表4. 分子標的薬による化学療法の臨床試験

薬剤	n	response rate(%)	median TTP/PFS(月)	median OS (月)	報告者(年)
erlotinib	42	7	2.6	7.5	Philip ら (2006)[33]
lapatinib	17	0	1.8	5.2	Ramananthan ら (2006)[34]
gemox/bevacizumab	26	25	7.6	—	Clark ら (2007)[35]
bevacizumab/erlotinib	34	12	—	—	Holen ら (2008)[36]
gemox/cetuximab	22	58	9.0	—	Gruenberger ら (2008)[37]
sorafenib	36	6	2.0	6.0	El-Khoueiry ら (2007)[38]
sorafenib	46	4	2.3	—	Dealis ら (2008)[39]

TTP : time to progression, PFS : progression free survival, OS : overall survival

助療法の効果を示唆したものととらえられる.

現在わが国において, 切除不能胆道癌に多く用いられているのはGEMとTS-1のみであり, 術後補助療法でもこれらの薬剤が期待されている. わが国では現在GEM単独あるいはGEM-basedによる臨床試験がいくつか行われている[41]. そのうち, NPO法人名古屋外科支援機構による第III相試験(BCAT)は胆管癌切除例におけるGEMと手術単独のランダム化比較試験であり, 300例の症例集積が予定されている.

一方, 海外では米国でGEM+docetaxelの化学療法後5-FUを用いた化学放射線療法による術後補助療法の忍容性をみる第II相試験が行われ, 英国ではcapecitabineとobservationによる第III相試験(n=360例)が行われている[31]. 切除不能胆道癌と同様, エビデンスに基づいた治療法が確立されるものと考えられる. 一方では, これらの大規模な第III相試験はいずれも300例以上の症例が必要としており, 症例数の比較的少ない胆道癌では完遂が容易ではない. また胆道癌の手術では胆道再建や消化管バイパスなどがほぼ全例で行われることから, 胆管炎や消化管障害などのリスクもある. GEM+CDDP併用療法や化学放射線療法では第I/II相試験が行われており, 新しい治療法では術後での忍容性を確認する臨床試験が必要かもしれない.

おわりに

わが国では胆道癌による死亡数は16,000人を超え, 決して少ない疾患ではない. 切除不能例はもちろん術後補助療法としての化学療法など, 有効な治療法の確立が胆道癌全体の治療成績の向上に必要である. 切除不能だけでなく術後補助療法の大規模な比較試験が行われてきており, 今後近い将来標準治療が確立されることが期待される.

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Advanced pancreatic cancer: the use of the apparent diffusion coefficient to predict response to chemotherapy

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ABSTRACT. The purpose of this study was to determine if the apparent diffusion coefficient (ADC) on diffusion-weighted MRI could predict the response of patients with advanced pancreatic cancer to chemotherapy. Diffusion-weighted MRI was performed in 63 consecutive patients with advanced pancreatic cancer who were subsequently treated with chemotherapy. The ADC values of the primary tumour with a middle *b*-value (400 s mm^{-2}) and a high *b*-value (1000 s mm^{-2}) were determined; cystic or necrotic components were avoided. The patients were classified into two groups: (i) those with progressive disease and (ii) those who were stable 3 months and 6 months after initial treatment. The groups were compared with respect to the ADC and clinical factors, including gender, age, Union International Contre le Cancer (UICC) stage, initial tumour size and chemotherapy agents used. Local tumour progression rates were evaluated using the Kaplan–Meier method. The middle *b*-value ADC of the pancreatic cancers ranged from 0.93–2.42 $\times 10^{-3}$ mm^2 s^{-1} (mean, 1.50 $\times 10^{-3}$ mm^2 s^{-1}), and the high *b*-value ADC ranged from 0.72–1.88 $\times 10^{-3}$ mm^2 s^{-1} (mean, 1.20 $\times 10^{-3}$ mm^2 s^{-1}). The high *b*-value ADC was significantly different between the progressive and stable groups at 3 months' and 6 months' follow-up ($p=0.03$ and $p=0.04$, respectively). The rate of tumour progression was significantly higher in those with a lower high *b*-value ADC than in those with a higher *b*-value ADC (median progression time, 140 days *vs* 182 days; $p=0.01$). In conclusion, a lower high *b*-value ADC in patients with advanced pancreatic cancer may be predictive of early progression in chemotherapy-treated patients.

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Pancreatic cancer is often diagnosed when the disease is in an advanced stage. Currently, radical surgery is the only curative therapy for pancreatic cancer; however, only 5–20% of patients present with potentially resectable disease [1–3]. Patients with inoperable pancreatic cancer have a limited survival rate, which averages only 3–4 months [4]. For locally advanced, unresectable and metastatic disease, palliative treatment with chemotherapy or chemoradiation is the only option. The results of chemotherapy for pancreatic cancer have generally been disappointing [5]. Recently, however, systemic chemotherapy with gemcitabine or gemcitabine plus platinum, or chemotherapy plus radiation, was reported to have some positive effects (1-year survival, 18–36%) [6–8]. Indications for chemotherapy should be carefully evaluated because of the relatively high risk of complications and side effects. Therefore, prognostic factors permitting the identification of patients who will benefit from such treatment would be clinically useful [9].

Diffusion-weighted MRI is a technique in which phase-defocusing and -refocusing gradients are used to evaluate the rate of microscopic water diffusion within tissue. Quantitative measurements of the diffusivity of water are described by the apparent diffusion coefficient (ADC). Investigators have reported the usefulness of ADC measurement for characterizing tumours [10–15]. The ability to measure the rate of water diffusion within tissue is important, as water diffusion is frequently altered in various disease processes and may reflect physiological and morphological characteristics, such as cell density and tissue viability [12, 16]. The results of several studies have suggested that the initial ADC of a tumour can serve as a predictive parameter for a patient's response to chemotherapy [12, 13, 15, 17]. Therefore, a method that enables pre-treatment imaging assessment of tumour malignancy and which would allow a more effective therapeutic strategy to improve prognosis would be of considerable clinical benefit. To the best of our knowledge, the predictive value of ADC in patients with advanced pancreatic cancer has not been reported. The purpose of this study was to evaluate the use of ADC to predict the response of patients with advanced pancreatic cancer to chemotherapy.

Methods and materials

Patients

From July 2003 to August 2006, 63 consecutive patients (31 male, 32 female; mean age, 64.6 years; age range, 43–83 years) with advanced pancreatic cancer who had

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not received any previous anticancer treatment were enrolled in this study. Their medical records, as well as their CT and MRI data, were reviewed retrospectively. The ethics committee of our institute approved this retrospective study and did not require patient informed consent. The initial diagnosis and the possibility of local tumour resection were assessed using contrast-enhanced dynamic CT, multiplanar reformation images, CT angiography and MR images. CT scanning was performed with either an 8- or a 16-detector CT scanner (Aquilion 8 or Aquilion 16; Toshiba Medical Systems, Tokyo, Japan). All images were assessed to determine the local extent of the tumour and the presence of metastases. The criteria used to consider a tumour non-resectable included the presence of a distant metastasis, multiple liver metastases, peritoneal dissemination with ascites, and involvement of a major vascular system (*i.e.* obstruction or bilateral invasion of the portal vein and/or tumour encasement of the coeliac axis or superior mesenteric arteries). Involvement of the superior mesenteric vein or the main portal vein was not a contraindication to resection, as the tumour could be resected and the portal venous system could be reconstructed. Chest CT was performed when necessary. Histopathological proof was obtained when possible; if histopathological confirmation was absent, the diagnosis was made on the basis of clinical and imaging findings. Tumour staging was performed using the Union International Contre le Cancer (UICC) classification [18].

MRI

All patients were examined using a 1.5 T superconducting MR system (Excelart XGS; Toshiba Medical Systems) with a 25 mT m^{-1} maximum gradient capability, a maximum slew rate of 130 mT m^{-1} ms^{-1} and gradient acoustic noise reduction system. An eight-element quadrature phased-array surface coil was used to optimize the signal-to-noise ratio. All patients underwent diffusion-weighted MRI in addition to the routine pancreatic MR protocol; pancreatic lesions suitable for ADC measurement were identified and selected. All MR examinations were performed with breath holding. The routine MR protocol included a transverse T_1 weighted fast gradient echo (fast field echo; repetition time/echo time (TR/TE), 187 ms/4 ms; flip angle, 77°; matrix, 160 × 320; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 300 mm; 19 slices; asymmetric *k*-space acquisition in the read-out), a transverse T_2 weighted fast spin-echo (TR/TE, 3000 ms/100 ms; echo train length, 19; matrix, 192 × 288; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 300 mm; 13 slices), and a transverse T_2 weighted single-shot fast spin-echo (TR/TE, 15 000 ms/80 ms; echo train length, 64; matrix, 192 × 192; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 300 mm; 15 slices; asymmetric k-space acquisition in the phase-encoding). MR cholangiopancreatography used a single-shot fast spin-echo sequence (effective TE, 250 ms; matrix size, 320 × 320; field of view, 350 mm) with thick (20–45 mm) or thin (4 mm) slices in the coronal or oblique coronal plane. Diffusion-weighted imaging was performed with different *b*-values to assess their ability for characterization of the tumour. Diffusion-weighted imaging was performed in a transverse plane using a spin-echo single-shot echo-planar imaging sequence with two sets of diffusion gradients, a middle *b*-value (b=400 s mm^{-2}) and a high *b*-value (b=1000 s mm^{-2}), along with three orthogonal directions: phase-encoding, frequency-encoding and section-select directions. In addition, images without motion-probing gradients (MPGs) (b=0 sec mm^{-2}) were obtained simultaneously. The following parameters were used to obtain the diffusion-weighted images: TR/TE, 4000 ms/110 ms; echo train length, 19; matrix, 128 × 208; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 350 mm; 11 slices; asymmetric k-space acquisition in the phase-encoding; and acquisition time, 24 s. To reduce chemical shift artefacts, the selective water excitation technique was used for fat suppression. Diffusion-weighted imaging was performed using the parallel imaging technique, with a reduction factor of 2 to improve the signal-to-noise ratio.

Data analysis

All diffusion-weighted imaging data were transferred to a commercially available workstation (MKDN-008A, Toshiba Medical Systems). Isotropic images were created by averaging the data from all three orthogonal diffusion-weighted images. The ADC maps were generated by the workstation using the following equation:

$$\mathrm{ADC} = \ln(S_1/S_2)/(b_2 - b_1) \qquad (1)$$

where S_1 and S_2 are the signal intensities of diffusion-weighted images obtained with one of the two b values (b_1 and b_2, respectively) on a voxel-by-voxel basis.

Each ADC of the primary tumour was determined by measurements of the region of interest (ROI) created on each ADC map. To analyse tumour characterization, cystic or necrotic areas were avoided when measuring the ADC. Several ROIs were placed within the largest area of the tumour on each ADC map, avoiding (if possible) cystic, necrotic or haemorrhagic components of the tumour seen on conventional MR images. The size of the ROI was chosen to be appropriate for each lesion, so that the maximum ROI was used without volume averaging. To ensure the same areas were measured, the ROI was copied and pasted onto each middle and high *b*-value ADC map. Tumour ADCs were determined by averaging each measured ADC. The tumour size was estimated by measuring the greatest diameter of the lesion on T_1 weighted MR images.

Patient follow-up

Patients were treated with gemcitabine at a dose of 1000 mg mm^{-2} given intravenously every week for 3 weeks, followed by 1 week's rest until disease progression or unacceptable toxicity was observed. When the patient agreed, both gemcitabine and TS-1 (a combination preparation consisting of tegafur, gimeracil and oteracil potassium [19]) were given simultaneously as part of a Phase I clinical trial. When severe toxicity

was observed, the next chemotherapy session was omitted and postponed to the next scheduled treatment day. Follow-up CT was performed every month to evaluate tumour response. Local tumour progression was determined according to RECIST (Response Evaluation Criteria in Solid Tumours) [20].

Statistical analysis

The patients were classified into two groups (progressive and stable) depending on their status 3 months and 6 months after the initial treatment. The groups were compared with respect to their ADC and clinical characteristics, including age, gender, tumour stage (UICC III/IV), anticancer agents used (gemcitabine only or gemcitabine and TS-1) and initial tumour size. The Wilcoxon signed rank test and the χ^2 test were used to compare the two groups.

To assess the relationship between progression and the ADC of the pancreatic cancer, patients were grouped based on the median value of each ADC. The two groups were compared with respect to tumour progression using the Kaplan–Meier method and the log-rank test. Statistical analyses were performed using SPSS software (Version 11.0; SPSS Inc., Chicago, IL). A difference with a p-value <0.05 was considered statistically significant.

Results

A diagnosis of pancreatic cancer was histologically confirmed in 54 (85.7%) patients; the biopsy was performed at the primary site in 42 (66.7%) patients and at a metastatic liver site in 12 (19.0%) patients. In the other nine (14.3%) patients, the final diagnosis was made on the basis of the clinical evaluation, including a complete history, physical examination, laboratory data and radiological findings. The UICC classification tumour stage was III in 27 (42.9%) patients and IV in 36 (57.1%) patients. Metastases included the liver in 25 patients, liver and para-aortic lymph nodes in 1 patient, liver and lungs in 2 patients, para-aortic lymph nodes in 5 patients, peritoneal dissemination in 2 patients, and vertebra in 1 patient. Pancreatic tumour size ranged from 1.8–12.0 cm (mean, 4.4 cm). The middle b-value ADC in the ROI ranged from 0.80–2.57 $\times$ 10^{-3} mm^2 s^{-1}, whereas the high b-value ADC ranged from 0.70–2.02 $\times$ 10^{-3} mm^2 s^{-1}. The size of the ROIs ranged from 0.63–2.87 cm^2. The average middle b-value ADC of the pancreatic cancer ranged from 0.93–2.42 $\times$ 10^{-3} mm^2 s^{-1} (mean, 1.50 $\times$ 10^{-3} mm^2 s^{-1}; median, 1.46 $\times$ 10^{-3} mm^2 s^{-1}), whereas the average high b-value ADC ranged from 0.72–1.88 $\times$ 10^{-3} mm^2 s^{-1} (mean, 1.21 $\times$ 10^{-3} mm^2 s^{-1}; median 1.23 $\times$ 10^{-3} mm^2 s^{-1}). The median duration between the initial MR examination and the first day of chemotherapy was 9 days (range, 2–36 days).

34 (54.0%) patients were treated with gemcitabine, whereas 29 (46.0%) patients were treated with concomitant gemcitabine and TS-1. On follow-up, progression was local in 39 (61.9%) patients and metastatic in 12 (19.0%) patients, including 10 patients with hepatic metastases and 2 patients with para-aortic lymph node metastases; newly recognized lesions were found in 10 (15.9%) patients, of whom 2 had hepatic metastases, 7 had peritoneal dissemination and 1 had a lung metastasis. Two (3.2%) patients did not show progression at the time of this analysis. 25 (40.0%) patients showed progression at 3 months, whereas 46 (73.0%) patients showed progression at 6 months after initial treatment. Progression time from the initial treatment ranged from 31–533 days (median, 123 days).

A comparison of the progressive and stable patients (Table 1) showed that the high b-value ADC of the progressive patients was significantly lower than that of the stable patients at 3 months (mean ADC, 1.11 $\pm$ 0.04 *vs* 1.25 $\pm$ 0.03 $\times$ 10^{-3} mm^2 s^{-1}; p=0.03) and 6 months (mean ADC, 1.17 $\pm$ 0.03 *vs* 1.28 $\pm$ 0.05 $\times$ 10^{-3} mm^2 s^{-1}; p=0.04) (Figures 1 and 2). The middle b-value ADC was not significantly different between progressive and stable patients. Clinical factors, including age, gender, UICC stage and tumour size, and the chemotherapy agents used, were not significantly different between the progressive and the stable patients at 3 months and 6 months.

Based on the Kaplan–Meier method and the log-rank test, the tumour progression rates were significantly higher in patients with a lower high b-value ADC than in those with a higher high b-value ADC (median progression time, 140 days *vs* 182 days; p=0.01) (Figure 3). Although patients with a lower middle b-value ADC showed a tendency towards higher rates of progression than those with a higher middle b-value ADC, there was

Table 1. Comparison of clinical factors and the apparent diffusion coefficent (ADC) with respect to tumour progression

	Clinical outcome					
	3 month			6 month		
Variable	Progressive	Stable	p-value	Progressive	Stable	p-value
Number of cases	25	38		46	17	
Age (years)	64.3 + 1.2	64.8 + 1.5	0.13	63.9 + 6.2	64.9 + 9.1	0.33
Gender (Male/female)	12/13	20/18	0.79	21/25	11/6	0.26
UICC stage (III/IV)	8/17	19/19	0.20	17/29	10/7	0.16
Tumour size (cm)	4.74 + 0.38	4.18 + 0.31	0.20	4.63 + 0.31	3.78 + 0.27	0.16
Chometherapy agent (gemcitabine/ gemcitabine and TS1)	16/9	18/20	0.21	27/19	7/10	0.26
ADC ($\times$ 10^{-3} mm^2 s^{-1})						
ADC (b=400 s mm^{-2})	1.48 + 0.05	1.50 + 0.05	0.89	1.48 + 0.05	1.51 + 0.06	0.68
ADC (b=1000 s mm^{-2})	1.11 + 0.04	1.25 + 0.03	0.03	1.17 + 0.03	1.28 + 0.05	0.04

Data comprise the number of patients, unless otherwise indicated.

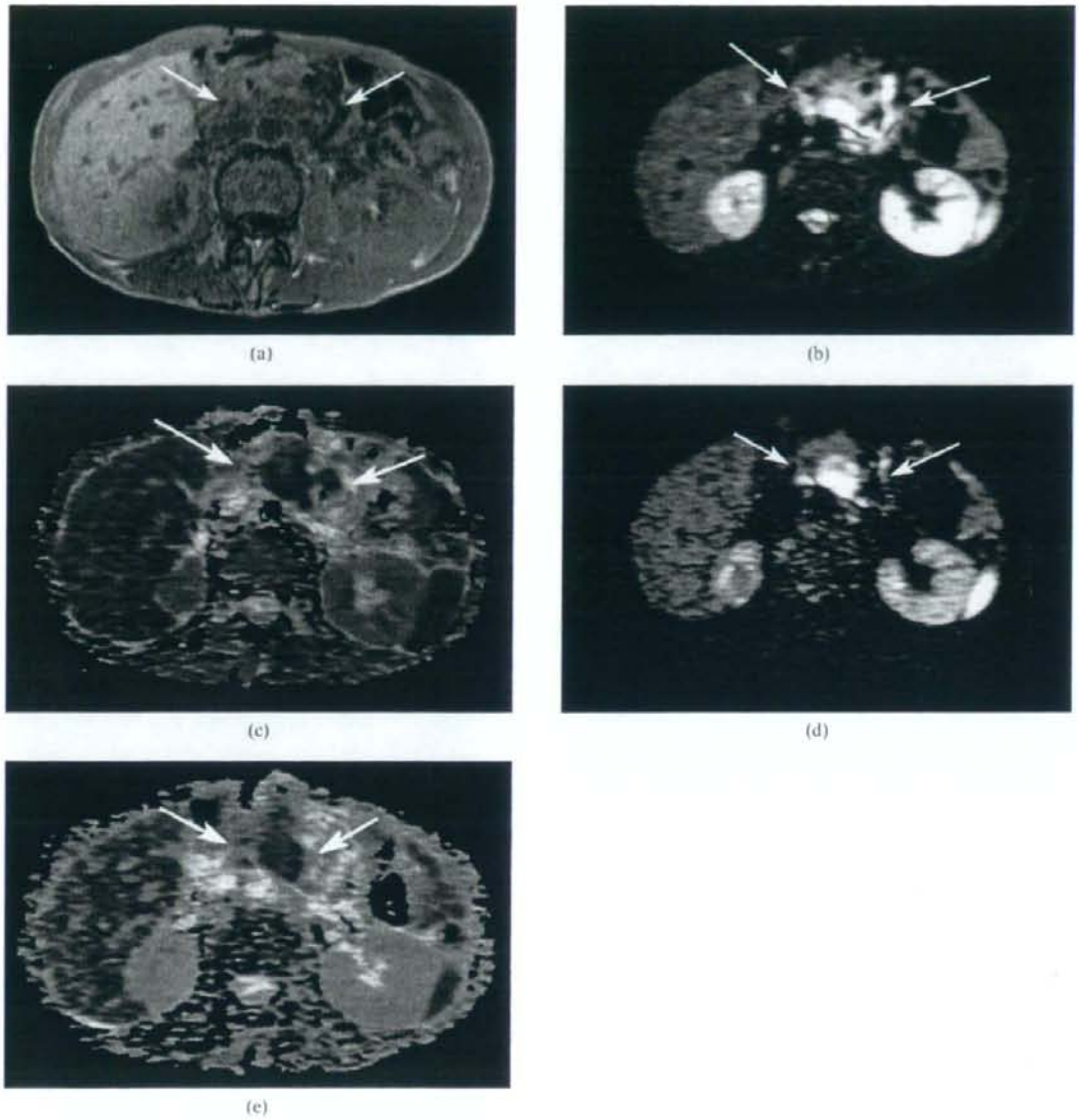

Figure 1. Images from a 65-year-old man with advanced pancreatic cancer who showed early progression. Progression was noted on the 2-month follow-up CT. (a) Transverse T_1 weighted fast-field echo image shows an irregularly shaped tumour at the pancreatic head (arrows). (b,c) Isotropic diffusion-weighted image (b) and the apparent diffusion coefficient (ADC) map (c) using the middle *b*-value (400 s mm^{-2}) show an inhomogeneous high-signal mass (arrows). The ADC was 0.98×10^{-3} mm^2 s^{-1}. (d) Isotropic diffusion-weighted image and (e) ADC map with a high *b*-value (1000 s mm^{-2}) show an inhomogeneous high-signal mass (arrows). The ADC was 0.84×10^{-3} mm^2 s^{-1}.

no significant difference using the log-rank test (median progression time, 101 days *vs* 140 days; $p=0.10$).

Discussion

Despite major recent advances in the management of cancer, pancreatic cancer remains a challenge to clinicians because of the difficulties encountered in early diagnosis and its relative chemoresistance. Some patients show improvements in survival and tumour response, whereas others only suffer from inconvenience and increased toxicity. It has been suggested that the burden of treatment should not add to the suffering of those with advanced pancreatic carcinoma. Therefore, the identification of prognostic factors before treatment would be helpful in

selecting the subgroups of patients for which chemotherapy improves survival and in determining efficient treatment strategies with reference to expected survival [21].

Among patients with advanced pancreatic cancer treated with chemotherapy, it was found that a lower pre-treatment high *b*-value ADC was correlated with early progression. Several reports relating to brain tumours and animal models have indicated a relationship between ADC and histological features [11–14, 16, 22]. ADC is a quantitative expression of the tissue

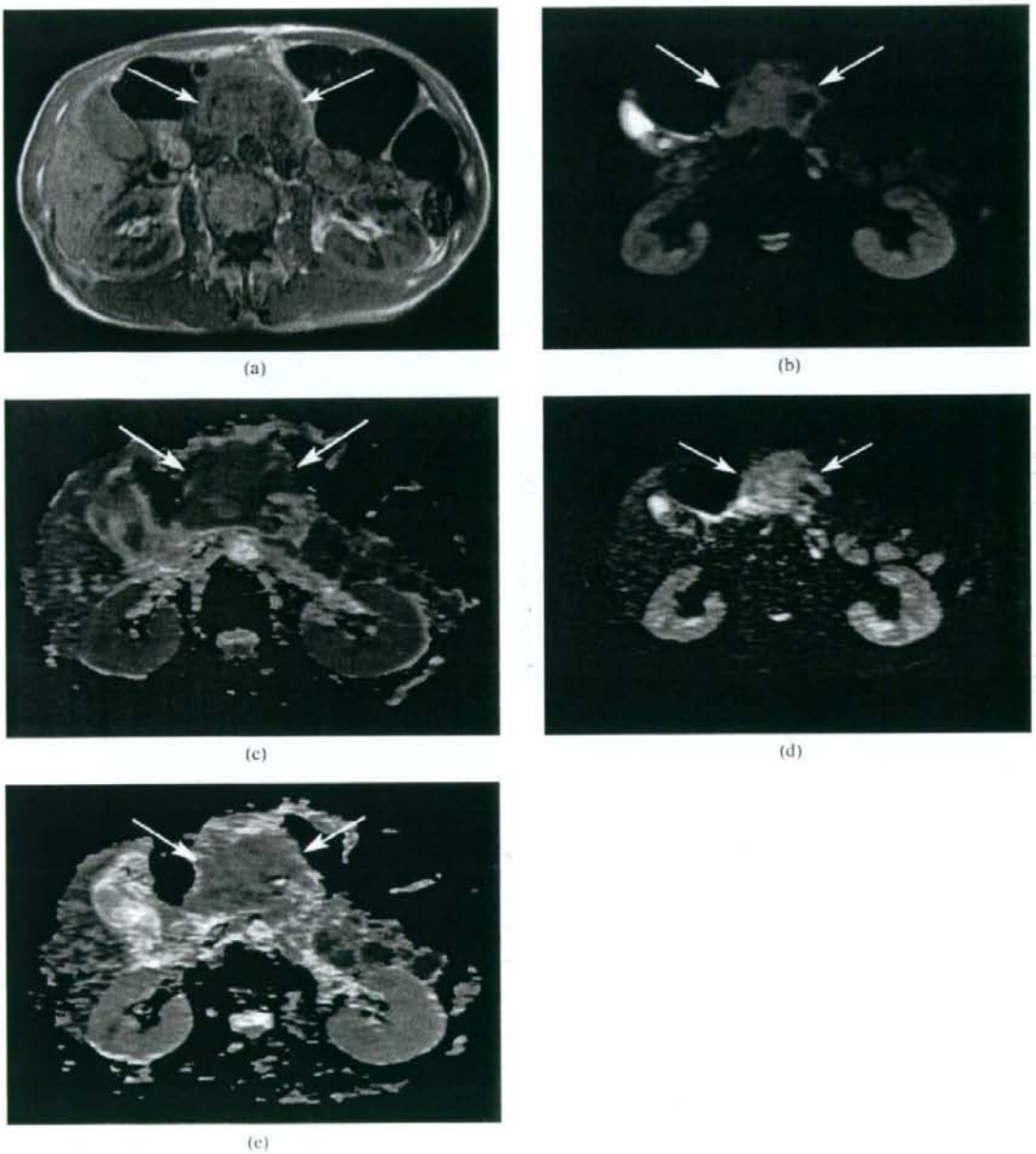

Figure 2. Images from a 66-year-old man with relatively stable advanced pancreatic cancer. Progression was noted on the 8-month follow-up CT. (a) Transverse T_1 weighted fast-field echo image shows an irregularly shaped tumour at the pancreatic head (arrows). (b) Isotropic diffusion-weighted image and (c) the apparent diffusion coefficient (ADC) map using the middle *b*-value (400 s mm $^{-2}$) show an inhomogeneous high-signal mass (arrows). The ADC was 1.42×10^{-3} mm^2 s^{-1}. (d) Isotropic diffusion-weighted image and (e) the ADC map with a high *b*-value (1000 s mm $^{-2}$) show an inhomogeneous high-signal mass (arrows). The ADC was 1.40×10^{-3} mm^2 s^{-1}.

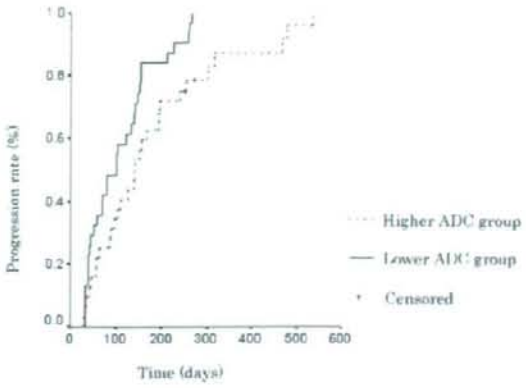

Figure 3. The graph shows the rates of local tumour progression in patients with advanced pancreatic cancer treated with chemotherapy. Patients with a lower apparent diffusion coefficient (ADC) using the high *b*-value (1000 s mm^{-2}) had a significantly higher rate of progression than those with a higher ADC ($p<0.01$, log-rank test).

diffusion characteristics; it is related to the proportion of extracellular and intracellular components. A high ADC is thought to reflect the presence of a necrotic fraction, which leads to increased extracellular water, whereas a low ADC is thought to reflect higher tumour cellularity or cell density, which results in more restricted water diffusion. Cell density may be indicative of tumour aggressiveness. The results of several clinical studies suggest that tumours with a high cellularity have an increased metastatic capacity [23]. Although the reason for the correlation between a lower pancreatic cancer ADC and early progression is unclear, it is possible that a lower ADC reflects a higher cellularity and a more aggressive tumour. Conversely, pancreatic cancers generally include desmoplastic tissue in the baseline tumour volume, which may also affect ADC independent of the cellularity. To the best of our knowledge, there have been no previously published reports dealing with the correlation between diffusion-weighted imaging and histological examination findings in pancreatic cancer. In this study, we did not look for any correlation between histology grade and ADC because it was inappropriate to analyse specimens of a part, small amount or metastatic site of the tumour. Further studies are needed to correlate the pancreatic cancer ADC with the tumours' histological features.

Several investigators have attempted to use the ADC as a pre-treatment predictor of response to chemotherapy or chemoradiation. Investigators have used various methods to analyse the data and their results have varied. Higano et al [24] reported that a lower minimum pre-treatment ADC correlated with brain tumour progression. The ADC of the tumour that was analysed avoided cystic or necrotic areas, and they hypothesized that the relationship between a lower tumour ADC and early progression was related to high cellularity or a highly proliferative portion of the tumour; our results are similar to these. Conversely, several investigators reported that a higher pre-treatment ADC was related to a poor response to chemotherapy in rectal cancer patients, patients with colorectal hepatic metastasis and animal models [12, 13, 15, 17]. In these studies, the ROI for ADC measurement involved the whole tumour; the investigators hypothesized that the reason for the poor response with a higher pre-treatment ADC may be due to the presence of necrosis in the tumour. In this situation, the tumour may experience hypoxia and thus have a slower metabolism, which would result in a lower sensitivity to chemotherapy [12]. Although measuring ADC values of a whole tumour might be less subjective and more reproducible, we attempted to measure the ADC while avoiding cystic or necrotic components of the tumour in this study, which might reflect tumour cell characterization. In the future, a proper method for analysis of pancreatic cancer needs to be developed.

In the present study, early progression did not correlate with the middle *b*-value ADC but did with the high *b*-value ADC. Middle *b*-value diffusion-weighted imaging produces relatively good imaging quality, but the middle *b*-value ADC is affected by so-called "T_2-shine through" and a local vessel perfusion effect. These factors may affect the middle *b*-value ADC in pancreatic cancer; as a result, the middle *b*-value ADC may not truly reflect tumour characteristics. Other scanning factors, such as MPG pulse direction, *b*-factor, matrix size and the reduction factor on parallel imaging, may also affect imaging quality.

The present study had several potential limitations. Firstly, single-shot echo planar imaging has a relatively low spatial resolution, a low signal-to-noise ratio and shows imaging distortion. We used all of the currently available techniques to improve imaging quality. However, the ADCs of small lesions may still be unreliable. The use of high field-strength imagers or pulse-triggered scanning can potentially improve the signal in diffusion-weighted MRI [25, 26]. Secondly, although a high *b*-value of 1000 s mm^{-2} on diffusion-weighted imaging was used to reduce confounding relaxation phenomena, the so-called T_2-shine through effects and the perfusion effect, these factors may still have affected the ADC [27–29]. Diffusion-weighted images with a higher *b*-value (*i.e.* 4000 s mm^{-2}) should provide more information about the slow diffusion of water molecules, which may be more sensitive at distinguishing cellular or tissue characteristics [12]. However, on abdominal scanning, current MR units cannot provide enough higher *b*-value signals. Thirdly, the patient population was relatively small, and substantial overlap was noted between progressive and stable patients. Tumour stage and size varied in this study; however, these factors were not significantly different between progressive and stable patients. In addition, some patients had not been histologically proven to have pancreatic cancer. Although primary pancreatic lymphoma might mimic pancreatic cancer, we carefully reviewed clinical data, and patients with a doubtful clinical diagnosis were not included in this study [30, 31]. Further larger clinical studies are needed to fully characterize pancreatic cancer for an appropriate analysis of ADC with tumour stage and size. Finally, the measurement reproducibility of ADC was not assessed in this study. Instead, we measured several ROIs in the tumour and then averaged these.

In conclusion, in patients with advanced pancreatic cancer treated with chemotherapy, a lower high *b*-value ADC may be predictive of early progression.

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≪局所進行膵癌の治療戦略≫
局所進行膵癌に対する化学療法

大川伸一*

要旨

- 局所進行膵癌に対する標準的治療については，長いあいだ論争がある．
- 米国，日本では放射線化学療法を標準治療とする傾向が強いと考えられるが，欧州では全身化学療法を標準とすることが多かった．
- 両者の治療を比較した無作為化試験は少なく，症例数も少なく，また結論もさまざまである．
- gemcitabine の登場以来，これが進行膵癌に対する標準薬となったため，局所進行膵癌にも全身化学療法が広く行われるようになった．
- gemcitabine を用いた放射線化学療法の試験もあるが，その方法，成績は一定ではない．
- 放射線化学療法と gemcitabine による全身化学療法の両者の治療成績に著明な差があるとは考えにくいが，今後は局所進行膵癌をさらに詳細に分析し，それぞれの治療に，より適した対象を見出すことが重要と考えられる．

はじめに

膵癌は早期発見が困難であり，多くの症例が診断時に遠隔転移を伴っているか切除不能な局所進行癌である[1]．局所進行膵癌とは，CT を主とする画像診断において明らかな遠隔転移を認めないが，根治切除は不可能な状態の膵癌である．すなわち一般には，上腸間膜動脈や腹腔動脈の根部に癌が明らかに進展している状態や，門脈に広範囲に浸潤している状態などであり，ほぼ UICC（The International Union Against Cancer）分類のⅢ期に等しい．

遠隔転移症例について適応となる治療法は全身化学療法であることは異論のないことであるが，新規膵癌患者の 3 割程度を占める局所進行膵癌の治療については，全身化学療法か放射線化学療法かは長いあいだ議論があり，現在でもまだ決着がついていない．しかし全身化学療法と放射線化学療法は，治療の質，期間，入院期間，起こりうる有害事象の内容などに大きな違いがあるため，どちらが推奨されるのかは臨床上，大きな問題である．

局所進行膵癌に対する放射線化学療法

局所進行膵癌に対して行われてきた放射線化学療法については，比較試験は多くはない．無作為化比較試験では 1969 年の Moertel[2]，1981 年の Moertel[3]，1988 年の GITSG（Gastrointestinal Tumor Study Group）[4]による試験で，放射線化学療法が化学療法に優っていたと報告された（Table 1）．いずれもかなり以前の試験であるが，米国はこれを根拠として今日にいたるまで，局所進行膵癌の治療として放射線化学療法を標準治療として推奨する立場をとってきた．

一方米国以外，とくに欧州では米国とは異なり，

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Table 1. 進行膵癌に対する放射線化学療法と全身化学療法の比較試験

報告者 研究グループ	報告年	症例数	放射線治療 (Gy)	化学療法	生存期間 中央値(月)	p 値
Moertel[2]	1969	32	35～40	なし	6.3	<0.05
		32	35～40	5-FU	10.4	
Moertel[3]	1981	25	60	なし	5.2	<0.01
		83	40	5-FU	9.6	
		86	60	5-FU	9.2	
GITSG[4]	1988	21		SMF	8.0	=0.02
		22	54	SMF	10.5	
Klaassen[5]	1985	44		5-FU	8.2	NS
		47	40	5-FU	8.3	
Chauffert[11]	2008	60		GEM	13.0	=0.03
		59	60	FP	8.6	
Loehrer[12]	2008	38		GEM	9.2	=0.034
		36	50.4	GEM	11.0	

GITSG：Gastrointestinal Tumor Study Group.
SMF：streptozocin, mitomycin, 5-FU.　FP：5-FU, CDDP.

Table 2. GEM 放射線化学療法の第 II 相試験

報告者	報告年	症例数	放射線治療 (Gy)	GEM 投与量 (mg/m²)	TTP (月)	1 年生存率 (%)	生存期間 中央値(月)
de Lange[8]	2002	24	24	300	7	—	10
Li[9]	2003	18	50.4～61.2	600	7.1	56	14.5
Okusaka[7]	2004	38	50.4	250	4.4	28	9.5
Murphy[10]	2007	74	20～42	1,000	6.6	46	11.2

TTP：time to progression.

上記のこれらの試験の症例数が 21 例から 86 例までの少数であること，また 1985 年の ECOG の試験[5]では有意差を認めなかったことから，放射線化学療法が必ずしも標準とはならなかった経緯がある．日本では米国の考え方に近いと考えられる．これらの放射線化学療法に用いられた薬剤は，当然ながらそれまで膵癌の key drug として長く用いられてきた fluorouracil (5-FU) が主体であった．5-FU の投与法はさまざまであり，bolus で行ったり持続投与が行われたりしたが，投与法について比較した大規模な試験はない．

1997 年に Burris ら[6]により，塩酸ゲムシタビン (gemcitabine：GEM) が進行膵癌に対する標準薬として登場してからは，これを併用薬剤とする放射線化学療法が，いくつか報告されている[7～10] (Table 2)．これらの試験における GEM の投与量は，実にさまざまである．

最近では，フランスの研究グループから GEM 単独療法と比較して放射線化学療法に否定的な報告[11]がされているが，一方で 2008 年の ASCO (米国がん治療学会) では，米国の研究グループから放射線化学療法に肯定的な報告[12]もされている．

局所進行膵癌に対する化学療法の背景○

過去長期間にわたり，膵癌の化学療法は 5-FU を主体として行われてきた[13～15]．奏効率は最大 28% くらい[14]でさまざまであったが，比較的奏効率のよい治療法も追試にて同様の成績をあげるこ

とが少なかったこと[13]や，survival の改善につながらない[15]，などの問題があった．

GEM が登場[6]して以来，これが標準薬となったため，欧米をはじめとして GEM を key drug とした化学療法の臨床研究が，この 10 年で盛んに行われている．しかし試験対象としての進行膵癌に，遠隔転移を伴う膵癌と局所進行膵癌を同時に含む試験が多いため，局所進行膵癌のみを扱った化学療法の第Ⅱ相試験はほとんど存在しない．両者を対象に含む試験[16,17]の内容からは，対象例のおおむね 20～30% が局所進行膵癌と考えられ，実際の臨床の現場の割合に即したものであることが多い．

局所進行膵癌の増悪様式○

局所進行膵癌の治療戦略を考えるうえで重要な点の一つは，その増悪様式であるが，一般には肝などへの遠隔転移をきたすか，または腹膜播種が多いと考えられる．一方で GEM を用いた最近の放射線化学療法の試験の報告では，局所再発率は数～50% とさまざまであり[7～10]，さらに局所の再発が生存期間に及ぼす影響については詳細な検討がされているとはいいがたく，増悪の主要因が特定された解析は少ない．

また膵癌はしばしば一つの要因だけで増悪するものではなく，画像上明らかな増悪が認められなくとも症状が増悪していく，いわゆる臨床的増悪も多い．こうした特徴から膵癌を「全身病」であると考えると，治療法の評価は，一般にはやはり生存期間で行うことになろう．

局所進行膵癌に対する全身化学療法○

前述したように局所進行膵癌の全身化学療法の評価は，放射線化学療法との比較試験で解析されていることが多い[4～5,11,12]．あるいは，遠隔転移のある膵癌と局所進行膵癌の両者を対象にした試験の subgroup 解析で述べられている[16,17]．その生存期間の成績を大まかにまとめると，化学療法単独の生存期間中央値は多くが約 8～10ヵ月くらいであろう．これらは前述した GEM を用いた最近の放射線化学療法の成績(Table 2)に対して，やや劣るようにもみえるが，一般には全身化学療法より放射線化学療法のほうが治療のための入院期間が長いことや有害事象の点などから，その差は結局著明なものではないと思われる．

しかし一方で，試験の endpoint である生存期間の比較だけでは治療効果の詳細な意義がつかめない点もある．たとえば長期間にわたり明らかな遠隔転移をきたさない例に対しては，放射線化学療法が有用であり，生存期間を延長させている可能性がある．この点に注目して，まず局所進行膵癌に全身化学療法を数コース行い，そのあいだに遠隔転移をきたさない症例だけを対象にして放射線化学療法を行う方法も注目されている[18]．

おわりに○

局所進行膵癌の標準治療が放射線化学療法か全身化学療法かは，大規模な第Ⅲ相試験が困難であること，放射線治療の quality control が問題であること，さらには局所進行膵癌の中でも進行度に幅があること，すなわち小さな転移が隠されている例が少なからず存在することなどから，結論を導くにはまだ時間を要するため，しばらくは controversial な状態が続くと予想される．

今後，さらに多くの臨床研究にて詳細な分析を積み重ねることにより，全身化学療法が推奨される対象と放射線化学療法により恩恵を受けられる対象を特定できるようになれば，難治癌である膵癌治療の進歩に，また一歩貢献できるであろう．

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第8章

膵・胆道癌に対する化学療法

日本における膵癌，胆道癌の死亡者数はともに年々増加しており，厚生労働省の統計調査表によると2005年の膵癌による死亡者数は23,000人近くであり，胆道癌による死亡者数は約16,500人であった．癌臓器別の死亡数では肺，胃，結腸・直腸，肝に次いで膵癌が第5位，胆道癌が第6位である．これらは日本の人口構成における高齢者の増加によるところが大きいとされており，したがって将来の日本の人口推移を考慮すると今後も発生者数および死亡者数とも増加することが予想されている．

膵癌は，初めの診断時にその多くが遠隔転移を伴っているか切除不能な局所進行癌であること，また切除可能であっても切除後の再発率がきわめて高い難治癌である[1]ことから，膵癌の治療において化学療法は大変重要な意義をもっている．胆道癌も膵癌と同様の傾向があり，かつ両者とも最近になって新しい薬剤が使用されるようになってきたため，今後この領域においてさらに化学療法が発展していく可能性が高い．

Ⅰ．膵癌に対する化学療法

膵癌については過去さまざまな化学療法についての報告がなされてきたが，最近まで膵癌の標準的治療と言える化学療法はなかったに等しい[2]．しかしgemcitabine hydrochloride(GEM)が登場して以来，欧米をはじめとしてこれをkey drugとした化学療法の臨床研究が盛んに行われるようになり，膵癌に対する化学療法の分野にとって少しずつ光が見え始めてきたといえる．

過去約30年間，膵癌の化学療法は5-fluorouracil(5-FU)を主体として行われ

表　GEM 対 5-FU

	GEM	5-FU	p value
症例数	63	63	
転移を有する例(%)	72	76	
KPS＞70(%)	30	32	
モルヒネ投与例(%)	70	73	
症状緩和効果(CBR)	23.8	4.8	0.0022
Time to progression(月)	2.33	0.92	0.0002
生存期間中央値(月)	5.65	4.41	0.0025
1 年生存率(%)	18	2	

KPS：Karnofsky performance status
(Burris et al.[5]をもとに作成)

てきた[2)~4)]．奏効率は最大 28%くらい[3)]でさまざまであったが，比較的奏効率の良い治療法も追試にて同様の成績をあげることが少なかったこと[2)]や，survival の改善につながらない[4)]などの問題があった．

1．GEM

GEM は，デオキシシチジンのアナログであり，DNA 合成がおもに行われている S 期に特異的な作用を示す代謝拮抗剤である．欧米では 1995～1996 年頃に膵癌に認可された．Burris ら[5)]は進行膵癌に対する GEM 対 5-FU の無作為化比較試験を行い，GEM が 5-FU に比べて症状緩和効果(clinical benefit response；CBR)に優れ，生存期間中央値(median survival time；MST)を延長させ，1 年生存者も多く，副作用は血液毒性，好中球減少が多かったが重篤な状態には至らなかったと報告した(表)．CBR は抗癌剤の評価法として考えられたものであり，具体的には①痛みと②performance status(PS)の改善度を比較するものである．この CBR による比較は，奏効率や MST が主体であった抗癌剤評価法に対して，quality of life の面から非常に有益な評価法として一種の break through となった．

以上の報告をはじめとして GEM に関する多くの追試が行われた結果，現在進行膵癌に用いる化学療法剤としてわが国のガイドライン[6)]においても GEM が first-line の標準薬となっている．

GEM の投与方法は，体表面積当り 1,000 mg を第 1，8，15 日に投与，第 22

Day	1	8	15	22
GEM (1,000 mg m^2・div 30min)	↓	↓	↓	休薬

※1 コース 28 日

投与例

第 1，8，15 日に投与．第 22 日は休薬

① 5-HT_3受容体拮抗型制吐剤またはデキサメタゾン＋生食(50 ml)
…… 15 分点滴静注

② GEM (1,000 mg/m^2) ＋生食(100 ml)
…… ①終了後 30 分以内点滴静注

図 1　GEM の投与方法(例)

日は休薬，28 日間を 1 コースとして繰り返し投与する(**図 1**)．投与量は年齢，副作用に応じ適宜減量する．制吐剤の使用は必ずしも必要ではないが，軽度の嘔気を含めると約 7 割に嘔気・嘔吐の副作用を認めるため必要な場合も多い．また投与翌日から嘔気が出現することも多いため，この場合，屯用として経口の制吐剤を 3 日間程度投与する．注意点としては投与日あるいは前日に必ず採血を行い，白血球数や血小板数をはじめとしたチェックを行い，規定の値に達していない場合や，あるいは他の検査項目値に許容範囲以上の異常変動がみられたときは治療をスキップする．進行膵癌はさまざまな症状を有していることが多く，できるだけ外来治療の負担を軽減させるために，骨髄抑制の対策として granulocyte-colony-stimulating factor(G-CSF)製剤を併用して続けるよりも，スキップを行い翌週以降に回復を待ってから投与を続けていく例も多い．

2．S-1

S-1 は，5-FU のプロドラッグである tegaful に 5-FU の分解阻害剤 gimeracil とリン酸化阻害剤 oteracil potassium を配合した経口抗癌剤であり，日本で開発された[7]．国内での第 II 相試験[8]を経て進行膵癌に対しては 2006 年に保険適応となった．第 II 相試験の結果からは奏効率が 37.5%，MST が 9.2 カ月と良好な

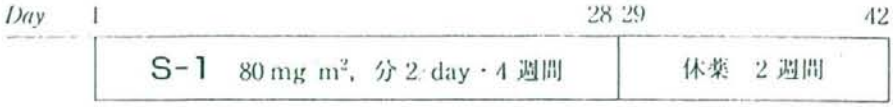

図 2　S-1 の投与方法

成績であった．S-1 は経口薬である簡便さから臨床の現場では普及しつつあると推定される．服用法は 80 mg/m²(目安として体表面積 1.5 m²以上：120 mg/day，1.25～1.5 m²：100 mg/day，1.25 m²未満：80 mg/day)を朝・夕の 2 回に分けて 4 週間連続内服し，その後 2 週間休薬し，6 週間を 1 コースとしてこれを継続する(図 2)．

3．膵癌化学療法の注意点

化学療法を行っていくうえで重要な点は，定期的に治療効果および有害事象を評価し，これにより治療を継続するか否かを決定していくことである．治療効果を評価する時期としては本来は各コースごとが良いが，現実的に各コースごとの CT 検査による治療効果判定は困難なことが多いため，2 コースごとあるいは 3 カ月ごとなどで行われることが多い．病状の悪化がみられた場合は second-line として次の治療法を考慮すべきであるが，膵癌の化学療法には多くの薬剤はないため大変難しい問題である．second-line についてはできれば試験治療として行うべきである．

4．放射線化学療法

明らかな遠隔転移を認めないが切除不能である局所進行膵癌に対する治療は，放射線療法と化学療法を併用する放射線化学療法または全身化学療法が行われている．GEM 登場後に，放射線化学療法と全身化学療法とどちらを選択すべきかについてはいくつかの臨床試験が行われており，現在まで決着がついていない．

放射線化学療法に用いられる薬剤は放射線増感作用のある 5-FU を用いることが多いが，決まった投与法はなく，多くはこれを持続投与(200 mg/m²/day)し，4 週で約 50 Gy 照射する方法がとられている[9]．また GEM を用いた方法も検討されている[10]が，まだ試験段階であり安全性の評価が定まっていない現在，practical には行うべきではなく必ず試験治療として行うべきである．

5．術後補助化学療法

切除後の再発率の高さから術後の adjuvant therapy として化学療法がしばしば行われる．術後補助化学療法の意義については欧米では第III相の臨床試験[11]を経た結果，行うべきであるとされており，日本でも次第に行われることが多くなった．薬剤としては GEM を用いることが標準的と考えられているが[11]，その投与量や投与期間，あるいは他の薬剤，併用療法の意義などの評価は今後の課題である．

II．胆道癌の化学療法

前述したように胆道癌による死亡者数は 2005 年で 16,000 人を超え，かつ年々増加の一途をたどっている．胆道癌は性別の死亡数では男性で第 8 位，女性で第 7 位と比較的少ない癌腫であるが，膵癌と同様に性差が少ないことが特徴であり，男女合わせると癌臓器別の死亡数では膵に次いで第 6 位である．胆道癌も診断時に進行している例が多く切除率は決して高くない．さらに切除後の再発率も高いため化学療法の発展が強く望まれる．胆道癌に対して用いられる薬剤は GEM が国内の第 II 相試験[12]を経て，2006 年に胆道癌に対しては 23 年振りの新薬として保険適応となり，続いて 2007 年に S-1 も適応となった．

1．GEM

胆道癌は膵癌と異なり発生率にかなり人種差があり，欧米と比べて日本などアジアに多い癌腫である．しかし現在まで進行胆道癌に対する全身化学療法の十分な例数のランダム化比較試験はほとんどない．よって標準的薬剤は現段階ではまだ十分な evidence をもったものがなく，日本においてもまだ確立されたガイドラインは存在していない．

胆道癌も膵癌と同様に 5-FU を用いた研究が比較的多く行われてきたが，近年では GEM を用いた研究が多くなってきている．また最近，英国を中心として進行胆道癌に対して GEM を主とした初めての本格的といえる第III相試験が行われていることもあり，実際には GEM が標準的治療に近いといえる．

治療法は膵癌とまったく同様である(図 1)．国内で行われた進行胆道癌に対する第II相試験[12]では partial response(PR)が 17.5%，stable disease(SD)も含めた病勢コントロール率は 55%，また MST は 7.6 カ月，1 年生存率は 25%であっ

た．有害事象は重篤なものはほとんど認めず，有効性と安全性が証明された．

2．S-1

S-1 も 2007 年に進行胆道癌に認可され使用され始めている．投与法は膵癌とまったく同様である(図 2)．国内の製剤であることから膵癌と同様に海外にてはまだ試験が少ないが，今後普及することが期待される．

おわりに

国内では膵癌に対する GEM と S-1 の併用療法の試験が行われており，単剤治療よりも成績の向上が期待されているが，現段階では試験治療として扱うべきである．今後第III相試験が行われればその結果を期待したい．

前述したように膵・胆道癌の化学療法についてはここ数年，報告が増えてきており，さらに分子標的薬をはじめとした新薬との併用療法の試験が盛んに行われているため，この分野の研究はさらに盛んになることが予想される．代表的な難治癌といえる両者に対して少しずつであっても，さらなる進歩が期待されている．

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