(a) Men (b) Women

Fig. 2. Posterior distribution of smoking effect $(\exp(\beta_1 + b_{1i}))$ in each cohort (smoking-by cohort interaction).

on stroke events across cohorts and the smoking is shown to be an independent risk factor for the events, while there appears to be substantial variation in the baseline risk across cohorts. This result indicates that the observed smoking effects might be generalized to a broader population.

4. Discussion

In this paper, we proposed to use a Poisson mixed effects model (1) with two random effects to investigate the exposure-by-cohort interaction. It is important to investigate the cohort effects on the exposure risk in addition to the baseline risk. This model is useful not only for the meta-analysis of individual epidemiologic data like in the JALS, but also for the analysis of multicenter clinical trials (Matsuyama et al. 1998).

Until recently, a potential limitation of generalized linear mixed models was their computational burden. Because there is no simple closed-form solution for the marginal likelihood, numerical integration (Pinheiro and Bates 1995) or pseudo-likelihood (Breslow and Clayton 1993; Wolfinger and O'Connell 1993) techniques are required. Maximum or restricted maximum likelihood estimation has only recently been implemented in standard statistical software, for example, PROC NLMIXED or PROC GLIMMIX in SAS. However, problems with convergence are likely to arise when complicated models with two or three random effects are fitted (Fitzmaurice et al. 2004; Evans et al. 2001). This non-convergence problem seems to frequently occur in highly unbalanced data or in sparse data, that is, the number of events is small relative to the adjustment variables. In fact, in our data analysis of the JALS data, the number of stroke events was small in each cohort as shown in Table 2, and the optimization algorithms by the NLMIXED/GLIMMIX procedures for the model (1) did not converge, although a number of things was tried, for example, change the initial values by using a grid search specification to obtain a set of good feasible starting values, change or modify the update or optimization

technique, or change the convergence criterion.

To overcome the above non-convergence problems, we chose a Bayesian viewpoint and the Gibbs sampling was used for estimating procedures. The Gibbs sampling is a useful technique for estimating complex Bayesian models, although it is computationally intensive. So long as conjugate priors can be found for model parameters, the implementation of the Gibbs sampling is straightforward as illustrated in this paper. When conjugate priors cannot be available, especially in generalized linear models or non-linear models, random variate generating technique can be used. In this paper we used a rejection sampling (Zeger and Karim, 1991), although it involved many evaluations of target distribution.

Another advantage of the Gibbs sampling is its flexibility. For example, the prior distribution for the random effects need not be the Gaussian as in the usual mixed effects model. The use of a limited class of distributions results in a limited and potentially inappropriate inferences. To account for outliers, it can be applied to the heavy-tailed multivariate random effects such as t-distribution with a small value of degrees of freedom (Matsuyama et al. 1998).

Bayesian approach described in this paper has other advantages and flexibilities over that of frequentist. For example, if we have some background information on the fixed effects, we can utilize such information explicitly in the analyses through the prior distributions. Greenland (2000) proposed the active use of the Bayesian viewpoints in the analyses of epidemiologic data. In this paper, because we do not have firm such information on the effects of fixed effects parameters, we set non-informative priors, therefore, our results via the Gibbs sampling were virtually identical with those of the maximum likelihood methods.

In conclusions, we proposed to use a Poisson mixed effects model for investigating the exposure-by-cohort interaction, and use a Gibbs sampling technique for model parameter inferences. It was found from the analyses of the JALS data for the association between smoking and stroke events that substantial variations across cohorts were seen in the baseline risk, but not in the effect of smoking. This result indicates that the observed smoking effects might be generalized to a broader population.

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Appendix

Calculation of the Gelman-Rubin's Potential Scale Reduction

Let m be the number of independent parallel sequences and n be the length of each sequence after discarding the first half of the simulations. For each parameter ψ_{ij} ($i = 1, \ldots, m$; $j = 1, \ldots, n$), we compute B and W, the between- and within-sequence variance;

$$B = \frac{n}{m-1} \sum_{i=1}^{m} (\bar{\psi}_{i.} - \bar{\psi}_{..})^2, \quad \text{where} \quad \bar{\psi}_{i.} = \frac{1}{n} \sum_{j=1}^{n} \psi_{ij}, \quad \bar{\psi}_{..} = \frac{1}{m} \sum_{i=1}^{m} \bar{\psi}_{i.}.$$

$$W = \frac{1}{m} \sum_{i=1}^{m} s_i^2, \quad \text{where} \quad s_i^2 = \frac{1}{n-1} \sum_{j=1}^{n} (\psi_{ij} - \bar{\psi}_{i.})^2$$

From the two variance components, we estimate the marginal posterior variance of each scalar summary ψ;

$$\hat{V}(\psi) = \frac{n-1}{n} W + \frac{1}{n} B,$$

which overestimates the marginal posterior variance, but is unbiased in the limit as $n \to \infty$. Then we monitor convergence of the simulation by estimating the factor by which the scale of the current distribution for ψ might be reduced;

$$\sqrt{\hat{R}} = \sqrt{\frac{\hat{V}(\psi)}{W}}$$

This PSR is the ratio of the estimated upper to lower bounds for the standard deviation of ψ. This statistics can be calculated sequentially as the runs proceed, and declines to 1 as the runs converge; the closer the estimate is to 1.0 the more likely is the Gibbs sampling to have converged.

Ultrasound-guided percutaneous pancreatic tumor biopsy in pancreatic cancer: a comparison with metastatic liver tumor biopsy, including sensitivity, specificity, and complications

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Background. The aims of this study were to investigate the diagnostic value and safety of ultrasound-guided percutaneous pancreatic tumor biopsy (pancreatic biopsy) in patients with suspected unresectable pancreatic cancer, and to compare the data with those obtained by metastatic liver tumor biopsy (liver metastases biopsy). **Methods.** Data were collected retrospectively from 388 patients (398 procedures) for whom a final diagnosis was available and who underwent ultrasound-guided pancreatic or liver metastases biopsy with a 21-gauge needle (core biopsy) or a 22-gauge needle (fine-needle aspiration biopsy: FNAB). The sensitivity, specificity, and accuracy of pancreatic and liver metastases biopsies were evaluated. Biopsy-related complications were collected and analyzed. **Results.** Data from 271 pancreatic and 112 liver metastases biopsy procedures were available. For pancreatic core biopsy and FNAB, the sensitivity, specificity, and accuracy were 93%, 100%, and 93%, and 86%, 100%, and 86%, respectively, all of which were comparable to those of liver metastases biopsy. The complication rate in pancreatic biopsy was 21.4%, including a 4.4% incidence of post-biopsy ephemeral fever. The complication rate in liver metastases biopsy was 38.7%, including an 8.0% incidence of ephemeral fever. Fever and infection occurred more frequently among patients who underwent liver metastases biopsy (4.4% vs. 11%: $P = 0.038$). In pancreatic biopsy cases, a prebiopsy high serum total bilirubin level was a statistically significant predictor of ephemeral fever. **Conclusions.** Ultrasound-guided percutaneous pancreatic biopsy is an effective and safe modality for confirming the pathologic diagnosis in patients with unresectable pancreatic cancer.

Introduction

The majority of patients with pancreatic cancers have metastatic or locally advanced disease at the time of diagnosis, and are not candidates for surgical resection. In such patients with unresectable disease based on imaging findings, it is important to verify the histopathologic diagnosis of cancer before starting nonsurgical treatment, so as to exclude patients with pseudotumors or benign diseases from inappropriate aggressive therapies such as chemotherapy and radiotherapy. It is also important to distinguish pancreatic cancer with predominantly exocrine differentiation from others, such as cancer with endocrine differentiation or lymphoma, because their treatment strategy and tumor biology are completely different.

Pancreatic biopsy is a common procedure for obtaining histological specimens for diagnosis of a pancreatic mass. It can be performed endoscopically, intraoperatively, or percutaneously with computed tomographic (CT) or ultrasound (US) guidance. In our department, US-guided percutaneous pancreatic tumor biopsy (pancreatic biopsy) is the preferred method in patients whose tumors are suggested to be unresectable from preoperative abdominal imaging, because it allows accurate placement of the biopsy needle tip during real-time imaging and is less invasive than an endoscopic procedure or diagnostic laparotomy.

However, the diagnostic value and safety of US-guided percutaneous pancreatic biopsy have not yet been fully evaluated in patients with unresectable pancreatic cancer. In the present study, we aimed to assess the sensitivity, accuracy, complication rate, and risk factors of this procedure in comparison with US-guided

metastatic liver tumor (liver metastases) biopsy, a common diagnostic procedure both in Japan and in other countries.

Patients and methods

Patients

We conducted a retrospective review of US-guided pancreatic or liver metastases biopsies performed during a 5-year period from January 1999 through December 2003. All patients were inpatients in whom preoperative abdominal imaging (dynamic CT or angiography) suggested that their pancreatic tumors were unresectable. Tumors encasing the celiac or superior mesenteric arteries or obstructing or bilaterally invading the portal vein were considered to be unresectable. Exclusion criteria were postoperative recurrence and pathological confirmation of cancer from biliary cytology, ascites cytology, or exploratory laparotomy.

For patients with both pancreatic tumor and liver metastases, the decision about which organ was to be targeted for biopsy was made by physicians on the basis of visualization of the lesion by transabdominal US, the patient's anatomy, and the physician's preference. The technique used for biopsy and the incidence of complications were reviewed from the clinical records. Coagulation measurements were performed before biopsy when the patient's history or presentation suggested an increased risk of bleeding, and we did not perform a biopsy if the results showed a bleeding tendency. We did not routinely use antibiotics prophylactically. A blood culture was routinely performed if patients had fever of $\geq 38.0°C$ after biopsy. All patients provided written informed consent for the biopsy procedures.

Biopsy techniques

In the case of both pancreatic biopsy and liver metastases biopsy, we used a convex probe or a linear-array probe, both of which were equipped with a guide attachment, and we performed biopsy with continuous real-time monitoring. The most appropriate approach was chosen after local sterilization with povidone–iodine, which was also used as the contact medium for the US probe. Local anesthesia was administered in all cases. The medial approach was always used for pancreatic biopsies. For liver metastases biopsies, in principle, the intercostal approach was used for tumors located in the right lobe and the medial approach for tumors in the left lobe. In pancreatic biopsies, the needle occasionally passed through the stomach. All patients who underwent pancreatic biopsy fasted from the night before the biopsy until after the biopsy itself to obtain

good visualization of the pancreatic mass and to reduce the risk of peritonitis as a complication.

We used two types of needle, a 21-gauge needle (Sonopsy-C1; Hakko, Tokyo, Japan) for tissue core biopsy to obtain both pathologic and cytologic materials, and a 22-gauge needle (15 cm PTCD needle; Top, Tokyo, Japan) for aspiration biopsy to obtain cytologic material. The physician who performed the biopsy selected the more appropriate needle on the basis of US imaging and tumor size. The number of passes varied, but one or two passes were common. Biopsy material obtained from one pass was always checked macroscopically for adequacy before making the next pass.

When we performed core biopsies with the 21-gauge needle, the needle was advanced gently and withdrawn within the tumor lesion several times to obtain enough tissue for histologic diagnosis. Tissue core specimens were immediately preserved in 10% formalin, then the residual mucus was expressed onto glass slides, thin smears were prepared, and these were immersed in 95% ethanol. The needle tip was also cleansed in heparin-containing saline, and the wash-through fluid was examined cytologically.

We performed fine-needle aspiration biopsy (FNAB) with the 22-gauge needle. Once the needle had been placed within the lesion, the stylet was removed and suction was applied to the needle with a 20-ml disposable syringe. During the application of suction, the needle was gently advanced and withdrawn in the lesion several times. The aspirates were expressed onto glass slides and the needle tip was cleansed, as in the case of core biopsies.

Each pathologic diagnosis was determined by two or three pathologists specialized in pancreatic cancer and other cancers. A core sample was defined as tissue with preserved histologic structure. The final diagnosis was determined on the basis of autopsy or the clinical course of the patient. A diagnosis of benign pancreatic tumor was made together with a follow-up of at least 1 year during which there was no evidence of malignancy. The clinical course of the patient was used to confirm the histologic and cytologic diagnoses of malignancy.

Complications

We examined the clinical records of all patients in this study, and identified all complications such as pain, fever, and some infections. We defined pain as the need for additional analgesics after biopsy. Fever was classified into two categories: ephemeral fever and persistent fever. Ephemeral fever meant that patients had fever of $\geq 38.0°C$ within 24 h after the biopsy, but just once and never again (without antibiotics). Persistent fever meant that patients had fever of $\geq 38.0°C$ of unknown origin for more than 2 days after the biopsy, without any clini

cally or microbiologically documented infection. Antibiotics were not used for ephemeral fever, but they were used for persistent fever.

Statistical analysis

The biopsy procedure for each organ was analyzed with regard to its ability to accurately diagnose malignancy or a benign tumor, and its safety in terms of the incidence of post-biopsy complications. The sensitivity, specificity, and accuracy of biopsies were calculated including specimens inadequate for diagnosis that were considered negative for malignancy. Biopsy specimens of both exocrine and endocrine carcinoma, including those diagnosed pathologically as neuroendocrine tumor, were considered positive for malignancy. For continuous variables, comparisons were made by t test. For categorical data, frequency comparisons were performed by χ-squared test. Logistic regression analysis was used to identify potential predictors of complications. Statistical significance was established at the $P < 0.050$ level.

The sensitivity of biopsies was calculated as the ratio of [true positives] / [true positives + false negatives]. The specificity of biopsies was calculated as the ratio of [true negatives] / [true negatives + false positives]. The accuracy of biopsies was defined as the ratio of [true positives] + [true negatives] divided by the total number of biopsy procedures.

Results

Patient characteristics

The study comprised 388 patients with suspected pancreatic cancer (Fig. 1); 170 had an unresectable pancreatic mass alone, 178 had liver metastases, and 40 had metastases to sites other than the liver. Among them, 274 patients underwent US-guided pancreatic biopsy, 110 underwent US-guided liver metastases biopsy, and four underwent both procedures on two separate occasions (Fig. 1). Six patients underwent biopsy of the same organ on two separate occasions (pancreas in five patients, liver in one); these were counted as two separate procedures. Among a total of 398 biopsy procedures, 15 (12 pancreas, 3 liver) that were performed with both types of needle during the same procedure were
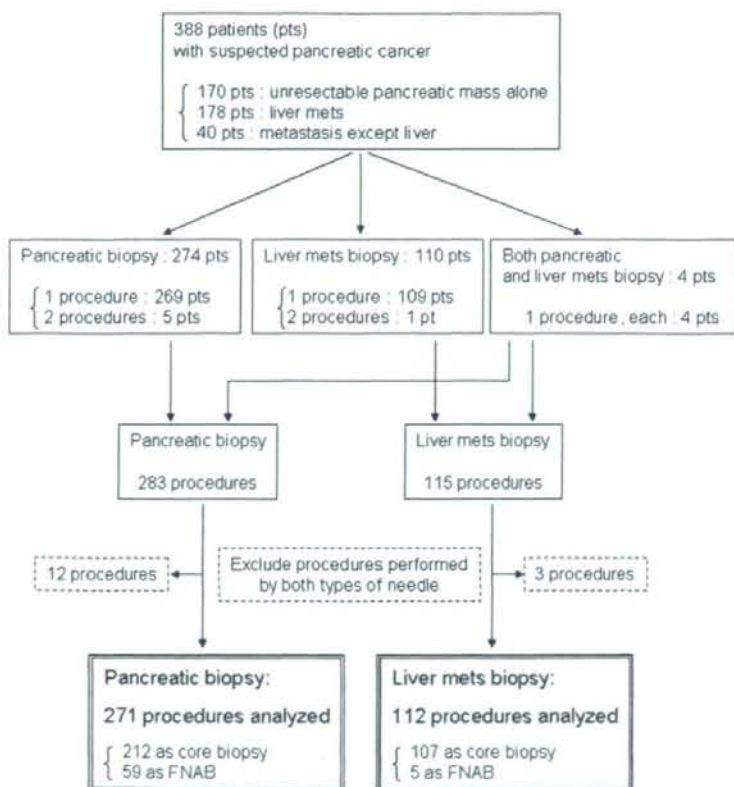

Fig. 1. A procedure-counting flow chart. "1 procedure" means that a patient underwent one organ biopsy on one occasion; "2 procedures" means that a patient underwent biopsy of the same organ on two separate occasions. We excluded procedures performed with both types of needle because it was impossible to determine which type provided the pathologic diagnostic material and produced the complications. Consequently, 271 (71%) pancreatic biopsy and 112 (29%) liver metastases (*mets*) biopsy procedures were performed. A total of 383 procedures were investigated and analyzed in this study. FNAB, fine-needle aspiration biopsy

Table 1. Patient demographics and clinical characteristics of targeted tumors

	Pancreatic biopsy			Liver metastases biopsy
	Total	Head	Body/tail	
No. of patients	266			111
Male	149			71
Female	117			40
Age, median years (range)	62 (32–86)			58 (37–79)
No. of biopsies, procedures	271			112
		106	165	
Mean tumor size, mm (SD)	42.2 (14.7)			26.2 (13.1)*
		37.0 (11.5)	45.6 (15.5)**	
Mean no. of passes	1.6			1.8
Core biopsy	1.6			1.8
FNAB	1.8			1.8

FNAB, fine-needle aspiration biopsy
* $P < 0.001$ vs. pancreatic biopsy
** $P < 0.001$ vs. pancreatic head biopsy

Table 2. Diagnostic value by site of biopsy in all 383 procedures

	Pancreatic biopsy	Liver metastases biopsy	P value
Final diagnosis			
Carcinoma, no. of procedures (patients)	266 (262)	112 (111)	
Benign disease, no. of procedures (patients)	5 (4)	0 (0)	
True positive, no. of procedures	244	109	
False positive, no. of procedures	0	0	
Sensitivity (95% CI)	92% (87.8–94.7)	97% (92.4–99.4)	0.713
Specificity (95% CI)	100% (47.8–100)	NE	
Accuracy (95% CI)	92% (88.0–94.8)	97% (92.4–99.4)	0.720

CI, confidence interval; NE, not evaluable

excluded because it was impossible to determine which type of needle had obtained the specimen from which pathologic diagnosis was made and which had caused any complications. Therefore, a final total of 383 biopsy procedures (271 pancreatic biopsy and 112 liver metastases biopsy procedures) were examined in the present study (Fig. 1).

At the time of analysis, 278 of the patients (73%) had died. The median follow-up time (from biopsy to death or the day to be censored) was 276 days.

In the pancreatic biopsy group, there were 149 men and 117 women with a median age of 62 years (range, 32–86 years) (Table 1). In the liver metastases biopsy group, there were 71 men and 40 women with a median age of 58 years (range, 35–79 years). In the pancreatic biopsy group, 106 targeted tumors were located in the pancreas head and 165 in the pancreas body and/or tail. The targeted tumors for pancreatic head biopsy were significantly smaller than those for pancreatic body/tail biopsy (37.0 mm vs. 45.6 mm; $P < 0.001$). The targeted tumors for liver metastases biopsy were significantly smaller than those for the pancreatic biopsies (26.2 mm vs. 42.2 mm; $P < 0.001$). There were no significant differences among the patient groups according to the site of biopsy with respect to the mean number of passes for core biopsies and FNABs.

Diagnostic value

Except for five procedures (four patients), the final diagnosis in all patients was pancreatic carcinoma (Table 2). The diagnoses of the four patients with benign pancreatic tumors were chronic pancreatitis (one), autoimmune pancreatitis (two), and retroperitoneal fibrosis (one). There were no false-positive histologic or cytologic interpretations in these four patients. The diagnosis of benign pancreatic tumor was confirmed again by long-term follow-up without anticancer treatment and without disease progression (median, 815 days; range 322–1030). The sensitivity, specificity, and overall accuracy of the pancreatic biopsies were 92%, 100%, and 92%, respectively (Table 2). The sensitivity and overall accuracy of the liver metastases biopsies were both 97%. The specificity of liver metastases biopsies was not evaluated, because all patients who underwent liver metastases biopsy were finally diagnosed as having pancreatic carcinoma. There were no significant differences in sensitivity ($P = 0.713$) or accuracy ($P = 0.720$

Table 3A. Diagnostic value of the core biopsy (21-gauge) by site and by type of specimen

Core biopsy (21-gauge) procedures	Pancreatic biopsy			Liver metastases biopsy ($n = 107$)
	Total ($n = 212$)	Head ($n = 78$)	Body/tail ($n = 134$)	
Tissue core specimen for histology				
Sensitivity (n)	77% (161/209)	68% (52/77)	83% (109/132)	84% (90/107)
Specificity (n)	100% (3/3)	100% (1/1)	100% (2/2)	NE (—)
Thin smears and needle-tip washing for cytology				
Sensitivity (n)	89% (187/209)	87% (67/77)	91% (120/132)	94% (101/107)
Specificity (n)	100% (3/3)	100% (1/1)	100% (2/2)	NE (—)

Table 3B. Diagnostic value by site and by type of biopsy needle

	Pancreatic biopsy			Liver metastases biopsy
	Total	Head	Body/tail	
Core biopsy (21-gauge) procedures[a]	$n = 212$	$n = 78$	$n = 134$	$n = 107$
Sensitivity (n)	93% (195/209)	90% (69/77)	96% (126/132)	97% (104/107)
Specificity (n)	100% (3/3)	100% (1/1)	100% (2/2)	NE (—)
Accuracy (n)	93% (198/212)	90% (70/78)	96% (128/134)	97% (104/107)
FNAB (22-gauge) procedures	$n = 59$	$n = 28$	$n = 31$	$n = 5$
Sensitivity (n)	86% (49/57)	85% (22/26)	87% (27/31)	100% (5/5)
Specificity (n)	100% (2/2)	100% (2/2)	NE (—)	NE (—)
Accuracy (n)	86% (51/59)	86% (24/28)	87% (27/31)	100% (5/5)

[a]Final diagnosis of core biopsy was defined as positive based on histological or cytological results

between pancreatic biopsy and liver metastases biopsy (Table 2).

Pancreatic biopsies yielded a sufficient amount of tissue to allow diagnosis in 93% of core biopsies, and an adequate yield of cells was obtained in 90% of FNABs. Liver metastases biopsies yielded a sufficient amount of material in 97% of core biopsies and in 100% of FNABs.

For procedures using the 21-gauge core biopsy needle, the sensitivity of the tissue core specimen for histology was 77% for pancreatic biopsy and 84% for liver metastases biopsy (Table 3A). The sensitivity of thin smears and needle-tip washing for cytology was 89% for pancreatic biopsy and 94% for liver metastases biopsy (Table 3A). When the result of the core biopsy procedure was defined as positive by histology or cytology, the total sensitivity, specificity, and accuracy were 93%, 100%, and 93%, respectively, for pancreatic biopsy and 97%, not evaluable, and 97%, respectively, for liver metastases biopsy (Table 3B).

For procedures using the 22-gauge aspiration biopsy needle (FNAB), the sensitivity, specificity, and accuracy were 86%, 100%, and 86%, respectively, and for pancreatic biopsy, and 100%, not evaluable, and 100%, respectively, for liver metastases biopsy (Table 3B).

There were no significant differences in sensitivity (core biopsy, $P = 0.810$; FNAB, $P = 0.819$) or accuracy (core biopsy, $P = 0.814$; FNAB, $P = 0.825$) between pancreatic biopsy and liver metastases biopsy according to the type of needle employed.

Complications

Regardless of the biopsy needle used, the proportion of patients with no complications was 79% for pancreatic biopsy and 75% for liver metastases biopsy (Table 4). There were no significant differences in the incidence of no complications ($P = 0.742$) or pain ($P = 0.999$). The total incidence of fever and infection, including ephemeral fever, cholangitis, and persistent fever, was significantly lower for pancreatic biopsy than for liver metastases biopsy ($P = 0.038$). None of the blood cultures collected from patients with fever and infection were positive.

For the core biopsy procedures, the incidence of pain was almost the same between pancreatic biopsy and liver metastases biopsy (Table 4). The incidence of ephemeral fever was lower for pancreatic biopsy (4.2%) than for liver metastases biopsy (7.5%), but not to a significant degree ($P = 0.252$). Cholangitis and persistent fever occurred only after liver metastases biopsy. For FNAB procedures, pain occurred only after pancreatic biopsy (15%). Cholangitis and persistent fever did not occur after either pancreatic or liver metastases FNAB.

There were no biopsy-related deaths, or life-threatening complications such as biopsy-related pan-

Table 4. Complications by site of biopsy

	Pancreatic biopsy	Liver metastases biopsy	P value
Core biopsy (21-gauge)	n = 212	n = 107	
No complication	168 (79%)	80 (75%)	
Pain[a]	38 (18%)	20 (19%)	
Ephemeral fever[b]	9 (4.2%)	8 (7.5%)	
Cholangitis	0	2 (1.9%)	
Persistent fever[c]	0	1 (0.9%)	
FNAB (22-gauge)	n = 59	n = 5	
No complication	47 (80%)	4 (80%)	
Pain[a]	9 (15%)	0 (0%)	
Ephemeral fever[b]	3 (5.1%)	1 (20%)	
Total	n = 271	n = 112	
No complication	215 (79%)	84 (75%)	0.742
Pain[a]	47 (17%)	20 (18%)	0.999
Fever and infection[d]	12 (4.4%)	12 (11%)	0.038*

* Statistically significant
[a] Patients needed additional analgesics after biopsy
[b] Patients had a single episode of fever of ≥38.0°C within 24h after biopsy (without antibiotics).
[c] Patients had fever of ≥38.0°C of unknown origin for more than 2 days after biopsy, without clinically or microbiologically documented infection
[d] Includes ephemeral fever, cholangitis, and persistent fever

creatitis, macroscopic or symptomatic hematoma, or obvious needle-tract seeding.

Since ephemeral fever was the only clinically problematic complication of the pancreatic biopsy procedure that could reduce a patient's performance status, a logistic regression analysis was performed to examine the potential predictors of ephemeral fever in pancreatic biopsy cases. Potential predictors were the serum levels of total bilirubin (T-bil), aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, amylase, and C-reactive protein before biopsy, age, and size and location of the targeted pancreas tumor, which were considered to be related to retention of bile or pancreatic juice, or inflammation. Univariate analysis showed that T-bil ($P = 0.008$) and ALT ($P = 0.048$) before biopsy were significant predictors of ephemeral fever (Table 5). Multivariate analysis showed that only T-bil was a statistically significant predictor of ephemeral fever ($P = 0.006$, relative risk = 2.45; 95% confidence interval, 2.01–66.39).

Discussion

Because of dramatic developments in the technology of imaging diagnosis in the past decade, the resectability of pancreatic cancer can now be determined very accurately purely on the basis of diagnostic imaging techniques such as high-resolution spiral CT scan. However, histopathologic confirmation is necessary in patients deemed to have inoperable tumors or those who are medically unsuitable for surgery. In the National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma,[1] it is strongly recommended that all patients with unresectable pancreatic cancer should have cancer confirmation prior to nonsurgical treatment, and that a negative biopsy result should be confirmed by at least one repeat biopsy. Our present retrospective study demonstrated that US-guided percutaneous pancreatic biopsy is an effective modality for confirmation of the pathologic diagnosis in patients with unresectable pancreatic cancer. We also confirmed that it is as safe as liver metastases biopsy in these patients.

The reported sensitivity of US- or CT-guided percutaneous pancreatic biopsy procedures ranges from 80% to 97% with various types of needle.[2-6] The sensitivity observed in our study (92%, Table 2) is slightly higher than that reported in studies of US-guided biopsy studies.[5,6] This may be attributable to the design of our study, which yielded a high level of sensitivity for US-guided pancreatic biopsy. This was a retrospective study of all patients who underwent attempted biopsies of pancreatic masses by US, preselecting only those individuals in whom the mass could be seen, although in general US is often unable to visualize the pancreas completely.

Another selection bias was the fact that we usually selected FNAB from the viewpoint of safety when US visualization of the targeted pancreatic lesion was poor or unclear, and this may have lowered the sensitivity and accuracy of pancreatic biopsies in FNABs compared with core biopsies (86% vs. 93%, Table 3B) although not to a significant degree.

The complication rate associated with US- or CT-guided percutaneous pancreatic biopsy procedures is extremely low, ranging between 0% and 2%.[4,7-10] Th

Table 5. Correlation of prebiopsy clinical data with ephemeral fever[a] after pancreatic biopsy

	Fever positive	
	No. of procedures (%)	P value[*]
Total bilirubin		**0.008**
≥2.0 mg/dl (n = 15)	3 (20%)	
<2.0 mg/dl (n = 256)	9 (3.5%)	
AST		0.995
≥40 IU/l (n = 45)	2 (4.4%)	
<40 IU/l (n = 226)	10 (4.4%)	
ALT		**0.048**
≥40 IU/l (n = 67)	6 (9.0%)	
<40 IU/l (n = 204)	6 (2.9%)	
Alkaline phosphatase		0.113
≥300 U/l (n = 98)	7 (7.1%)	
<300 U/l (n = 173)	5 (2.9%)	
Amylase		0.842
≥100 IU/l (n = 79)	4 (5.1%)	
<100 IU/l (n = 178)	8 (4.5%)	
CRP		0.095
≥0.5 mg/dl (n = 76)	6 (7.9%)	
<0.5 mg/dl (n = 195)	6 (3.1%)	
Age, years		0.571
≥65 (n = 114)	6 (5.3%)	
<65 (n = 157)	6 (3.8%)	
Size of targeted pancreas tumor		0.261
≥4.0 cm (n = 160)	9 (5.6%)	
<4.0 cm (n = 111)	3 (2.7%)	
Location of targeted pancreas tumor		0.853
Head (n = 106)	5 (4.7%)	
Body/tail (n = 165)	7 (4.2%)	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein
[*] Univariate analysis with logistic regression; statistically significant P values are shown in bold
[a] Single episode of fever of ≥38.0°C within 24 h after biopsy (without antibiotics)

most serious complications are postbiopsy pancreatitis, hemorrhage, and peritoneal dissemination.[4,7] Although a review of the literature has reported six deaths resulting from pancreatic biopsy,[7] there were no deaths or cases of biopsy-related pancreatitis in our series. Although acute pancreatitis after pancreatic biopsy is rare, it can be serious and sometimes fatal when it occurs, and this may be the main reason why the procedure is not commonly performed. The reported rate of postbiopsy pancreatitis ranges from 0% to 1.7%.[4,5,8,11–13] In patients with unresectable pancreatic cancer, the tumors are large and usually located just under the surface of the pancreas, allowing percutaneous puncture of the tumor without penetrating the normal pancreatic tissue. This is probably why biopsy-related pancreatitis is unlikely to develop, as Smith[7] has suggested.

Although the exact frequency of pancreatic biopsy-related peritoneal dissemination is not known, it may not have any influence on the prognosis of patients with unresectable pancreatic cancer, which is invariably poor.[14] On the other hand, in patients with resectable pancreatic cancer, preoperative percutaneous pancre-

atic biopsy is regarded as controversial because some studies have suggested a high frequency of procedure-related peritoneal dissemination (16.3%–75%).[15,16] The NCCN guidelines state that biopsy proof of malignancy is not required before surgical resection and that a non-diagnostic biopsy should not delay surgical resection, which is the only curative therapy for pancreatic cancer.[1]

In the present study, no cases of clinically or microbiologically documented infection were associated with pancreatic biopsy. There were, however, 12 cases (4.4%) of postbiopsy ephemeral fever, a lower incidence rate than that following liver metastases biopsy. We are not aware of any other published data on this type of fever. We routinely checked the serum level of amylase, but not that of lipase. Among 12 patients with postbiopsy ephemeral fever, two had amylase levels higher than the upper normal limit after pancreatic biopsy. Since leakage of pancreatic juice can occur after pancreatic biopsy, ephemeral fever could be an initial sign of pancreatitis, which has the potential to become life-threatening.

Pancreatic tumor biopsy can be performed using CT guidance with a complication rate ranging from 3.8% to 7%,[4,17,18] and our data showed a very similar rate. It can also be performed under endoscopic ultrasound guidance with a complication rate similar to that observed in our study.[19-22] However, we consider that US-guided pancreatic biopsy may be most useful in patients with unresectable pancreatic cancer, because their tumors are usually large enough to warrant a safe US-guided biopsy (mean size in our study, 42.2mm, Table 1). Furthermore, although we did not perform a cost and patient satisfaction analysis, the procedure for US-guided pancreatic biopsy is obviously more time-saving and less stressful to patients than other biopsy modalities.

In conclusion, in patients with unresectable pancreatic cancer, US-guided percutaneous pancreatic biopsy is an effective and safe modality for confirmation of the pathologic diagnosis. If US visualization is obtained with enough care, pancreatic biopsy is as accurate and safe as liver metastases biopsy, which is well established and commonly perceived as safer. Another important conclusion is that even if a mass in the pancreas seems to be cancer and is large enough to warrant US-guided biopsy, 1.5% (4/266, Table 2) of such cases are not cancer. This indicates that all patients with unresectable pancreatic cancer should have cancer confirmation prior to nonsurgical treatment. Our study was a retrospective analysis, which precludes any firm conclusion. Therefore, a prospective study is needed for adequate evaluation of US-guided pancreatic biopsy as a diagnostic tool.

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Prognostic Factors in Japanese Patients with Advanced Pancreatic Cancer Treated with Single-agent Gemcitabine as First-line Therapy

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Objective: The purpose of the retrospective analysis is to elucidate the treatment efficacy and toxicity as well as to identify prognostic factors in Japanese patients with advanced pancreatic cancer treated with gemcitabine.

Methods: Two hundred and sixty-four patients with pathologically confirmed locally advanced or metastatic pancreatic cancer, who had received gemcitabine monotherapy as first-line chemotherapy for pancreatic cancer, were analyzed. A dose of 1000 mg/m² gemcitabine was administered intravenously for 30 min on Days 1, 8 and 15 of a 28-day cycle.

Results: One patient achieved a complete response (0.3%) and 27 patients showed a partial response (10.2%), with an overall response rate of 10.6% (95% confidence interval: 6.9–14.3%). The main grade 3/4 toxicities were neutropenia in 94 patients (35.6%) and leukocytopenia in 52 patients (19.7%). The median survival time, 1-year survival proportion and median progression-free survival time were 6.8 months, 21.6% and 3.7 months, respectively. A multivariate analysis using the Cox proportional hazards model demonstrated that a Karnofsky performance status ≥ 90 ($P = 0.01$), Stage III ($P = 0.01$), serum carbohydrate antigen 19-9 level $< 10\,000$ U/ml ($P = 0.02$), serum hemoglobin level ≥ 10 g/dl ($P = 0.01$) and serum C-reactive protein level < 5.0 mg/dl ($P < 0.01$) were the independent favorable prognostic factors.

Conclusions: The treatment efficacy, toxicity and prognostic factors of single-agent gemcitabine in Japanese patients with advanced pancreatic cancer are comparable to those that have been reported in Western patients. These results may be useful as reference data in determining treatments strategies and planning for further clinical trials in Japanese patients with advanced pancreatic cancer.

Key words: pancreatic cancer – gemcitabine – prognostic factor – survival

INTRODUCTION

The prognosis for pancreatic cancer remains extremely dismal with an overall 5-year survival proportion of less than 6% (1). It causes around 22 000 deaths per year and is the fifth cause of cancer-related deaths in Japan. The nonspecific nature of its early symptoms results in delayed diagnosis, so that 80% or more of patients initially diagnosed have locally advanced or metastatic disease that is no longer treatable by

surgical resection (2). Therefore, effective chemotherapeutic agents are needed to improve the prognosis of pancreatic cancer. A landmark study suggesting that single-agent gemcitabine was superior to 5-fluorouracil in improving survival proportion has been reported by Burris et al. (3). Since then, to improve treatment efficacy, many clinical trials of combination treatments with gemcitabine have been conducted in patients with advanced pancreatic cancer. Of these combinations, gemcitabine plus erlotinib showed prolonged survival in comparison with single-agent gemcitabine for the treatment of this disease (4). However, the difference in the median overall survival between the two regimens was 0.3 months, which may be disregarded clinically In addition,

the incidence of adverse events with gemcitabine plus erlotinib tended to of higher frequencies. Therefore, single-agent gemcitabine is regarded as a standard treatment for advanced pancreatic cancer even now.

In Western countries, there have been many prospective studies on advanced pancreatic cancer treated with single-agent gemcitabine (3–12), the results of which could reliably be used to assess treatment efficacy and toxicity because of the large number of the study populations. On the contrary, in Japan, there has been only one prospective study, which was a phase I trial with 11 patients; the population was too small to assess the results accurately in patients with advanced pancreatic cancer treated with single-agent gemcitabine (13). Furthermore, the treatment efficacy and toxicity of gemcitabine have not been fully evaluated even with retrospective studies in Japan. In addition, in the West, the prognostic factors based on the large population numbers for patients with advanced pancreatic cancer treated with gemcitabine (14,15) have been investigated, but in Japan, no such studies exist. Though we previously reported the prognostic factors in 103 patients with advanced pancreatic cancer (16), the chemotherapeutic regimen was varied among patients and only eight patients were in fact treated with gemcitabine monotherapy. Therefore, in the current analysis, we re-evaluated the prognostic factors based on the large population numbers for patients with advanced pancreatic cancer treated with gemcitabine monotherapy. The analysis of prognostic factors is useful in determining the treatment strategies and planning further clinical trials. The objectives of this current retrospective analysis were to elucidate treatment efficacy and toxicity as well as to identify prognostic factors for advanced pancreatic cancer in Japanese patients treated with single-agent gemcitabine.

PATIENTS AND METHODS

PATIENTS

The study subjects consisted of 268 patients with locally advanced or metastatic pancreatic cancer who received single-agent gemcitabine from August, 1998 to March, 2006 at the National Cancer Center Hospital, with no previous chemotherapy for pancreatic cancer. Four patients were excluded from this analysis because of insufficient follow-up records and a total of 264 patients were thus analyzed to elucidate the treatment efficacy and the toxicity of gemcitabine monotherapy, and to identify the prognostic factors in Japanese patients with advanced pancreatic cancer. Overlapping of subjects occurred only in the eight study subjects from our previous report who underwent gemcitabine monotherapy (16).

A pathological confirmation was obtained in all patients by surgical procedure, fine-needle aspiration biopsy or cytological examination. To assess the extent of the disease, imaging modalities such as chest X-ray, abdominal ultrasound and computed tomography (CT) were performed. If necessary, further imaging modalities such as magnetic resonance imaging (MRI) and bone scintigraphy were added. Tumors that extended to the celiac trunk/the superior mesenteric artery, or tumors that occluded the bilateral superior mesenteric-portal venous confluence were regarded as unresectable. The stage of each tumor was judged according to the TNM classification system by the International Union Against Cancer (UICC) 6th edition. Biliary obstruction was controlled before treatment in all patients, by percutaneous transhepatic or endoscopic retrograde biliary drainage or palliative surgical procedures.

TREATMENT

A dose of 1000 mg/m^2 gemcitabine 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 occurred. In principal, the treatment was suspended to allow recovery from the following toxicities: leukocyte count <2000/mm^3, platelet count <70 000/mm^3 or grade 3/4 non-hematologic toxicity.

ASSESSMENT OF EFFICACY AND TOXICITY

All patients underwent physical examination and assessment of toxicity at least once every 1 or 2 weeks until the completion of gemcitabine treatment. Toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 3.0. The antitumor effect of the gemcitabine on the tumor was evaluated by CT/MRI repeated every 4–8 weeks after treatment. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) (17). For this analysis, the tumor response was reviewed, and the best overall response was recorded, for each patient.

FACTORS ANALYZED

The various factors were chosen on the basis of previously published reports or our own clinical experience (16). The following variables were divided into two subgroups at the clinically meaningful value: age (<60 or ≥60 years), gender (male or female), prior pancreactomy (present or absent), Karnofsky performance status (70, 80 or 90, 100), location of primary tumor (head or body–tail), locally advanced or metastatic disease (Stage III or IV), serum hemoglobin level (<10 or ≥10 g/dl), serum total bilirubin level (<2.0 or ≥2.0 mg/dl), serum C-reactive protein (CRP) level (<5.0 or ≥5.0 mg/dl), serum carcinoembryonic antigen (CEA) level (<10 or ≥10 ng/ml) and serum carbohydrate antigen 19-9 (CA19-9) level (<10 000 or ≥10 000 U/ml).

STATISTICAL ANALYSIS

Progression-free survival was calculated as the time interval from the first day of treatment to the date of disease progression. If no disease progression was observed, progression-free survival was calculated from the first day of treatment to the last day of the follow-up period or the date of death. Overall survival was calculated as the time interval from the first day of treatment to the date of death or to the last day of the follow-up period. In the univariate analysis, cumulative survival proportions were calculated with the Kaplan–Meier method and any differences were evaluated with the log-rank test. Only variables that achieved statistical significance in the univariate analysis were subsequently evaluated in the multivariate analysis using the Cox's proportional hazards regression model. A P value of less than 0.05 was considered statistically significant and all tests were two-sided. All statistical analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for windows).

RESULTS

PATIENT CHARACTERISTICS

Patient characteristics are shown in Table 1. The Karnofsky performance status was 100 in 89 patients (33%), 90 in 129 patients (49%), 80 in 35 patients (13%) and 70 in 11 patients (5%). The performance status was 0–1 in 259 patients (98%) and two in five patients (2%). Two hundred and forty-one patients (91%) were diagnosed as having metastatic pancreatic cancer and 23 patients (9%) had locally advanced pancreatic cancer. The histological diagnosis was adenocarcinoma in 261 patients, adenosquamous carcinoma in two patients and anaplastic carcinoma in one patient. The median number of cycles administered on gemcitabine monotherapy was 2.7 (range: 0–34.7). Fifty-five patients (21%) received second-line chemotherapy, such as S-1 monotherapy (28 patients) and 5-fluorouracil combined with cisplatin (11 patients) or concurrent radiotherapy with 5-fluorouracil (six patients).

EFFICACY

Of 264 patients, 243 patients were evaluable for tumor response. One patient achieved a complete response (0.3%) and 27 patients had a partial response (10.2%), with an overall response rate of 10.6% (95% confidence interval: 6.9–14.3%). One hundred and twenty-four patients (47.1%) and 91 patients (34.3%) showed stable disease and progressive disease, respectively. At the time of analysis, 235 patients had died of cancer-related causes. The median survival time, the 1-year survival proportion and median progression-free survival time for all patients were 6.8 months, 21.6% and 3.7 months, respectively. (Fig. 1).

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Gender	
Male	154 (58)
Female	110 (42)
Age, median (range)	63 (34–80)
Karnofsky performance status	
100	89 (33)
90	129 (49)
80	35 (13)
70	11 (5)
Performance status	
0–1	259 (98)
2	5 (2)
TNM stage[a]	
III	23 (9)
IV	241 (91)
Prior pancreatectomy	
Present	42 (16)
Location of primary tumor	
Head	126 (48)
Body–tail	138 (52)
Histological type	
Adenocarcinoma	261 (99)
Adenosquamous carcinoma	2 (1)
Anaplastic carcinoma	1 (<1)
Metastatic site	
Liver	174 (66)
Lymph node	69 (26)
Peritoneum	49 (18)
Lung	38 (14)
Bone	4 (2)
CEA (ng/ml), median (range)	5.6 (0.6–2090)
CA19-9 (U/ml), median (range)	1153 (1–1 620 000)

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9. [a]The International Union Against Cancer 6th edition.

TOXICITY

The worst hematological and non-hematological toxicities during entire treatment are summarized in Table 2. With regard to Grade 3/4 hematological toxicities, neutropenia was observed in 94 patients (35.6%), leukocytopenia in 52 patients (19.7%), anemia in 27 patients (10.2%) and thrombocytopenia in 20 patients (7.6%). In the main grade 3/4 non-hematological toxicities, an elevated alkaline phosphatase level was observed in 22 patients (8.3%), and other adverse events occurred in less than 5%. Interstitial pneumonia was observed in three patients (1.1%), but in all of them
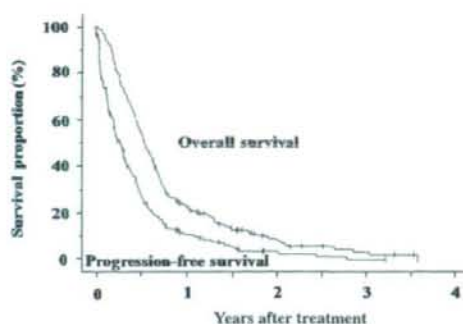
Figure 1. Overall survival and progression-free survival in patients with pancreatic cancer treated with single-agent gemcitabine. Tick marks indicate censored cases.

Table 2. Toxicity

	Number of patients				
	Grade 1	2	3	4	3/4 (%)
Hematological toxicity					
Leukocytopenia	59	79	52	0	52 (19.7)
Neutropenia	34	46	80	14	94 (35.6)
Anemia	115	104	23	4	27 (10.2)
Thrombocytopenia	116	32	19	1	20 (7.6)
Non-hematological toxicity					
Fatigue	114	17	1	0	1 (0.4)
Appetite loss	114	29	5	1	6 (2.3)
Nausea	19	0	0	0	0 (0)
Vomiting	16	7	0	0	0 (0)
Diarrhea	29	1	0	0	0 (0)
Rash	25	14	1	0	1 (0.4)
Decreased albumin level	150	51	2	0	2 (0.8)
Elevated total bilirubin level	38	12	1	0	1 (0.4)
Elevated alkaline phosphatase level	110	37	22	0	22 (8.3)
Elevated aspartate aminotransferase level	131	33	6	2	8 (3.0)
Elevated alanine aminotransferase level	122	45	6	1	7 (2.7)
Hyponatremia	74	1	4	0	4 (1.5)
Interstitial pneumonia	0	0	3	0	3 (1.1)
Cerebrovascular ischemia	0	0	2	0	2 (0.8)

Table 3. Univariate analysis of prognostic factors

Variable	Number of patients	Median OS (months)	Hazard ratio (95% CI)	P value
Gender				
Male	154	7.2	1	0.26
Female	110	6.4	1.16 (0.90–1.51)	
Age (years)				
<60	102	6.9	1	0.83
≥60	162	6.9	1.03 (0.79–1.34)	
Prior pancretectomy				
Present	42	7.0	1	0.10
Absent	222	6.7	1.38 (0.94–2.03)	
Karnofsky performance status				
90–100	89	8.8	1	0.01
70–80	175	6.3	1.63 (1.23–2.15)	
Location of primary tumor				
Head	126	6.7	1	0.76
Body–tail	138	7.3	0.88 (0.41–1.93)	
TNM stage				
III	23	10	1	<0.01
IV	241	6.7	2.28 (1.35–3.85)	
Hemoglobin (g/dl)				
≥10	247	7.2	1	0.01
<10	17	4.7	2.19 (1.31–3.66)	
C-reactive protein (mg/dl)				
<5.0	236	7.4	1	<0.01
≥5.0	28	3.5	2.46 (1.63–3.70)	
Total bilirubin (mg/dl)				
<2.0	250	6.9	1	0.78
≥2.0	14	6.9	1.08 (0.62–1.90)	
CEA (ng/ml)				
<10	172	7.4	1	<0.01
≥10	92	5.9	1.51 (1.15–1.97)	
CA19-9 (U/ml)				
<10 000	212	7.4	1	<0.01
≥10 000	52	4.3	1.79 (1.31–2.44)	

OS, overall survival; CI, confidence interval.

recovery was achieved with medical treatment such as administration of corticosteroid hormones. Cerebral infarction with incomplete paralysis was observed in two patients (0.8%). There were no other life-threatening toxicities and no treatment-related deaths.

PROGNOSTIC FACTOR

Table 3 lists the results of univariate analyses of the factors considered to be prognostic for survival. Six factors closely associated with longer survival were as follows: Karnofsky performance status 90, 100 ($P = 0.01$), stage III ($P < 0.01$), serum hemoglobin level ≥10 g/dl ($P = 0.01$), serum CRP level <5.0 mg/dl ($P < 0.01$), serum CEA level <10 ng/ml ($P < 0.01$) and serum CA19-9 level <10 000 U/ml ($P < 0.01$). The multivariate analysis of the independent favorable prognostic factors for survival was as follows (Table 4): Karnofsky performance status 90, 100 ($P = 0.01$), stage III ($P = 0.01$), serum CA19-9 level <10 000 U/ml ($P = 0.02$),

Table 4. Multivariate analysis of prognostic factors

Variable	Number of patients	Hazard ratio (95% CI)	P value
Karnofsky performance status			
90–100	218	1	0.01
70–80	46	1.56 (1.11–2.21)	
TNM stage			
III	23	1	0.01
IV	241	2.16 (1.27–3.68)	
Hemoglobin (g/dl)			
≥10	247	1	0.01
<10	17	2.10 (1.25–3.54)	
C-reactive protein (mg/dl)			
<5.0	236	1	<0.01
≥5.0	28	1.86 (1.22–2.85)	
CA19–9 (U/ml)			
<10 000	212	1	0.02
≥10 000	52	1.48 (1.07–2.06)	

serum hemoglobin level ≥10 g/dl ($P = 0.01$) and serum CRP level <5.0 mg/dl ($P < 0.01$).

DISCUSSION

At present, gemcitabine monotherapy has a consensus as first-line therapy for advanced pancreatic cancer world wide. However, reliable data regarding gemcitabine monotherapy for advanced pancreatic cancer in a large number of Japanese patients are lacking because of the lack of prospective studies of gemcitabine except for one trial (13), and no retrospective analysis exists based on a large population of patients with pancreatic cancer. This is the first study that comprises a large number of consecutive Japanese patients with pathological disease confirmation, and in which a unified method for tumor staging and identical procedures for treatment and supportive care were undertaken throughout its the duration, in a single institution.

In Western countries, there have been several randomized controlled trials, including the treatment results of gemcitabine monotherapy (3–12). These studies demonstrated that gemcitabine monotherapy for advanced pancreatic cancer yielded response rates ranging from 4.4 to 17.3% and median overall survival ranging from 5.4 to 7.2 months (Table 5). Comparing these studies with the current study, the baseline patient characteristics such as the rate of performance status and the TNM stage were almost similar. These results of the response rate (10.6%), progression-free survival (median: 3.7 months) and overall survival (median: 6.8 months) in the current study were also similar to those in the Western studies cited. Additionally, adverse events, especially grade 3/4 neutropenia and thrombocytopenia in this study were also equivalent to those cited studies. To sum up, the treatment efficacy and toxicity of gemcitabine monotherapy in Japanese patients with advanced pancreatic cancer is comparable to those that have been reported in the Western literature.

The multivariate analysis indicated the following five independent prognostic factors in patients with advanced pancreatic cancer treated with gemcitabine: Karnofsky performance status, TNM stage, serum CA19-9 level, serum CRP level and serum hemoglobin level. Karnofsky performance status (14), TNM stage (14) and serum CA19-9 level (15,16) have been widely recognized as important prognostic factors in patients with advanced pancreatic cancer. Serum CRP level and serum hemoglobin level have also been well recognized as prognostic factors in pancreatic cancer

Table 5. A summary of the treatment results of gemcitabine monotherapy for advanced pancreatic cancer

No. of patients	PS (0,1) (%)	KPS (100,90) (%)	Stage IV (%)	Median OS (month)	Median PFS (month)	RR (%)	Grade 3/4 toxicity (%)		Study
							Neutropenia	Thrombocytopenia	
162	86	NA	90.1	5.4	2.2	5.6	5	11	Berlin et al. (5)
159	NA	53	79	7.2	3.9	8	19	8	Herrmann et al. (6)
282	90.8	NA	91.1	6.3	3.3	7.1	12.8	6.2	Oettle et al. (7)
156	82	NA	70	7.1	3.7	17.3	27.6	3.2	Louvet et al. (8)
180	73.9	NA	80.6	6.6	3.0*	4.4	32	14.2	Rocha Lima et al. (9)
174	NA	52	78	6.2	3.8*	7.1	14	4	Abou-Alfa et al. (10)
139	79	NA	65	6.59	3.5	5	41	9	Moore et al. (11)
347	87	NA	77	6.5	3.9	8	30	12	Van Cutsem et al. (12)
284	81.7	NA	75	5.91	3.55	8	27	11	Moore et al. (4)
264	98	82	91	6.8	3.7	10.6	35.6	7.6	Current study

PS, performance status; KPS, Karnofsky performance status; PFS, progression-free survival; RR, response rate; NA, not applicable. *The data represent the median time to progression.

(16,18,19) or other cancers such as stomach, breast, and head and neck (20–22). The kinetics of an elevation in serum CRP level and a decrease in serum hemoglobin level are considered to be tumor-induced activation of the immune and inflammatory systems, which release cytokines including interleukin-6 and tumor necrosis factor alpha (23,24). The activation links to cancer cachexia, characterized by a malnutrition and an accelated starvation state, and results in shorter survival (25). These five prognostic factors in Japanese patients with advanced pancreatic cancer are also similar to those that have been reported in Western patients.

Nowadays, promising regimens superior to gemcitabine monotherapy for advanced pancreatic cancer are being reported. In Western countries, the combination of gemcitabine and erlotinib resulted in a longer survival period compared with gemcitabine monotherapy, although the difference in the median overall survival was trivial (4). In addition, the combination of gemcitabine and axitinib, a selective oral inhibitor of vascular endothelial growth factor receptors, is also a promising strategy (26). On the other hand, in Japan, S-1 monotherapy and the combination of gemcitabine and S-1 have been reported as having a favorable response rate and increased overall survival in patients with advanced pancreatic cancer (27,28). One of these regimens may demonstrate an adequately superior survival time compared with gemcitabine monotherapy in future clinical trials.

In conclusion, this study could confirm the reproducibility of treatment efficacy, toxicity and prognostic factors of single-agent gemcitabine in Japanese patients in comparison with the results in Western patients. These results could be useful as reference data in determining treatment strategies and planning further clinical trials in Japanese patients with advanced pancreatic cancer.

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Conflict of interest statement

None declared.

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