Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

FULL PAPER

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Keywords: pentraxin family; pancreatic carcinoma; cancer inflammation

Clinical impact of pentraxin family expression on prognosis of pancreatic carcinoma

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Background: Inflammatory mediators may have decisive roles at different stages of tumour development. Mediators within the pentraxin family may be used as strong biomarkers in prognosis of advanced pancreatic carcinoma patients.

Methods: Using pancreatic carcinoma cell lines and gene transfectant, we measured long pentraxin (PTX3) level in culture solution and carried out cellular migration assay *in vitro*. *In vivo* study of the treatment-naive patients with advanced pancreatic carcinoma assigned to undergo gemcitabine therapy was prospectively conducted to measure and investigate the role of plasma PTX3, C-reactive protein (CRP), and eight inflammatory mediators by using collected clinical data.

Results: Elevated PTX3 production was observed in several cell lines, and a direct relationship between migratory activity and PTX3 level was identified *in vitro*. High PTX3 level (117 days) was significantly less than that of patients with low PTX3 level (357 days, $P<0.001$). Multivariate analysis of the pancreatic carcinoma revealed a strong correlation between pentraxin family member expression and prognosis of pancreatic carcinoma. The relationship between PTX3 expression and the expression of other pro-inflammatory mediators indicated that PTX3 level is positively correlated with levels of CRP, interleukin-6, and macrophage-inhibitory factor.

Conclusion: Pentraxin family members, especially PTX3, may be used as promising biomarkers in the prognosis of pancreatic carcinoma patients.

Pancreatic carcinoma is one of the most lethal cancers and is the fourth leading cause of cancer-related death in developed nations (Jemal *et al*, 2011). As pancreatic carcinoma has a high propensity for both local invasion and distant metastasis, surgical treatment is precluded for most patients who present with an advanced stage of the disease. Despite many treatment advances that have improved the outcomes of some pancreatic carcinoma patients, standard therapy has been found to have only a modest beneficial impact on advanced-stage patients (Vincent *et al*, 2011), as reflected in their 5-year overall survival (OS) of <5% (Jemal *et al*, 2011).

Identification of biomarkers that accurately predict disease recurrence, response to chemotherapy, and/or prognosis would be of substantial aid in individual risk assessment and treatment selection. Identification of targets for molecular intervention in specific subsets of patients may even lead to the development of novel therapies. There is thus a need to identify a superior marker of prognosis to enable the improved survival of advanced pancreatic carcinoma patients.

Inflammatory responses have decisive roles at different stages of tumour development, including initiation, promotion, malignant conversion, invasion, and metastasis, and affect immune surveillance and response to therapy. The invasive capacity of malignant cells has been observed to increase in the presence of inflammatory cytokines, including TNF-alpha, interleukin (IL)-1beta, and IL-6, as well as transcription factors, including AP-1, NF-κB, and STAT3 (Mantovani *et al*, 2008). In a previous study, we identified C-reactive protein (CRP), which is produced via IL-6 and TNF-alpha stimulation in the liver, as an important factor in the prognosis of pancreatic carcinoma (Morizane *et al*, 2011). In other studies, long pentraxin (PTX3), a member of the pentraxin family, which includes CRP and whose members may have a significant role in tumour inflammatory and malignant behaviours, was

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reported to be overexpressed in several malignancies, including liposarcomas (Germano *et al*, 2010) and lung cancer (Diamandis *et al*, 2011). These findings indicate that reduction of the key inflammatory mediators may be an important means of promoting antitumour activity.

In a previous study, we had observed direct secretion of PTX3 from pancreatic carcinoma cell lines *in vitro*. Building on this finding, we aimed to determine the biological significance of PTX3 in pancreatic cancer via further *in vitro* study of several pancreatic carcinoma cells lines, as well as prospective clinical investigation of the clinical significance of plasma PTX3 expression in chemotherapy-naive pancreatic carcinoma patients. We found that PTX3 expression might be a promising biomarker for pancreatic carcinoma prognosis.

MATERIALS AND METHODS

Cells, plasmids, and transfection procedures. The PANC-1 (ATCC number: CRL-1469), MIA PaCa-2 (ATCC number: CRL-1420), BxPC-3 (ATCC number: CRL-1687), and AsPC-1 (ATCC number: CRL-1682) pancreatic carcinoma cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA). Dulbecco's Modified Eagle's Medium with 10% fetal bovine serum (FBS) was used as the base medium for the PANC-1 and MIA PaCa-2 lines, and RPMI with 10% FBS was used as the growth medium for the BxPC-3 and AsPC-1 lines. We used the transfectant pCMV6-entry PTX3 open reading frame (ORF) clones (OriGene Technologies, Inc., Rockville, MD, USA; cat. no. RC207922) to investigate the cellular activity induced by intracellular PTX3 overexpression. The plasmids were transfected into cells using Lipofectamine 2000 (Life Technologies Corp., Carlsbad, CA, USA). In experiments using neomycin-resistant vectors, transfected cells were selected using 0.5 mg ml^{-1} of G-418 to establish stable transformants.

Cell migration and invasion assay. Cell migration assay was performed as described previously using Transwell inserts (5-μM pore size; Corning Inc., Corning, NY, USA). Cells were placed in 100 μl of 0.6% FBS medium in the upper chamber at 1×10^5 cells ml^{-1}, and the bottom chamber contained VEGF (Cat. no. PHC9391; *Life Technologies Corp.*), PTX3 (Cat. no. 1826-TS-025; R&D System, Minneapolis, MN, USA), and CRP (Cat. no. 1707-CR-200; R&D System) in a medium containing 0.6 or 20% FCS. After 12 h, the inserts were fixed and stained with Diff-Quick (Symex International Reagents Co. Ltd., Kobe, Japan). After the cells that had not migrated were removed from the upper surface of the inserts using cotton swabs, images from three different high-power fields were captured from each insert and the number of migratory cells was counted (Kondo *et al*, 2012a).

Cytokine measurement. Pancreatic carcinoma cells at 75–80% confluence were growth-arrested by FBS deprivation for 24 h and cultured in fresh FBS-free medium. Supernatants were collected at 6 h. Plasma samples collected from patients before initiation of gemcitabine treatment were stored at − 80 °C until being subjected to enzyme-linked immunosorbent assay (ELISA) and antibody-suspension bead array analysis. Serum CRP levels were measured according to the manufacturer's directions by using a commercially available kit (Nanopia CRP; Sekisui Medical Co., Ltd., Tokyo, Japan) capable of assaying a wide range of values (0.01–100 mg dl^{-1}) without the prozone phenomenon. Plasma-PTX3 levels were measured according to the manufacturer's directions by using a commercially available ELISA kit (Cat. no. PP-PD03-E0; Perseus Proteomics, Inc, Tokyo, Japan) capable of measuring a wide range of values (0.1–20 ng ml^{-1}) linearly. After being drawn into prechilled tubes containing ethylenediaminetetraacetic acid (EDTA), peripheral blood was immediately subjected to centrifugation at 1000 **g** and 4 °C for 15 min. The plasma was then transferred into microtubes and subjected to further centrifugation at 10 000 g and 4 °C for 10 min to remove contaminating platelets.

The plasma concentrations of the pro-inflammatory mediators IL-1beta, IL-6, C-C motif ligand (CCL) 2, CCL3, CCL4, CCL7, C-X-C motif ligand 9, and macrophage-inhibitory factor (MIF) were assayed in a subgroup of patients and control individuals using the Bio-Plex suspension array system (Bio-Rad, Hercules, CA, USA), which allows for simultaneous detection of cytokines in a 96-well filter plate. In brief, the appropriate cytokine standards and diluted plasma samples were added to a 96-well filter plate and incubated at room temperature for 30 min with antibodies chemically attached to fluorescent-labelled micro beads. After three filter washes, premixed detection antibodies were added to each well and incubated for 30 min. After three additional washes, premixed streptavidin–phycoerythrin was added to each well for 10 min of incubation. Subsequent to three more washes, the beads were resuspended in 125 μl of assay buffer and the reaction mixture was quantified by using the Bio-Plex protein array reader. Data were automatically collected and analysed using Bio-Plex Manager Software 4.1, and the standard curve was obtained using a recombinant cytokine standard (Kondo *et al*, 2012b).

Study approval. Prior to initiation, this prospective study had been approved by the Institutional Review Board of the National Cancer Center, and written informed consent had been obtained from all patients. This study is registered with the University Hospital Medical Information Network in Japan (UMIN; number UMIN000002323) and has been completed.

Patient selection and blood sample collection. A total of 78 chemotherapy-naive patients with histologically or cytologically confirmed advanced or recurrent invasive ductal pancreatic carcinoma were prospectively enroled in this study between April 2009 and March 2010 for treatment with gemcitabine chemotherapy. Patients with coexisting infections and/or cardiovascular illness were excluded from participation. Prior to initiation of gemcitabine treatment, each patient had undergone collection of a detailed history; physical examination; assessment of pretreatment baseline laboratory parameters; and determination of baseline tumour status by computed tomography (CT) of the chest, abdomen, and pelvis. Baseline and post-treatment laboratory parameters were evaluated by performing peripheral blood sampling prior to treatment initiation and on day 28 ± 7 after treatment initiation, respectively. Gemcitabine at a dosage of 1000 mg m^{-2} was administered intravenously for 30 min on days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or patient refusal to continue treatment. The data collected included those pertaining to standard demographics; disease characteristics; and disease chronology, including the dates of initial treatment, best response to treatment, progression, and death or final follow-up. Tumours were evaluated every 6–8 weeks after initiation of each course of gemcitabine, and the best responses were documented according to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST ver1.1).

Statistical analyses. The cutoff points used in the assessment of high and low expression levels of each mediator were based on the mean values of these mediators, whereas those of the CRP and CA19-9 levels were based on previous reports (Morizane *et al*, 2011). Associations between patient characteristics were assessed by χ^2 statistics. Survival in terms of both progression-free survival (PFS) and OS; demographic factors, including age and gender; and clinical factors, including Eastern Cooperative Oncology Group (ECOG) performance status (PS) and clinical stage was examined using the Cox proportional hazards model. The survival curves for PFS and OS were estimated using the Kaplan–Meier method, with the resulting Kaplan–Meier curves used only to identify trends in the associations between the inflammatory mediators and PFS and

OS, as determination of the optimal cutoff point for the mediators relative to PFS and OS was beyond the scope of this study. All statistical analyses were performed using IBM SPSS Statistics 18 software (IBM Corp, Somers, NY, USA).

RESULTS

PTX3 expression in pancreatic carcinoma cell lines. Measurement of expression of elevated levels of PTX3 by pancreatic carcinoma cells in culture solution, considered an indication of direct PTX3 secretion by these cells, revealed that the PANC-1 and MIA PaCa-2 cell lines expressed higher levels of PTX3 compared with the AsPC-1 and BxPC-3 lines (Figure 1A).

Effect of PTX3 on migratory and invasive potential of pancreatic carcinoma cell lines. To determine the association between the intra- and extracellular levels of PTX3 and the migratory or invasive behaviour of pancreatic carcinoma cells, pCMV6-entry PTX3 ORF clones were used to establish stable transfectants. As shown in Figure 1B, introduction of PANC-1 and AsPC-1 cells increased recombinant human (rh) PTX3-induced cell migration, with the level of migration activity depending on the concentration of extracellular PTX3. On the other hand, CRP was

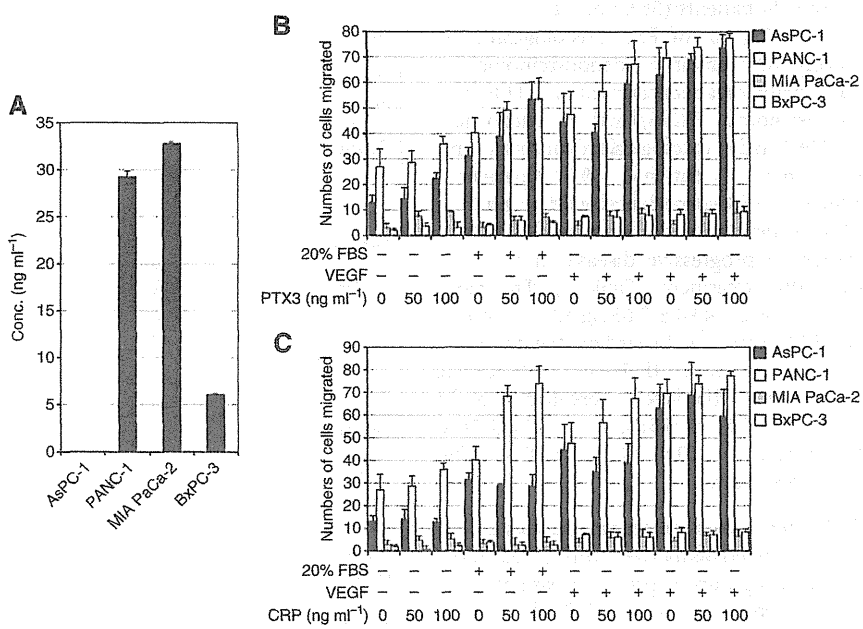

Figure 1. (A) Pentraxin 3 production levels of supernatants used for culturing of pancreatic carcinoma cell lines. (B, C) Cell migration assay in the presence or absence of the indicated reagents. NT (non-treated), FBS, 20% in the lower chamber; VEGF, 50 ng ml^{-1} in the lower chamber; PTX3, 50–100 ng ml^{-1}; CRP, 50–100 ng ml^{-1}. Statistical significance was evaluated by comparison with or without the presence of PTX3 and CRP.

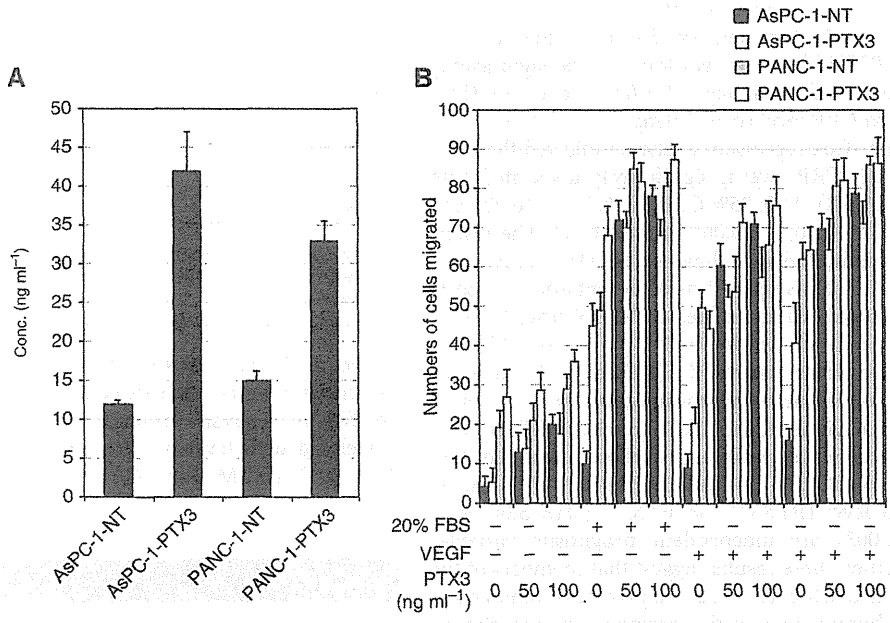

Figure 2. (A) Pentraxin 3 production levels of supernatants used for culturing of PTX3 and NT-control transfectant of pancreatic carcinoma cell lines. (B) Cell migration assay using pancreatic carcinoma cell lines (AsPC-1 and PANC-1) transfected with pCMV6-entry PTX3 ORF in the presence or absence of the indicated reagents. NT (non-treated), FBS, 20% in the lower chamber; VEGF, 50 ng ml^{-1} in the lower chamber; PTX3, 50–100 ng ml^{-1}; CRP, 50–100 ng ml^{-1}. Stable transformants were subjected to cell migration assay.

observed to have a significant role in the regulation of migration activity in pancreatic carcinoma cell lines (Figure 2C). Transformants of PTX3 clone was not observed to increase migration activity significantly (Figure 2B). These results indicate that the extracellular PTX3 in the pancreatic carcinoma cell lines had promoted migratory activity.

Patient characteristics. Of the 78 pancreatic carcinoma patients prospectively enroled in this study, 42 (54%) were male and the median age was 68 years (range, 44–79 years). Regarding prior diagnosis and treatment, 25 patients (32%) presented with locally advanced pancreatic carcinoma, 47 (60%) presented with metastases, and 6 (8%) had been enroled following recurrence after surgery. Regarding the ECOG PS score, 44 patients (56%) had an ECOG PS of PS0, 27 (35%) of PS1, and 7 (9%) of PS2. Histologically, 31 patients (40%) had a poorly differentiated adenocarcinoma, 27 (35%) had a moderately differentiated adenocarcinoma, 1 (1%) had a well-differentiated adenocarcinoma, 2 (2%) had an adenosquamous carcinoma, and 17 (22%) had a cytological adenocarcinoma. Regarding response to treatment, 0 patients (0%) experienced complete response to treatment, 5 (6%) experienced partial response (PR) to treatment, 43 (55%) experienced stable disease (SD) after treatment, 27 (35%) experienced progressive disease, and 3 (4%) patients were not evaluable after treatment (Table 1). The mean PTX3 level of all patients was $4.94 \pm 3.63\,ng\,ml^{-1}$ (range, $0.9–17.7\,ng\,ml^{-1}$; median, $3.76\,ng\,ml^{-1}$). Regarding the values of other inflammatory mediators, the mean IL-1beta, IL-6, CCL2, CCL3, CCL4, CCL7, CXCL9, and MIF levels were found to be 95.48 ± 37.62, 294.38 ± 516.6, 746.58 ± 518.12, 177.8 ± 58.4, 2886.28 ± 1974.73, 80.81 ± 13.72, 3161.89 ± 2146.07, and $7240.52 \pm 5461.4\,pg\,ml^{-1}$, respectively.

Relationship between PTX3 level and treatment outcome. For comparison of the clinical parameters associated with PTX3 level, the patients were divided into two groups: a group of patients with a PTX3 level $\geqslant 4.94\,ng\,ml^{-1}$, referred to as the $PTX3^{high}$ group ($n = 22$), and a group with a PTX3 level $< 4.94\,ng\,ml^{-1}$, referred to as the $PTX3^{low}$ group ($n = 56$). The median PFS of the $PTX3^{high}$ group was 76 days (95% confidence interval (CI), 43–109) and that of the $PTX3^{low}$ group was 150 days (95% CI, 131–197; log-rank test, $P = 0.002$; Figure 3A). The median OS of the $PTX3^{high}$ group was 117 days (95% CI, 82–152) and that of the $PTX3^{low}$ group was 357 days (95% CI, 239–475; log-rank test, $P < 0.001$; Figure 3B).

Placement in the $PTX3^{high}$ group was found to be significantly associated with advanced clinical stage ($P < 0.01$), poor PS (PS2, $P = 0.01$), and elevated CRP level (over $1.0\,mg\,dl^{-1}$, $P < 0.01$). The results of the univariate Cox regression analysis indicated that high PTX3 level and/or high CRP level is significantly associated with poor OS (hazard ratio (HR), 4.80; 95% CI, 2.62–8.78; $P < 0.001$ and HR, 6.56; 95% CI, 3.32–12.96; $P < 0.001$, respectively). The results of univariate analysis indicated that clinical stage (IV + recurrence *vs* III), PS (2 *vs* 0 + 1), histological differentiation (poorly differentiated *vs* not poorly differentiated), CA19-9 level (> 3000 *vs* $< 3000\,U\,ml^{-1}$), and IL-6 level ($IL\text{-}6^{high}$ *vs* $IL\text{-}6^{low}$) are significantly associated with improved OS (Table 2), whereas age, gender, and levels of several pro-inflammatory mediators (IL-1beta, CCL2, CCL3, CCL4, CCL7, CXCL9, and MIF) are not. Subsequent multivariate Cox regression analysis indicated that CRP level (CRP^{high} *vs* CRP^{low}; HR 2.59, 95% CI 1.05–6.36, $P = 0.04$), and PTX3 level ($PTX3^{high}$ *vs* $PTX3^{low}$; HR 3.00, 95% CI 1.47–6.14, $P = 0.003$) are independent prognostic variables (Table 2). Taken together, these results suggest that members of the pentraxin family, particularly PTX3, may be predictive biomarkers in the prognosis of human pancreatic carcinoma in the clinical setting.

Relationship between PTX3 level and expression of pro-inflammatory mediators. Examination of the relationship between PTX3 expression and the expression of other pro-inflammatory mediators using Spearman's rank correlation coefficient analysis indicated that PTX3 level is positively correlated with level of CRP ($r = 0.56$, $P < 0.001$), IL-6 ($r = 0.59$, $P < 0.001$), and MIF ($r = 0.38$, $P = 0.001$; Table 3).

Table 1. Patient demographic and clinical characteristics

	PTX3 group (number of patients)			
	$PTX3^{high}$ group	$PTX3^{low}$ group	Total	*P*-value*
Age (years)				
Over 70	7	21	28	0.79
Below 70	15	35	50	
Sex				
Male	15	27	42	0.14
Female	7	29	36	
Stage				
III	1	24	25	0.005
IV	19	28	47	
Recurrence	2	4	6	
ECOG PS score				
0	7	37	44	0.01
1	13	14	27	
2	2	5	7	
Histology				
Well differentiated	0	1	1	0.12
Poorly differentiated	7	24	31	
Moderately differentiated	12	15	27	
Adenosquamous	1	1	2	
NE (cytology only)	2	15	17	
Tumour response				
Partial response	2	3	5	0.29
Stable disease	9	34	43	
Progressive disease	10	17	27	
NE	0	3	3	
CA19-9 ($U\,ml^{-1}$)				
Over 10 000	11	24	35	0.62
Below 10 000	11	32	43	
CRP ($mg\,dl^{-1}$)				
Over 1.0	12	10	22	0.002
Below 1.0	10	46	56	

Abbreviations: CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NE = not evaluable; PTX3 = pentraxin 3. *P-values calculated using χ^2 statistics.

DISCUSSION

The findings of the present study provide the first evidence of the clinical importance of PTX3 expression as a prognostic factor in pancreatic carcinoma due to its involvement in cancer cell behaviour. Specifically, several pancreatic carcinoma cell lines

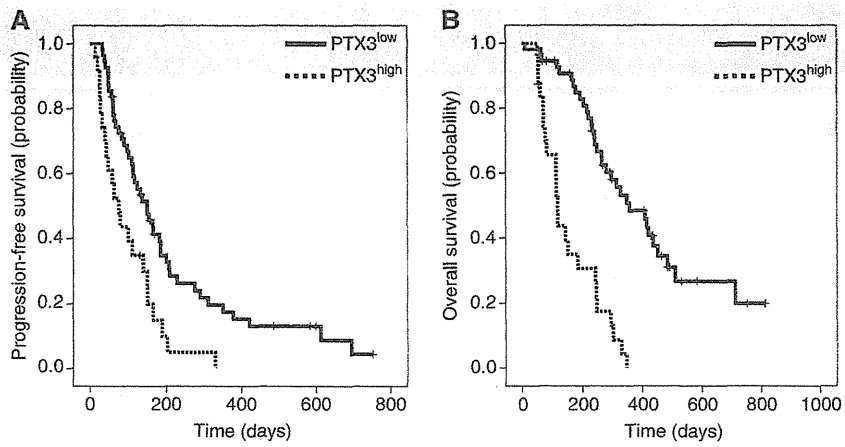

Figure 3. Kaplan–Meier curves for (**A**) progression-free survival according to blood-PTX3 level and (**B**) overall survival according to blood-PTX3 level. Cutoff points for PTX3 level were based on mean PTX3 level.

Table 2. Results of univariate and multivariate analyses

	HR	95% CI	*P*-value*
Univariate analysis			
Age: over 70 *vs* below 70	1.16	0.66–2.05	0.61
Gender: male *vs* female	1.12	0.85–1.47	0.41
Stage: IV + recurrence *vs* III	1.93	1.05–3.56	0.03
ECOG PS score: 0 + 1 *vs* 2	3.42	1.40–8.37	0.007
Histology: poorly differentiated *vs* not poorly differentiated	2.34	1.34–4.12	0.003
CA19-9 (U ml^{-1}): over 10 000 *vs* below 10 000	1.96	1.12–3.44	0.02
CRP (mg dl^{-1}): over 1.0 *vs* below 1.0	6.56	3.32–12.96	<0.001
PTX3: PTX3^{high} *vs* PTX3^{low}	4.80	2.62–8.78	<0.001
IL-6: IL-6 ^{high} *vs* IL-6^{low}	7.72	3.88–15.35	<0.001
IL-1beta: IL-1beta^{high} *vs* IL-1beta^{low}	0.84	0.48–1.47	0.84
CCL2: CCL2^{high} *vs* CCL2^{low}	1.40	0.79–2.45	0.25
CCL3: CCL3^{high} *vs* CCL3^{low}	1.57	0.92–2.68	0.10
CCL4: CCL4^{high} *vs* CCL4^{low}	1.15	0.64–2.06	0.65
CCL7: CCL7^{high} *vs* CCL7^{low}	1.08	0.62–1.88	0.79
CXCL9: CXCL9^{high} *vs* CXCL9^{low}	1.51	0.87–2.63	0.15
MIF: MIF^{high} *vs* MIF^{low}	1.21	0.70–2.09	0.50
Multivariate analysis			
Stage: IV + recurrence *vs* III	1.14	0.42–2.37	0.72
ECOG PS: 0 + 1 *vs* 2	2.11	0.71–6.25	0.18
Histology: poorly differentiated *vs* not poorly differentiated	1.19	0.60–2.38	0.62
CA19-9 (U ml^{-1}): over 10 000 *vs* below 10 000	1.52	0.84–2.74	0.16
CRP (mg dl^{-1}): over 1.0 *vs* below 1.0	2.59	1.06–6.36	0.04
PTX3: PTX3^{high} *vs* PTX3^{low}	3.00	1.4–6.14	0.003
IL-6: IL-6 ^{high} *vs* IL-6^{low}	2.57	1.00–6.59	>0.05

Abbreviations: CCL = chemokine (C-C motif) ligand; CI = confidence interval; CRP = C-reactive protein; CXCL = chemokine (C-X-C motif) ligand; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; IL = interleukin; MIF = macrophage-migration-inhibitory factor; PTX3 = pentraxin 3; *P-values calculated using the Cox proportional hazards model.

were observed to secrete PTX3 to a remarkable extent, with expression of extracellular PTX3 promoting pancreatic carcinoma cell migration in a concentration-dependent, highly efficient manner and expression of transformants of PTX3 promoting migration in a less-efficient manner. Supporting this observation, evaluation of clinical blood samples of pancreatic carcinoma patients revealed a strong correlation between blood-PTX3 level and prognosis of the disease.

PTX3 is known to be produced by a variety of cells at the site of infection or inflammation, including macrophages, dendritic cells (Doni *et al*, 2003), neutrophils (Jaillon *et al*, 2007), endothelial cells (Norata *et al*, 2008), epithelial cells (Han *et al*, 2005), fibroblasts (Doni *et al*, 2008), and vascular smooth muscle cells (Klouche *et al*, 2004). In human liposarcomas, increased levels of PTX3 RNA and intracellular PTX3 have been detected (Willeke *et al*, 2006), whereas elevated levels of serum PTX3 have been observed in patients with lung cancer (Diamandis *et al*, 2011) and prostate cancer (Sardana *et al*, 2008). In the present study, detection of the direct secretion of extracellular PTX3 by several pancreatic carcinoma cell lines indicated the existence of a PTX3 autocrine–paracrine loop that regulates angiogenesis and stromal cell activity.

Table 3. Relationship between PTX3 level and levels of other immunological factors

	Average (SD)	CRP	PTX 3	IL-6	IL-1beta	CCL 2	CCL 3	CCL 4	CCL 7	CXCL 9	MIF
CRP (mg dl^{-1})	1.57 (3.06)		*r= 0.56 P<0.001	0.71 <0.001	0.25 0.03	0.13 0.26	0.10 0.40	0.04 0.73	0.03 0.77	0.31 <0.01	0.28 0.01
PTX3 (ng ml^{-1})	4.94 (3.63)	0.56 <0.001		0.59 <0.001	0.19 0.09	0.17 0.15	−0.04 0.71	0.07 0.56	0.15 0.21	0.16 0.17	0.38 0.001
IL-6 (pg ml^{-1})	294.38 (516.6)	0.71 <0.001	0.59 <0.001		0.44 <0.001	0.31 <0.01	0.27 0.02	0.31 <0.01	0.18 0.12	0.29 0.01	0.43 <0.001
IL-1beta (pg ml^{-1})	95.48 (37.62)	0.25 0.03	0.19 0.09	0.44 <0.001		0.44 <0.001	0.11 0.35	0.50 <0.001	0.25 0.03	0.01 0.91	0.70 <0.001
CCL2 (pg ml^{-1})	746.58 (518.12)	0.13 0.26	0.17 0.15	0.31 <0.01	0.44 <0.001		0.21 0.06	0.43 <0.001	0.10 0.37	0.24 0.03	0.08 0.47
CCL3 (pg ml^{-1})	177.80 (58.40)	0.10 0.40	−0.04 0.71	0.27 0.02	0.11 0.35	0.21 0.06		0.29 <0.01	0.04 0.73	0.06 0.60	−0.11 0.36
CCL4 (pg ml^{-1})	2886.28 (1974.73)	0.04 0.73	0.07 0.56	0.31 <0.01	0.50 <0.001	0.43 <0.001	0.29 <0.01		−0.005 0.96	0.03 0.80	0.34 <0.01
CCL7 (pg ml^{-1})	80.81 (13.72)	0.03 0.77	0.15 0.21	0.18 0.12	0.25 0.03	0.10 0.37	0.04 0.73	−0.005 0.96		0.15 0.20	0.40 <0.001
CXCL9 (pg ml^{-1})	3161.89 (2146.07)	0.31 <0.01	0.16 0.17	0.29 0.01	0.01 0.91	0.24 0.03	0.06 0.60	0.03 0.80	0.15 0.20		003 0.77
MIF (pg ml^{-1})	7240.52 (5461.40)	0.28 0.01	0.38 0.001	0.43 <0.001	0.70 <0.001	0.08 0.47	−0.11 0.36	0.34 <0.01	003 0.77	0.40 <0.001	

Abbreviations: CCL = chemokine (C-C motif) ligand; CRP = C-reactive protein; CXCL = chemokine (C-X-C motif) ligand; IL = interleukin; MIF = macrophage-migration-inhibitory factor; PTX3 = pentraxin 3. *r and P-values calculated using Spearman's rank correlation coefficient analysis.

Known to be a soluble recognition receptor, PTX3 binds to selected pathogens and has a non-redundant protective role against these pathogens as part of an innate immunological response. PTX3 also interacts with other biologically active molecules, such as fibroblast growth factor-2 (FGF2; Camozzi *et al*, 2006), to suppress FGF2-mediated cell-migration angiogenesis (Basile *et al.*, 2013). In androgen-regulated breast cancer cells, PTX3 inhibits FGF8-driven cell proliferation (Leali *et al*, 2011). In contrast, PTX3 promotes VEGF-stimulated migration of pancreatic carcinoma cells, although exerting no influence on VEGF-dependent angiogenesis and cell migration and not interacting with VEGF (Basile *et al*, 2013).

Invasion of malignant cells was found to result in increased levels of inflammatory mediators, such as TNF-alpha, IL-1beta, and IL-6, that increase the ability of malignant cells to infiltrate, migrate, and metastasise, possibly as a result of the upregulation of chemokine-receptor expression elicited by these mediators (Mantovani *et al*, 2008). The results of this study indicate that direct PTX3 stimulation promotes pancreatic carcinoma cell-migration activity. This finding and that of the present study, specifically that high PTX3 level is significantly correlated with a more advanced stage of pancreatic cancer, indicates that PTX3 acts as a mediator of inflammation that has a tumour-promoting effect in pancreatic carcinoma cells. In a previous study, PTX3 expression was found to be higher in high-Gleason-grade prostate tumour tissue compared with contralateral prostate lobes, possibly in association with pro-inflammatory and repair-process activation (Ravenna *et al*, 2009). Similar results have been reported for

human mammary-invasive carcinoma in association with hypoxia-driven HIF-1α and NF-κB activation (Tafani *et al*, 2010). These findings, along with the knowledge that pro-inflammatory signals upregulate PTX3 expression in different mesenchymal and epithelial cell types (Garlanda *et al*, 2005), suggest that PTX3 has a role in tumour activation, invasion, and migration in some types of cancer. On the other hand, some results suggest that PTX3 expression is silenced in cancer cells at a relatively early stage of tumour progression in parallel with hypoxia- or inflammation-driven cytokine production by stromal components and inflammatory cell infiltrates. To clarify these contradictory findings and determine the true nature of the effect of PTX3 expression on cancer cells, further studies are required.

Previous studies of advanced pancreatic carcinoma patients have found median OS to be 8–12 months for patients who present with locally advanced unresectable disease but only 3–6 months for those who present with metastases or recurrent pancreatic carcinoma. Several studies of advanced pancreatic carcinoma patients who have undergone gemcitabine monotherapy reported that median OS after treatment ranged from 5.4 to 7.2 months (Burris *et al*, 1997; Berlin *et al*, 2002; Herrmann *et al*, 2007). In the present study, the median OS of patients with high PTX3 levels was remarkably brief, found to be only 117 days. Other well-known prognostic factors in pancreatic carcinoma patients are elevated serum level of CA19-9, a widely used prognostic marker and indicator of disease activity (Ueno *et al*, 2000; Berger *et al*, 2008; Tanaka *et al*, 2008; Morizane *et al*, 2011), and elevated CRP level, which is likely to be part of the systemic inflammatory response to tumour development. Activation of CRP has also been linked to cancer cachexia, characterised by malnutrition and an accelerated starvation state, and shorter OS (Ebrahimi *et al*, 2004). Despite the importance of these factors, the findings of this study indicate that elevated PTX3 level is associated with more advanced disease and poorer PS, and is therefore a more useful neo-factor in prognosis than CA19-9 and CRP in pancreatic carcinoma patients.

Pro-inflammatory mediators are frequently expressed in the tumour microenvironment after they have infiltrated leukocyte, stromal, and cancer cells (DeNardo *et al*, 2008; Mantovani *et al*, 2008). Several mediators, such as IL-1beta, enhance the production of PTX3 elicited by inflammatory signalling (Polentarutti *et al*, 1998), whereas others, such as IL-6, CCL2, and interferon-gamma, have negligible effects on PTX3 expression (Alles *et al*, 1994; Polentarutti *et al*, 1998). Previous studies have found PTX3 levels to be correlated with CRP, IL-6, and elevated levels of MIF, which are known to control autonomous properties of tumour cells, such as proliferation, apoptosis, DNA-damage response, senescence, and invasion (Dessein *et al*, 2010), in the tumour and serum of pancreatic cancer patients (Winner *et al*, 2007).

In consideration with these findings, the present study aimed to clarify the profile of these mediators in pancreatic carcinoma patients and the correlations among them. Although this study yielded significant findings, it was limited by several phenomena, for instance the insufficient insolubility of the mechanism between each mediator and the inability to examine the intricate interrelations among the inflammatory mediators of cancer patients, each of which has multiple roles in various tumorigenic behaviours.

In conclusion, the results of this study provide strong evidence that elevated levels of pentraxin family members, especially PTX3, are associated with poor prognosis in pancreatic carcinoma patients. Expression of PTX3 appears to be a promising biomarker for pancreatic carcinoma prognosis. However, the mechanism of tumour inflammation and exact nature of the role of PTX3 expression remains unclear, calling for investigation of the mechanisms underlying PTX3 activity in carcinoma cells and the tumour environment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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特集　膵がん治療の新たな展開

膵がんに対する術後補助療法のエビデンスと今後の展望*

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Key Words: pancreatic cancer, adjuvant therapy, chemotherapy, chemoradiotherapy, gemcitabine

はじめに

膵がんにおいて，根治を期待できる唯一の治療が切除術であるが，早期発見が困難ながん腫なため，診断時に約80％が切除不能進行例である．また切除例においても高率に再発をきたすため，術後の5年生存割合は10から20％程度[1)~3)]にとどまる．そのため，治療成績向上をめざし，術後補助療法として化学療法，化学放射線療法などの集学的な治療が試みられ，術後補助療法による生存割合の向上が報告されている．

本稿では，術後補助療法について今までに報告された研究，現在進行中の研究を中心にレビューし，今後の展望を考察する．

背　景

膵がんは近年増加傾向にあり，本邦の人口動態統計では，2011年に約2万9千人が膵がんで死亡している(男性5位，女性4位)[4)]．

膵腫瘍は組織学的には，外分泌腫瘍と内分泌腫瘍とに分けられ，さらに外分泌腫瘍は嚢胞腫瘍，膵管内腫瘍，異型性過形成および上皮内がん，浸潤性膵管がん，腺房細胞腫瘍に細分される．膵がんの約90％は浸潤性膵管がんであり，その中でも最も頻度が高い組織型は管状腺がんである．

膵がん患者によくみられる自覚症状には腹痛や背部痛，食欲不振，体重減少，黄疸などがあるものの，膵がんに特異的な症状ではないため，画像診断の進歩がみられた現在でも早期診断が困難である．診断の時点で切除不能な進行がんの状態が多いことや，切除可能な状態で発見され切除術を受けても80％前後が再発をきたすことから，膵がんの予後は不良である．

Stage別の予後としては，Stage I～IIでは生存期間中央値：16.4～36か月，5年生存割合：16.6～45.2％，stage IIIでは生存期間中央値：12.5か月，5年生存割合：7.3％，stage IVでは生存期間中央値：7.8か月，5年生存割合：3.5％と報告されている[5)6)]．

術後補助療法

前述したように，膵がんでは切除術を受けた場合でも高率に再発し，術後の5年生存割合は10から20％程度と不良である．そのため，治療成績向上をめざし，補助療法として術後に放射線療法や化学療法などの集学的治療が試みられてきた．

* Current status and future prospects of adjuvant therapy for resected pancreatic cancer.

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表1　膵がん術後補助化学放射線療法に関する第III相試験

試験名	報告年	術後補助療法	患者数	無再発生存期間中央値(月)	全生存期間中央値(月)	2年生存割合(%)	P値(log-rank)	備考
GITSG9173[7]	1985	5-FU併用放射線療法	21	11	20	43	0.035	
		経過観察のみ	22	9	11	18		
EORTC40891[8]	1999	5-FU併用放射線療法	104(60)	17.4	24.5(17.1)	51(37)	0.208	乳頭部領域がんを含む
		経過観察のみ	103(54)	16	19.0(12.6)	41(23)	(0.099)	( )は膵頭部がんのみ
ESPAC-1[1]	2004	5-FU併用放射線療法あり	145	10.7	15.9	29	0.053	
		5-FU併用放射線療法なし	144	15.2	17.9	41		

1．術後補助化学放射線療法

1985年に米国のGastrointestinal Tumor Study Group(GITSG)から，膵がん術後に5-FU併用放射線療法を受けた患者群のほうが経過観察のみの群よりも有意に生存期間が優れていたことを示す小規模な第III相試験が報告[7]された．以降，現在にいたるまで，米国では術後補助化学放射線療法が標準的な補助療法として認識され，実臨床で実施されている．しかし，その後欧州で行われた2つの第III相試験では，いずれも術後補助化学放射線療法の延命効果を証明することはできなかったため，国際的なコンセンサスは得られていない．以下に主な術後補助化学放射線療法(表1)を概説する．

GITSG9173試験は，術後補助療法の有効性を最初に報告したランダム化比較試験である．1974年から1982年までかけて49例を，術後5-FU併用放射線療法(5-FU＋RT)と手術単独群に分けて比較したもので，中間解析で生存期間に有意差を認めたため有効中止されている．この試験では5-FU＋RT後に2年間の維持化学療法(5-FU)を継続するプロトコールであったため，予後向上が術後補助化学放射線療法によるものか維持化学療法によるものか疑問が残る試験であったこと，また症例集積に長時間を要し，予定症例の半分以下の症例登録で中止されているなど試験自体に質の問題があったことから，解釈が分かれる試験であった．

これに対し，欧州においてEuropean Organization for Research and Treatment of Cancer(EORTC)1987年から1995年にかけて218例を対象に，維持化学療法を行わず5-FU＋RTによる術後補助化学放射線療法群と手術単独群を比較するEORTC40891試験が実施された[8]．結果としては，両群に生存期間の有意差は認められず(生存期間中央値：17.1か月 vs. 12.6か月，2年生存割合：37% vs. 23%，$P=0.099$)，術後補助化学放射線療法の意義は証明されなかった．一方，この試験では対象に乳頭部領域がんを含んでおり，膵がんのサブグループでは生存曲線が術後補助化学放射線療法群のほうが良好に推移していたことから，試験としてunderpoweredであったという意見もある．

さらに，欧州にて1994年から2000年までに289例を対象に，術後補助療法として化学療法，または化学放射線療法の有効性を検討するEuropean Study Group for Pancreatic Cancer-1(ESPAC-1)試験が実施された[1]．この試験では，対象患者を手術単独群，5-FUを用いた術後補助化学放射線療法群，5-FU＋ロイコボリン(LV)による術後補助化学療法群，術後補助化学放射線療法→化学療法群の4群に割り付け，2×2 factorial designによって，それぞれ化学放射線療法と化学療法の有無による予後の違いが検討された．その結果，化学放射線療法を含む治療を受けた群の生存期間は同治療を受けなかった群に対して劣っていた(生存期間中央値：15.9か月 vs. 17.9か月，$P=0.053$)が，化学療法を含む治療を受けた群は同治療を受けなかった群よりも有意に良好(生存期間中央値：20.1か月 vs. 15.5か月，$P=0.009$)であった．

これらの結果から，その後の術後補助療法の

表2 膵がん術後補助化学療法に関する第III相試験

試験名	報告年	術後補助療法	患者数	無再発生存期間中央値(月)	全生存期間中央値(月)	2年生存割合(%)	P値(log-rank)	備考
Bakkevoldら[9]	1993	ADR+MMC+5-FU	31	NA	23	43	0.02	
		経過観察のみ	30	NA	11	32		
Takadaら[10]	2002	5-FU+MMC	81	NA	12.8	24.2	NS	
		経過観察のみ	77	NA	12.4	29.6		
ESPAC-1[1]	2004	5-FU+LVあり	147	15.3	20.1	40	0.009	
		5-FU+LVなし	142	9.4	15.5	30		
JSAP-01[11]	2006	5-FU+CDDP	45	8.6	12.5	NA	0.94	
		経過観察のみ	44	10.2	15.8	NA		
CONKO-001[2][12]	2007	GEM	179	13.4	22.8	48.5	0.045	
		経過観察のみ	175	6.9	20.2	40.0		
JSAP-02[3]	2009	GEM	58	11.4	22.3	48.3	0.19	
		経過観察のみ	60	5.0	18.4	40.0		
RTOG9704[13]	2008	5-FU併用放射線療法+GEM	221 (187)	NA (11.4)	18.8 (20.5)	NA	0.15	( )膵頭部がんのみ
		5-FU併用放射線療法+5-FU	230 (201)	NA (5.0)	16.9 (16.9)	NA	(0.09)	
ESPAC-3[14]	2010	GEM	537	14.3	23.6	49.1	0.39	
		5-FU+LV	551	14.1	23.0	48.1		
JASPAC-1[15][16]	2013	S-1	187	23.2	NA	70	<0.0001	
		GEM	191	11.2	25.9	53		

NA：not available

開発は，米国では化学放射線療法を，欧州では化学療法をベースに進められていくこととなった．

2．術後補助化学療法

術後補助化学療法に関しては，欧州や本邦で研究が進められており，近年いくつかの第III相試験が報告された(表2)．それらの中で，5-FUを用いた術後補助化学療法に関しては，症例数の少ない第III相試験では明らかな延命効果は証明されなかったものの[9)~11)]，欧州で行われたESPAC-1(前述)では5-FU+LVによる術後補助化学療法を受けた群は受けなかった群よりも生存期間が有意に長かったことが示された．ESPAC-1は膵がん補助療法の第III相試験としては大規模であり，試験デザインの複雑さなどの批判はあるものの，切除患者に対する補助化学療法の延命効果を初めて示した試験として評価されている．

一方，進行膵がんでは標準薬となっているゲムシタビンは，術後補助療法としての有用性を示す第III相試験が2000年後半に相次いで報告された．まず2007年にドイツから，Charite Onkologie-001(CONKO-001)試験が報告[2)]された．この試験では，1998年から2004年に膵がん切除患者368例が登録され，術後ゲムシタビンの投与は経過観察のみよりも無再発生存期間を有意に延長(無病生存期間中央値：13.4か月 vs. 6.9か月，$P<0.001$)することが確認された．2007年時点で生存期間に関しては有意差が証明されなかった(生存期間中央値：22.1か月 vs. 20.2か月，5年生存率：22.5% vs. 11.5%，$P=0.06$)が，ゲムシタビン群で優れた傾向にあったことが示された．その後2008年に長期フォローアップ後の解析結果が報告され，生存期間に関してもゲムシタビンが経過観察よりも有意に優れていたことが示された(生存期間中央値：22.8か月 vs. 20.2か月，5年生存割合：21.0% vs. 9.0%，$P=0.045$)[12)]．

また，本邦でJapanese Study Group of Adjuvant Therapy for Pancreatic Cancer-02(JSAP-02)試験により，術後補助療法におけるゲムシタビンの有効性が検討され，2009年にその結果が報告された[3)]．2002年から2005年までに119例が登録され，CONKO-001試験と同様にゲムシタビン群の無病生存期間は手術単独群よりも有意に良好で

表3　進行中の膵がん術後補助化学療法に関する第III相試験

試験名	相	術後補助療法	治療期間	患者数	登録開始
ESPAC-4(Europe)	III	GEM vs. GEM＋CAP	6か月	1,396	2008/04
CONKO-005(Germany)	III	GEM vs. GEM＋elrotinib	6か月	436	2008/02
JSAP-04(Japan)	III	GEM vs. GEM＋S-1	6か月	300	2010/11
Prodige/Accord 24(France)	III	GEM vs. mFOLFIRINOX	6か月	490	2012/01
HEAT(Germany)	III	GEM vs. GEM/CDDP＋hyperthermia	6か月	336	2012/03

あること(無病生存期間中央値：11.4か月 vs. 5.0か月，P=0.01)が示された．生存期間については有意な差は認めなかったが，ゲムシタビン群に良好な傾向が示された(生存期間中央値：22.3か月 vs. 18.4か月，5年生存割合：26.4% vs. 14.9%，P=0.19)．

これらの試験にて5-FUやゲムシタビンを用いた術後補助化学療法の効果が示されたため，さらに5-FUとゲムシタビンを比較した第III相試験が実施された．米国で行われたRTOG9704では，1998年から2002年に451例が登録され，いずれの群に対しても術後の5-FU併用放射線療法を行い，その前後に5-FUを投与した群とゲムシタビンを投与した群を比較した[13]．その結果，全登録患者を対象とした解析では差は認められなかった(生存期間中央値：18.8か月 vs. 16.9か月，P=0.15)が，膵頭部がんのみを対象とした解析ではゲムシタビンの方が5-FUよりよい傾向にあること(生存期間中央値：20.5か月 vs. 16.9か月，P=0.09)が示された．

2010年には，術後補助化学療法としての5-FU＋LVとゲムシタビンを比較する第III相試験(ESPAC-3)が報告[14]された．ESPAC-3では，2000年から2007年までに切除後の膵がん患者が1,088人登録され，術後補助化学療法として5-FU＋LVとゲムシタビンとの比較検討が行われた．この結果，5-FU＋LV群とゲムシタビン群の生存曲線に差は認められなかった(生存期間中央値：23か月 vs. 23.6か月，2年生存割合：48.1% vs. 49.1%，P=0.39)が，下痢などの重篤な有害事象はゲムシタビン群の方が少なく安全性が高いことが示唆された．

これらの結果に基づき米国以外ではゲムシタビンを用いた術後補助化学療法が，米国では化学放射線療法とゲムシタビンが日常診療の主軸となった．またゲムシタビンは，臨床試験のcontrol armとして位置づけられ，2000年後半からの研究はいずれも術後補助ゲムシタビンを上回る術後補助化学療法の開発をめざし，さまざまなランダム化比較試験が行われている(表3)．

その中から，本邦で行われていた術後補助化学療法としてゲムシタビンとS-1の第III相試験(Japan Adjuvant Study Group of Pancreatic Cancer-01：JASPAC-01)の中間解析の結果が2013年の米国臨床腫瘍学会(ASCO)Gastrointestinal Cancers Symposiumにて報告[15]された．その結果，ゲムシタビン群に対して，S-1群の生存期間における非劣性が証明されたばかりではなく，さらにS-1群の成績が大きく上回っていたことが示された(ハザード比0.56%，2年生存割合：53% vs. 70%，P<0.0001)．同年のASCO総会では，サブセット解析やquality of life(QOL)解析の結果が追加されたが，いずれもS-1群で良好な結果であった[16]．このJASPAC-01の結果を受けて，本邦では今後，術後補助化学療法としてS-1が標準治療になり，また日本での治療開発はS-1がcontrol armとして採用されるものと考えられる．

なお，術後補助化学療法の至適投与期間に関する研究はなく，明確なエビデンスはない．今まで報告されている主な術後補助化学療法に関する第III相試験(CONKO-001やESPAC-1，ESPAC-3，JASPAC-01)にて治療期間が約6か月に設定されていたことから，一般臨床でも6か月前後の補助化学療法を行うことが多い．

以上，膵がん切除患者の補助療法に関しては，放射線療法に対する欧米の見解の相違があり国際的な標準治療は確立していないが，術後補助化学療法のエビデンスレベルは高く，世界的に広く支持されているといえる．

今後の治療展開

1．さらなる治療開発

ゲムシタビンが術後補助化学療法の日常診療の主軸となり，臨床試験のcontrol armと位置づけられたことから，現在多くのランダム化比較試験がゲムシタビンを上回る術後補助化学療法の開発を目指して行われている(表3)

その一つであるJASPAC-01試験については前述したとおりであるが，その他切除不能膵がんにおいて良好な成績を示したゲムシタビン併用療法，またFOLFIRINOXが試験治療として設定したランダム化比較試験が行われている．具体的には海外で，ゲムシタビンとカペシタビンの併用療法とゲムシタビン単独療法を比較するESPAC-4試験，ゲムシタビンとエルロチニブの併用療法とゲムシタビン単独療法を比較するCONKO-005試験，FOLFIRINOXとゲムシタビンを比較するProdige/Accord 24試験などの第III相試験が現在進行している．本邦では，術後のゲムシタビンに対するゲムシタビンとS-1併用療法の優越性を検証するJSAP-04がリクルートを終了し，現在追跡期間に入っている．

化学放射線療法については，補助療法としての意義は定まっていないが，R1症例に対しては術後補助化学療法に比較し成績が良好な傾向があるとするメタ解析[17]がある．そのため，高い局所コントロールを期待して化学放射線療法を組み込む治療戦略が検討されている．具体的には術後補助療法としてまず化学療法を先行して行い，早期に遠隔転移再発をきたすなどの予後不良例には放射線療法を回避し，放射線治療の局所コントロールで予後の向上が期待される症例にのみに絞って化学放射線療法を追加する戦略である．EORTC-40013[18]，PACT-7[19]といった探索的な試験が報告されているが，現在米国にて大規模な第III相試験(RTOG-0848試験)での検証が進められている．

2．バイオマーカー

今後，術後補助化学療法の選択肢が増えていくことが予想されるなかで，まだ前向きに検証されてはいないが，バイオマーカーを用いた治療内容の選択についても期待されている．

ゲムシタビンを細胞内へ輸送するtransporterのうちの主要な役割を果たすhuman equilibrative nucleoside transporter 1(hENT1)の発現が低い群において，治療成績が不良であることが，RTOG9704試験やESPAC-3試験といった第III相試験の付随研究の結果[20)21)]から報告されている．またCONKO-001試験の付随研究にて，術後補助ゲムシタビンを受けた患者ではsecreted protein acidic and rich in cysteine(SPARC)の高発現している群の予後が不良であることが報告[22)]されている．hENT1低発現群やSPARC高発現群ではゲムシタビンの効果が得られない可能性が示唆されており，これらの患者に対してはフッ化ピリミジン系薬剤を使用することが予後延長に寄与する可能性がある．

その他，*Smad4 (Dpc4)*発現の低下やchemokine receptor 4(CXCR4)の高発現を認める膵がんは遠隔転移による増悪をきたすものが多く，逆に*Smad4*正常発現やCXCR4低発現であれば局所増悪を主体とすることが多いと報告[23)~25)]されており，前者では補助療法として化学療法を選択し，後者であれば化学放射線療法を選択するといった戦略が考えられる．

おわりに

現在，補助療法としてのエビデンスがあるのは術後補助化学療法のみである．しかしながら，有効な化学療法のレジメンが限られており，術後に化学療法を行うだけでは限界がくるものと考えられる．今後は違うアプローチとして，バイオマーカーによる治療戦略の構築や，他の周術期補助療法(術前補助療法など)の研究が行われ，より有効な集学的治療の開発が進められていくことを期待したい．

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Ⅱ　抗癌薬各論

8. 胆管癌・膵癌の薬物療法
a) 切除不能・再発癌*

森実千種　奥坂拓志　上野秀樹　林　秀幸**

Ⅰ. 切除不能・再発胆道癌の全身化学療法

Union for International Cancer Control (UICC) / TNM分類や日本の癌取扱い規約では肝外胆管癌，胆嚢癌，Vater膨大部癌が胆道癌に，肝内胆管癌は原発性肝癌に分類されるが，薬物療法をはじめとする内科的治療を考える際には，肝内胆管癌も胆道癌に含められることが多い．2009年の米国臨床腫瘍学会（ASCO）で報告された進行胆道癌に対するgemcitabine（GEM）療法とcisplatin（CDDP）＋GEM療法の第Ⅲ相試験（ABC-02試験）の結果CDDP＋GEM療法の生存期間における優越性が示された[1]〔ハザード比（HR）0.68，95％信頼区間（CI）0.53～0.86，GEM群対CDDP＋GEM群の生存期間中央値8.3ヵ月対11.7ヵ月，$p=0.002$〕（図1）．日本でもGEM療法とCDDP＋GEM療法のランダム化第Ⅱ相試験（BT22試験）が行われ，プライマリーエンドポイントである1年生存割合はGEM療法群で31.0％，CDDP＋GEM療法群で39.0％と併用療法群で良好であった[2]．これらの結果を受けて，国内外問わずCDDP＋GEM療法が標準治療として日常診療で多用されている．日本では2012年2月にCDDPの胆道癌の効能追加が承認された．

投与スケジュールは図2に示すとおりである．CDDP＋GEM療法では腎障害予防のため，1*l*以上の補液を行う．CDDPは繰り返し投与することで（総投与量250～500 mg/m^{2}より）蓄積性に末梢神経障害や腎障害のリスクが上昇することが知られており，治療が長期化する場合はこれらの有害事象の出現に十分注意しながら治療を行う．嘔気対策としては，ASCOやNational Comprehensive Cancer Network（NCCN）のガイドラインによるとCDDPを用いているためhigh riskレジメンに該当し[3,4]，aprepitant，dexamethasone，5HT3受容体拮抗薬の予防投与が推奨されるが，胆道癌に対して用いられるCDDPの1回投与量が25 mg/m^{2}と比較的少ないことから，そこまでの制吐薬が必要でない場合も多い．

現在胆道癌の分野でも分子標的薬に対する関心は高まっており，上皮増殖因子受容体（EGFR）阻害薬であるcetuximab，erlotinib，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，MEK阻害薬であるselumetinibなど，いくつかの分子標的治療薬に関する臨床試験結果が報告されている．しかし現時点では進行胆道癌に対して有効性が証明された分子標的治療薬はなく，今後の開発に期待したい．

Ⅱ. 切除不能・再発膵癌の全身化学療法

1996年以前は，進行膵癌に対する化学療法の延命効果は明らかにされておらず，標準治療は存在していなかったが，fluorouracil（5-FU）vs GEMの第Ⅲ相試験でGEMの延命効果と症状緩和効果

キーワード：胆道癌，膵癌，gemcitabine，cisplatin，S-1

* Systemic chemotherapy for advanced biliary tract cancer and pancreatic cancer

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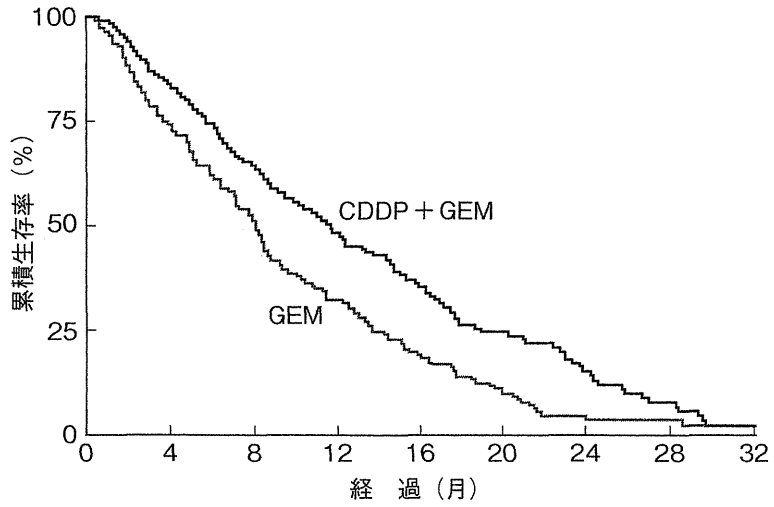


No. at risk

GEM	206	151	97	53	28	15	4	3	2
CDDP＋GEM	204	167	120	76	51	28	17	8	2

	CDDP＋GEM	GEM
全生存期間中央値	11.7ヵ月	8.1ヵ月
無増悪生存期間中央値	8.0ヵ月	5.0ヵ月
奏効率	25.5％	19.5％

図1. 進行胆道癌に対するGEM療法とCDDP＋GEM療法の第Ⅲ相試験（ABC-02試験）における両群の生存曲線（文献1より引用改変）

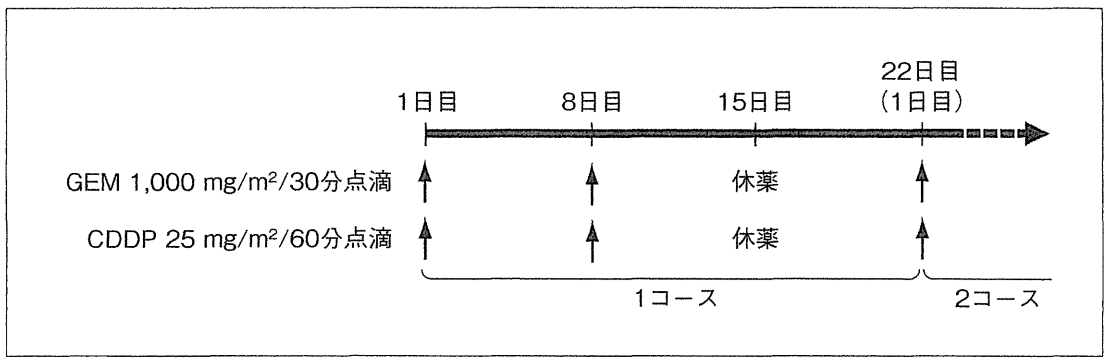
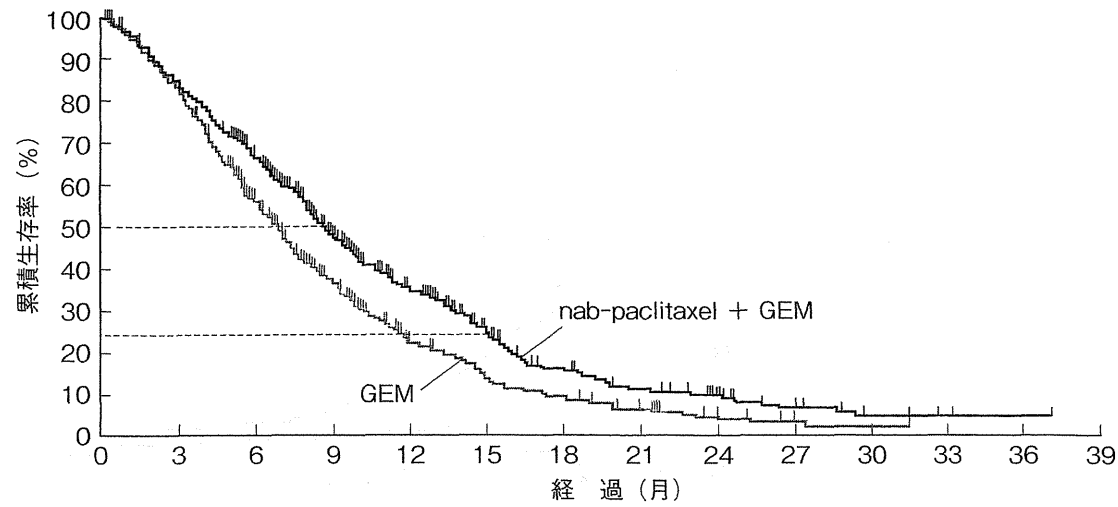


図2. CDDP＋GEM療法

が示され，それ以降GEMが標準治療に位置づけられた[5]．その後，GEMをベースとする2剤併用療法が積極的に試みられた．そのうち，現在までに第Ⅲ相試験でGEMに対する生存期間の優越性が証明された組み合わせとして，EGFRチロシンキナーゼ阻害薬のerlotinib＋GEMと，ヒト血清アルブミンにpaclitaxelを結合させナノ粒子化したnab-paclitaxel＋GEMの二つがあげられる．

Erlotinib＋GEMについては，2005年に報告された第Ⅲ相試験の結果でGEM単剤に対する優越性が示された（HR 0.82, 95％ CI 0.69～0.99, GEM群対erlotinib＋GEM群の生存期間中央値5.91ヵ月対6.24ヵ月，$p=0.038$）[6]．しかし副作用やコストの増加に見合う臨床的有益性に乏しいという意見もあり，GEM単剤療法にとってかわる標準療法というよりは，全身状態がよい患者に対する治



No. at risk

nab-paclitaxel+GEM	431	357	269	169	108	67	40	27	16	9	4	1	1	0
GEM	430	340	220	124	69	40	26	15	7	3	1	0	0	0

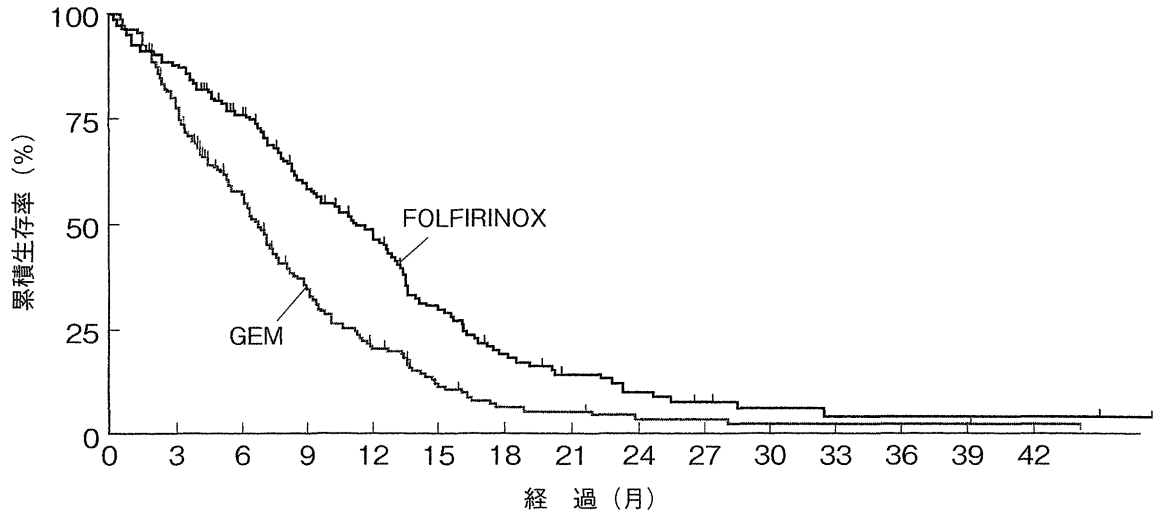
	nab-paclitaxel + GEM	GEM
全生存期間中央値	8.5 ヵ月	6.7 ヵ月
無増悪生存期間中央値	5.5 ヵ月	3.7 ヵ月
奏効率	23 %	7 %

図3. 進行膵癌に対するGEM療法とnab-paclitaxel + GEM療法の第Ⅲ相試験（MPACT試験）における両群の生存曲線（文献8より引用改変）

療オプションとの位置づけにとどまっていた．

また，2013年のASCOで局所進行膵癌を対象とした第Ⅲ相試験（LAP 07）の結果が報告され，その中でerlotinibに関する重要な情報が報告された．この試験は局所進行膵癌患者に対する化学放射線療法の有用性（主要評価項目）と，erlotinibのGEMへの上乗せ効果（副次的評価項目）の両者を評価するデザインであったが，erlotinibの上乗せ効果が示されなかった（HR 1.19，95 % CI 0.97～1.45，GEM群対erlotinib + GEM群の生存期間中央値13.6 ヵ月対11.9 ヵ月 $p = 0.093$）[7]．このことから，erlotinibの進行膵癌治療へのインパクトはさらに小さなものになることが予想される．この研究では主要評価項目である化学放射線療法についても全身化学療法に対する優位性は示されなかった．従来局所進行膵癌に対する化学放射線療法については，有用性についても支持する報告と否定的な報告の両者があり議論されてきたが，この試験の結果はそこにも一石を投じる結果となった．Nab-paclitaxel + GEMに関しては2013年のASCO-Gastrointestinal Symposiumで第Ⅲ相試験の結果が報告され，有意な延命効果が示された（図3）〔HR 0.72，95 % CI 0.617～0.835，GEM群対nab-paclitaxel + GEM群の生存期間中央値6.7 ヵ月対8.5 ヵ月，$p = 0.00015$〕[8]．日本でも現在治験が進行中である．GEM単剤に対する上乗せ効果が明確に示されており，有害事象も現在までの報告をみる限り好中球減少（38 %），疲労（17 %），末梢神経障害（17 %）など，比較的管理がしやすく生命に直結しないものが主体である．そのためこの報告は臨床医からは好意的に受け入れられており，今後のGEM含有レジメンの第一候補として期待されている．

GEMを含まない併用療法としては，2010年に5-FU/calcium folinate + irinotecan + oxaliplatin（FOLFIRINOX）のGEMに対する優越性が第Ⅲ相試験で示された（図4）〔HR 0.57，95 % CI 0.45～0.73，GEM群対FOLFIRINOX群の生存期間中央



No. at risk

GEM	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

	CDDP＋GEM	GEM
全生存期間中央値	11.1ヵ月	6.8ヵ月
無増悪生存期間中央値	6.4ヵ月	3.3ヵ月
奏効率	31.6％	9.4％

図4. 進行膵癌に対するGEM療法とFOLFIRINOX療法の第Ⅲ相試験（PRODIGE4/ACCORD11試験）における両群の生存曲線（文献9より引用改変）

値6.8ヵ月対11.1ヵ月，$p<0.0001$][9]．国内でもFOLFIRINOXの治験は終了しており，2013年5月に承認申請が提出され承認まちの状態である．Grade 3以上の有害事象として好中球減少（45.7％），発熱性好中球減少（5.4％），下痢（12.7％），嘔吐（14.5％），疲労（23.6％）などが報告されており，副作用の強いレジメンと考えるべきで，国内での臨床導入後も慎重な観察と十分な副作用対策が望まれる．国内外で，投与量を減らしたりボーラスの5-FUを抜くなど，副作用の軽減をめざしてレジメン自体をmodifyする提案も散見するが，その際には有効性まで減弱しないか十分な評価が必要である．有効性の観点からnab-paclitaxel＋GEMとFOLFIRINOXのうちどちらがより進行膵癌に対して優れているかについては今後の検討課題である．

一方，S-1は膵癌に対するkey drugとして日本を中心に単剤あるいはGEMとの併用で独自に開発がすすめられてきた．そこで進行膵癌を対象にGEM単剤療法に対するS-1単剤療法の非劣性，GEM＋S-1併用療法（GS療法）の優越性を検証するためのランダム化第Ⅲ相試験（GEST試験）が日本と台湾で実施された[10]．その結果，生存期間中央値はGEM群8.8ヵ月，S-1群9.7ヵ月，GS群10.1ヵ月でGEM単剤療法に対するS-1単剤療法の非劣性が示された（HR 0.96，97.5％CI 0.78～1.18，$p<0.001$）が，GS療法の優越性は示されなかった（HR 0.88，97.5％CI 0.71～1.08，$p=0.15$）．本試験の結果により，S-1単剤療法は進行膵癌に対する一次治療の選択肢の一つとなることが示された．

以上より，進行膵癌に対する化学療法の現状をまとめると，1996年来の標準療法であるGEMと同等の治療成績が示されたのがS-1単剤療法，明確にアドバンテージを示すことができた多剤併用レジメンがnab-paclitaxel＋GEMとFOLFIRINOX