに凌駕する併用療法はないが，例えば治療対象を更に細分化し，PSの良い患者にはcytotoxicな薬剤の併用療法を選択したり，また分子標的薬は特定の人種や性などを選んで効率的に使用されることになるかもしれない．

おわりに

前述のように世界中の多くの研究者がgemcitabineと新たな薬剤との有効な併用療法を開発すべく努力しているが，今後も当分はgemcitabineが膵癌化学療法のkey-drugであると考えられる．

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