4. Establishing a prior

In clinical trials with Bayesian model-based study designs, the prior should reasonably represent the physician's uncertainty. We established the prior distribution used in the Japanese CEX study based on the knowledge and experience of the participating clinical oncologists with regards to the CEX regimen. As described in Section 3, we assumed a gamma distribution $\mathrm{Ga}(a,b)$ for the prior distribution of the slope parameter b_1. Subject to $a=b$, the hyperparameter a determines the credible interval of the prior dose–toxicity curve under the gamma prior $\mathrm{Ga}(a,b)$. Thus, we determined that the hyperparameter a appropriately depicted the pre-study perceptions of the surveyed oncologists regarding the dose–toxicity relationship. By adjusting the hyperparameter a, i.e. $a=2$, 8, 20, 40, in addition to $a=5$ (Figure 1(a)) we created several graphical presentation patterns as shown in Figure 3. The clinical oncologists consulted in this study came to the consensus that the DLT probability at dose level 1 would be unlikely to be higher than 0.7 (more than double the target DLT level of 0.33) and the DLT probability at dose level 4 would be at least higher than 0.15 (around half of the target DLT level). The oncologists also concurred that the prior dose–toxicity curve and its credible interval constructed at $a=5$ reasonably reflected their knowledge and contained a sufficiently large degree of clinical uncertainty.

Although we determined the hyperparameters of the prior of b_1 based on an extensive discussion of the previous data using meticulous graphical presentations, our choice of the hyperparameters was arbitrary. If an established prior is overly informative, the prior may unduly influence posterior inferences and decisions, particularly early in the trial. Since dose levels must be selected sequentially in phase I dose-finding trials based on very small amounts of data, it may be important to quantify information contained in the chosen priors. These concerns may be addressed by quantifying the prior information

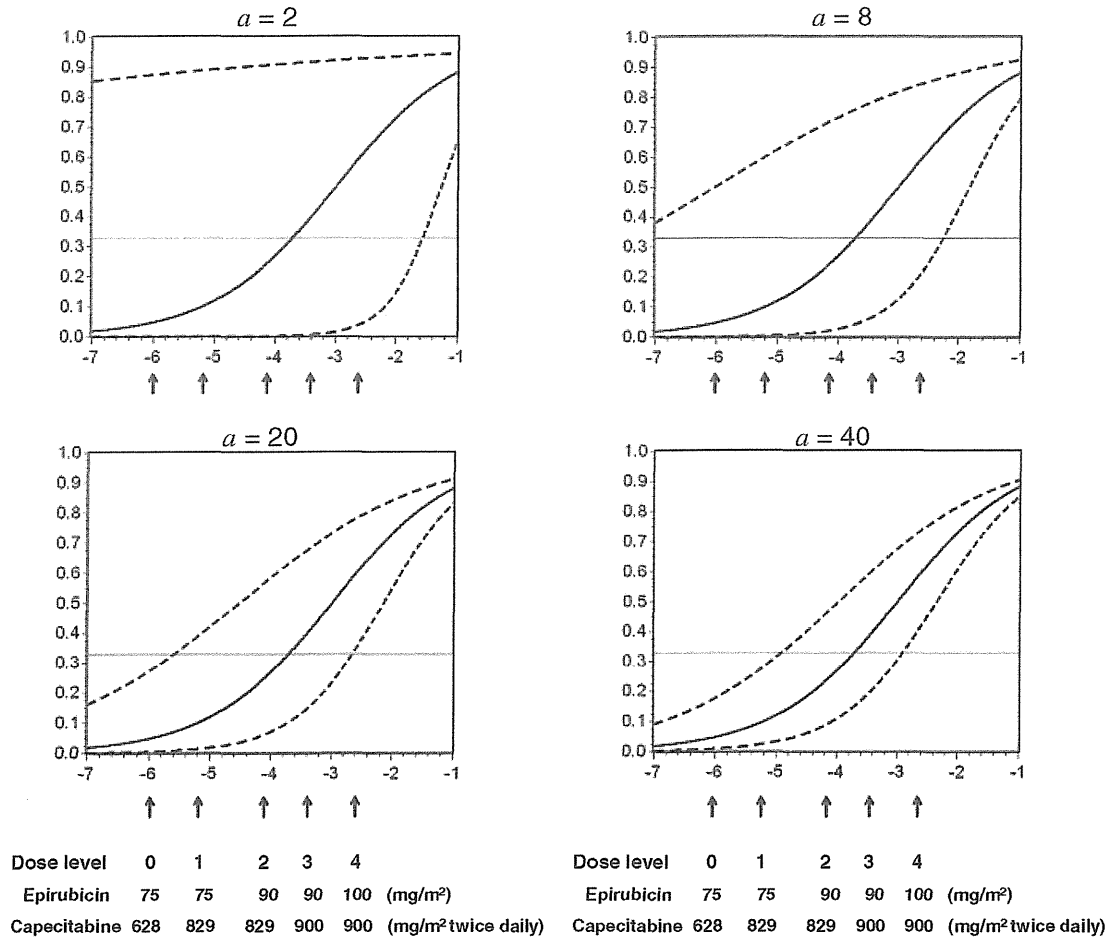

Figure 3. *Prior dose–toxicity curves with hyperparameters a=2, 8, 20, and 40.* Dashed lines indicate its 90 per cent credible intervals.

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in terms of an equivalent number of hypothetical patients, i.e. a prior ESS. Such a summary would allow one to judge the relative contributions of the prior and the data to the decisions. We applied an ESS method proposed recently by Morita *et al.* [5] to the Japanese CEX trial in a retrospective fashion. The prior ESS computed at $a=5$ was 2.1. Thus, after enrolling three patients, the information from the likelihood started to dominate the prior, as desired. In addition, under Ga(5,5), the coefficient of variation (=standard deviation/mean) of the slope parameter b_1 was approximately 0.45, which might indicate some uncertainty in the slope parameter. Hence the prior specified in the Japanese CEX trial seemed quite reasonable.

As for the sensitivity analysis of the prior, the prior ESS values computed at $a=2$, 6, 7, 8, 20, and 40 are 0.86, 2.6, 3.0, 3.4, 8.6, and 17.1, respectively. It appears that $a<7$ may be needed to ensure an ESS<3. The prior with $a=40$ has ESS$=17.1$, so that it has impact roughly equal to that of the data on the posterior inference, as suggested by comparing Figures 2 and 3. In addition, under $a=40$, the *a priori* 90 per cent credible interval for the increase in the odds of a DLT occurrence, e.g. for the dose escalation from level 1 to level 2, is computed as 2.3–4.1, which may be excessively narrow compared with the 90 per cent credible interval of 1.5–7.5 computed under $a=5$. Thus, given the limited amount of information available during the design stage of the Japanese CEX study, the prior with $a=40$ may be criticized as being overly informative.

5. Discussion

When designing a phase I dose-finding study using a Bayesian CRM, certain choices must be made regarding details involved in a dose–toxicity model, numerical values of dose levels, prior distributions of model parameters, etc., and these should be sensible and plausible. If a one-parameter logistic model is chosen for modeling a dose–toxicity relationship, as was our approach in the Japanese CEX study, the intercept has to be specified at a certain real value. The actual dose levels of the combination therapy planned in the Japanese CEX study were based on information from the identical regimen conducted earlier in Caucasian patients, the EORTC CEX trial. In order to reduce the dimension of the dose levels, we specified the numerical values of the dose levels in the dose–toxicity formulation using backward fitting. In addition, we established the prior distribution of the slope parameter in the Japanese phase I trial by eliciting pre-study perceptions regarding the dose–toxicity relationship from Japanese clinical investigators.

So far, in many cases Japanese clinical investigators have conducted phase I studies assuming that a RD in Japanese patients should be lower than in Caucasian patients, based on results of clinical trials conducted in Western countries. That is, a large amount of historical data based on numerous studies has been integrated to design Japanese phase I trials. The Japanese CEX study, however, did not take full advantage of the pre-study information on dose–toxicity relationships derived from the EORTC CEX study to formally establish the prior distribution of the model parameter in the CRM.

Differences in RDs may be caused by specific differences between the abilities of Japanese and Caucasian populations to tolerate particular toxicities. These interracial differences can be regarded as patient prognostic covariates, but unfortunately such covariates have not yet been identified. Extensions of methods to find RDs for ordered prognostic subgroups have been proposed by O'Quigley and Paoletti [18], Yuan and Chappell [19], and Ivanova and Wang [20]. These methods may be applied to identifying RDs within racial subgroups in the setting of a multinational phase I study. Thall *et al.* [21] have proposed a Bayesian sequential phase I/II dose-finding design accounting for patient covariates and dose–covariate interactions. This method may also prove useful in modeling the Japanese–Caucasian association in a multinational study setting. It may be a significant challenge, however, to construct informative prior(s) on such an interracial difference in dose–toxicity curves [22].

In the context of Bayesian clinical trial design, well-chosen priors are important to ensure that posterior-based decision rules have good study operating characteristics. Some appropriate criteria for calibrating priors may be desired to obtain sensible prior distributions. A prior ESS quantifying the prior information in terms of the number of hypothetical patients may provide a useful tool for understanding the impact of prior-related assumptions. A useful property of prior ESS is that it is readily interpretable by clinical investigators who are involved in designing a clinical trial. ESS_RegressionCalculator.R, a computer program used to calculate the ESS for a normal linear or logistic regression model, is available from the website http://biostatistics.mdanderson.org/SoftwareDownload.

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Acknowledgements

Satoshi Morita's research was supported in part by Grant H20-CLINRES-G-009 from the Ministry of Health, Labour and Welfare of Japan. He is grateful to Dr Masakazu Toi and Dr Junichi Sakamoto for providing important advice and suggestions. The author thanks the associate editor and the two referees for their constructive and helpful comments and suggestions.

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Hepatology Research

Hepatology Research 2011; 41: 296–302 doi: 10.1111/j.1872-034X.2011.00778.x

Original Article

Higher discontinuation and lower survival rates are likely in elderly Japanese patients with advanced hepatocellular carcinoma receiving sorafenib

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Aim: Sorafenib is approved for the treatment of advanced hepatocellular carcinoma (HCC) in Japan; however, its tolerability and efficacy in elderly patients with HCC have not been clarified. We aimed to evaluate the tolerability and efficacy of sorafenib with increasing age.

Methods: As part of a retrospective, multicenter cohort study conducted between May 2009 and February 2010, patients with advanced HCC received 400 mg sorafenib twice daily (standard dosage) or once daily (half-dosage) until disease progression or treatment intolerance.

Results: The mean age of the enrolled patients ($n = 76$) was 70.3 years, and 24 of them were ≥75 years old. The prognostic factors for survival were age < 75 years, performance status score zero, α-fetoprotein level < 1000 ng/mL, des-gamma-carboxy prothrombin level < 1000 ng/mL, and treatment duration ≥ 1 month. The median treatment duration and overall incidence of adverse drug reactions (ADRs) were not statistically different with increasing age. However, subgroup analysis revealed that treatment discontinuation because of ADRs was more frequent among the ≥75-year-old patients (41.7%) than among the <75-year-old ones (15.0%) with the standard dosage ($P = 0.047$); this trend was not observed among those who received the half-dose regimen.

Conclusions: Sorafenib has modest efficacy and acceptable toxicity in younger (<75 years) patients with HCC; however, elderly patients experience some side effects when it is administered at the standard dosage.

Key word: adverse drug reaction, dosage, elderly, hepatocellular carcinoma, sorafenib, survival

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common type of cancer worldwide. It is highly prevalent in the Asia-Pacific region and Africa, and its incidence is increasing in Western countries.[1] Infection with hepatitis B or C virus is the greatest risk factor for hepatocarcinogenesis.

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Received 10 October 2010; revision 6 December 2010; accepted 1 January 2011.

Sorafenib is the current standard drug for the first-line systemic treatment in patients with advanced HCC who are not candidates for curative treatments, such as surgical resection or locoregional therapies.[2] This multikinase inhibitor, with activity against Raf kinase and vascular endothelial cell growth factor (VEGF) receptor,[3] has been approved for the treatment of unresectable HCC by regulatory agencies of the European Union, United States, and other countries. This approval was based on the positive results of a placebo-controlled randomized phase III study of patients with advanced HCC.[4] Subsequently, a phase III study conducted in the Asia-Pacific region where hepatitis B virus infection is the predominant etiologic factor for chronic liver disease also demonstrated the survival benefits of sorafenib.[5]

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In global trials including non-Japanese populations, sorafenib was generally well tolerated;[4–7] however, their average age at presentation was relatively young (age range, 51–69 years). On the other hand, in our previous study of sorafenib treatment in Japanese patients with HCC,[8] the average age at presentation (70.3 years) was much older than in the previous trials,[4–7] and increasing age (≥75 years) was an important prognostic factor for lower overall survival (OS). At present, the efficacy and tolerability of this drug in elderly patients with advanced HCC is not clear; therefore, we conducted a secondary retrospective analysis of this multicenter trial[8] to evaluate the efficacy and tolerability of sorafenib with increasing age.

METHODS

Patients

THIS RETROSPECTIVE, MULTICENTER cohort study included patients with histopathologically and/or radiographically proven advanced HCC at four institutes of the Kanagawa Liver Study Group. All patients had measurable disease at baseline according to the response evaluation criteria in solid tumors (RECIST).[9] Further, all patients provided written informed consent. The institutional review board or ethics committee approved the study protocol, which complied with the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

Patients were excluded if they had previously received molecular-targeted therapies or any other systemic treatment. The inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) score of 2 or less, Child–Pugh liver function class A or B, adequate hematologic function (platelet count > 5.0×10^{10}/L and hemoglobin level > 8.0 g/dL), adequate hepatic function (albumin level > 2.5 g/dL, total bilirubin level < 3.0 mg/dL, and alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels < five times the normal upper limit), and adequate renal function (serum creatinine level < 1.5 times the normal upper limit).

Treatment regimens

All of the patients received sorafenib between May 2009 and February 2010. The dosage was 400 mg twice daily (the standard dose); treatment interruptions and dose reductions (first 400 mg twice daily, then 400 mg once daily, and finally 400 mg every 2 days) were permitted for adverse drug reactions (ADRs). In some elderly patients (≥75 years) and those with poor liver function, the initial dose was reduced to half the standard dose, a 400-mg once-daily regimen. The patients received the therapy until any of the following criteria for discontinuation of therapy was met: ADRs that required termination of medication, disease progression, deterioration of ECOG PS score to 4, and withdrawal of consent. Other criteria for discontinuation included the concomitant use of an illicit drug that, in the opinion of the investigator, could induce toxicity or noncompliance with follow-up.

Response assessments

The patient response to treatment was evaluated according to the RECIST.[9] OS was measured from the date of administration of sorafenib until the date of death from any cause. The time to radiologic progression (TTRP) was defined as the time from the date of administration of sorafenib to disease progression, according to RECIST. Tumor measurements were performed at screening and every 4–6 weeks during treatment. Safety assessments included documentation of ADRs, clinical laboratory tests, physical examination, and measurement of vital signs. ADRs were defined according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Statistical analysis

Continuous variables are represented as the mean ± standard deviation, and categorical variables are represented as the absolute and relative frequencies. The Mann–Whitney *U*-test was used to compare continuous variables between groups of patients; categorical variables were compared by using the Fisher's exact test or its equivalent for more than two categories. The TTRP and OS were calculated by Kaplan–Meier survival curves with log-rank survival comparisons and 95% confidence intervals (95% CI). Twenty-two variables were assessed using a univariate analysis to identify possible prognostic factors: age (≥70 years vs. <70 years and ≥75 years vs. <75 years), gender (male vs. female), etiology (hepatitis C vs. other), Child-Pugh class (A vs. B), tumor-node-metastasis (TNM) staging system revised by the Liver Cancer Study Group of Japan in 2008[10] (II or III vs. IV), tumor staging revised by Barcelona Clinic Liver Cancer (BCLC) group[11] (B vs. C), macrovascular invasion (absent vs. present), extrahepatic spread (absent vs. present), ECOG PS (score 0 vs. 1 to 2), initial dose of sorafenib (400 mg/day vs. 800 mg/day), total sorafenib

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dose (≥30 000 mg vs. <30 000 mg), sorafenib-treatment duration (≥1 month vs. <1 month), average sorafenib dose (≥400 mg/day vs. <400 mg/day, ≥500 mg/day vs. <500 mg/day, and ≥600 mg/day vs. <600 mg/day), grade 3–4 ADRs (absent vs. present), platelet count (≥10 000 /μL vs. <10 000 /μL), serum albumin level (≥3.5 g/dL vs. <3.5 g/dL), α-fetoprotein (AFP) level (≥1000 ng/mL vs. <1000 ng/mL), des-gamma-carboxy prothrombin (DCP) level (≥1000 ng/mL vs. <1000 ng/mL), and treatment response according to the RECIST[9] (complete response, partial response, and stable disease vs. progressive disease). A Cox proportional hazards model was used to investigate prognostic factors for OS. All statistical analyses were carried out with the PASW Statistics 17.0 software (IBM SPSS, Inc., Chicago, IL, USA) and SAS (version 9.2).

RESULTS

Baseline characteristics

TABLE 1 SHOWS the baseline characteristics of the 76 patients enrolled in the study. Their mean age was 70.3 years (range, 37–88 years), and 24 (31.6%) patients were aged ≥75 years. Most of the patients (82.9%) were male, and 57 (75%) patients had a documented history of viral hepatitis (hepatitis B, hepatitis C, or both hepatitis B and C). Forty-one (53.9%) patients underwent transcatheter arterial chemoembolization, 10 (13.2%) received arterial infusion therapy, 13 (17.1%) received percutaneous ablation therapy, six (7.9%) underwent surgical resection, three (3.9%) received radiotherapy or other therapy, and three (3.9%) patients were never treated previously. Seventy-one (93.4%) patients presented with Child–Pugh class A liver cirrhosis and the remaining (6.6%) presented with Child–Pugh class B disease. Further, 24 (31.6%) patients had vascular invasion and 19 (25%) had extrahepatic spread of HCC. There were no significant differences in the baseline characteristics between the <75-year-old and the ≥75-year-old patients except in the case of previous therapy: arterial infusion chemotherapy was employed more often in the elderly patients ($P = 0.041$).

The standard dosage of sorafenib was administered to 52 (68.4%) patients and the half-dose regimen was administered to the remaining (31.6%). The patients in the latter group were significantly older and had Child-Pugh class B liver disease more often.

Safety and tolerability

Table 2 shows the incidence of ADRs (based on CTCAE v3.0) in relation to age and the treatment regimens. The incidence of any grade of ADRs (96.2% vs. 100%, $P = 0.230$) and grade 3–4 ADRs (44.2% vs. 54.2%, $P = 0.420$) were not significantly different between the <75-year-old and the ≥75-year-old patients. However, in the subgroup analysis of the two treatment regimens, anorexia (any grade) was significantly more common in the ≥75-year-old patients who received the standard dosage (75.0% vs. 22.5%, $P = 0.001$) compared with the half-dose regimen (50.0% vs. 16.7%, $P = 0.083$). Similarly, grade 3–4 anorexia was significantly more common in the ≥75-year-old patients who received the standard dosage (33.3% vs. 2.5%, $P = 0.001$) compared with the half-dose regimen (16.7% vs. 8.3%, $P = 0.537$).

The median treatment duration of all the patients was 1.7 months, without a significant difference between the age groups (1.9 months for <75 years vs. 1.4 months for ≥75 years). Sorafenib treatment was discontinued because of radiologic tumor progression and ADRs in 22 (42.3%) and nine (17.3%) of the <75-year-old patients, respectively, and eight (33.3%) and eight (33.3%) of the ≥75-year-old patients, respectively (Table 3). There was no statistical difference in the incidences of discontinuation due to radiologic tumor progression and ADRs between the <75-year-old and the ≥75-year-old patients ($P = 0.457$ and $P = 0.119$, respectively). In the subgroup analysis of the two treatment regimens, a higher percentage of the ≥75-year-old (41.7%) patients who received the standard dosage discontinued the therapy because of ADRs (vs. 15.0% of those <75 years old, $P = 0.047$); however, this trend was not observed in the half-dose regimen (25.0% for ≥75 years vs. 25.0% for <75 years, $P = 1.000$).

Efficacy and response

Overall, two (2.6%) patients had a complete response, three (3.9%) had a partial response, and 20 (26.3%) had stable disease. The response rate, defined as the percentage of patients with a complete or partial response, was 6.6%. Twenty-four deaths had occurred on endpoint during observation periods. The median OS of all the patients was 8.1 months (95% CI, 5.4–10.7), and the median TTRP was 2.9 months (95% CI, 2.0–3.7). A univariate analysis with a Kaplan–Meier model identified 10 variables as prognostic indicators of OS: age (<75 years vs. ≥75 years, $P = 0.022$), TNM staging system by the Liver Cancer Study Group of Japan (II+III vs. IV, $P = 0.027$), tumor staging by the BCLC group (B vs. C, $P = 0.015$), macrovascular invasion (absent vs. present, $P = 0.005$), ECOG PS (score 0 vs. 1–2, $P < 0.001$), total dose of sorafenib (≥30 000 mg vs. <30 000 mg, $P = 0.001$), treatment duration (≥1 month

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Table 1 Demographic and baseline characteristics of the patients

Characteristics	<75-year-olds ($n = 52$)	≥75-year-olds ($n = 24$)	P
Age (years)			
Gender			0.945
Male	43 (82.7)	20 (83.3)	
Female	9 (17.3)	4 (16.7)	
Etiology			0.059
Hepatitis C only	28 (53.8)	16 (66.7)	
Hepatitis B only	10 (19.2)	0 (0.0)	
Hepatitis B and C	3 (5.8)	0 (0.0)	
Other	11 (21.2)	8 (33.3)	
Previous therapy			0.041
TACE	30 (57.7)	11 (45.8)	
Arterial infusion	3 (5.8)	7 (29.2)	
Percutaneous ablation	9 (17.3)	4 (16.7)	
Surgical resection	6 (11.5)	0 (0.0)	
Radiotherapy or others	3 (5.8)	0 (0.0)	
None	1 (1.9)	2 (8.3)	
ECOG PS score			0.110
0	38 (73.1)	14 (58.3)	
1	11 (21.2)	10 (41.7)	
2	3 (5.8)	0 (0.0)	
TNM stage			0.219
II	5 (9.6)	0 (0.0)	
III	21 (40.4)	13 (54.2)	
IVA	11 (21.2)	7 (29.2)	
IVB	15 (28.8)	4 (16.7)	
BCLC stage			0.876
B (intermediate)	25 (48.1)	12 (50.0)	
C (advanced)	27 (51.9)	12 (50.0)	
Child–Pugh class			0.564
A	48 (92.3)	23 (95.8)	
B	4 (7.7)	1 (4.2)	
Macrovascular invasion			0.451
Absent	37 (71.2)	15 (62.5)	
Present	15 (28.8)	9 (37.5)	
Extrahepatic spread			0.254
Absent	37 (71.2)	20 (83.3)	
Present	15 (28.8)	4 (16.7)	
Bone	7 (13.5)	1 (4.2)	
Lung	6 (11.5)	1 (4.2)	
Lymph nodes	1 (1.9)	1 (4.2)	
Other	1 (1.9)	1 (4.2)	
Biochemical analysis			
ALT (IU/L)	60 ± 54	45 ± 19	0.190
Total bilirubin (mg/dL)	1.0 ± 0.5	1.1 ± 0.5	0.686
Albumin (g/dL)	3.6 ± 0.5	3.5 ± 0.4	0.188
Platelets ($\times 10^4/\mu L$)	14.2 ± 7.2	15.9 ± 7.4	0.338
AFP (ng/mL)	13 791 ± 50 308	53 445 ± 142 974	0.198
AFP-L3 (%)†	33 ± 28	36 ± 27	0.805
DCP (ng/mL)‡	14 378 ± 54 696	13 108 ± 24 667	0.914

†$n = 48$.
‡$n = 75$.
The data represent the mean ± standard deviation or the number of patients (percentage).
AFP, α-fetoprotein; AFP-L3, fucosylated fraction of AFP; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system;[11] DCP, des-gamma-carboxy prothrombin; ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transcatheter arterial chemoembolization; TNM, tumor-node-metastasis staging revised by the Liver Cancer Study Group of Japan in 2008.[10]

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Table 2 Incidence of adverse drug reactions (ADRs) according to age and treatment regimens

ADR	<75-year-olds			≥75-year-olds		
	Total	400 mg q.d. ($n = 12$)	400 mg b.i.d. ($n = 40$)	Total	400 mg q.d. ($n = 12$)	400 mg b.i.d. ($n = 12$)
All ADRs	96.2/44.2	100/50.0	95.0/42.5	100/54.2	100/41.7	100/66.7
Fatigue	63.5/3.8	41.7/8.3	70.0/2.5	50.0/8.3	58.3/16.7	41.7/0.0
Anorexia	21.2/3.8	16.7/8.3	22.5*/2.5*	62.5/25.0	50.0/16.7	75.0*/33.3*
Diarrhea	65.4/1.9	25.0/0.0	77.5/2.5	45.8/0.0	16.7/0.0	75.0/0.0
Hand-foot-skin reaction	53.8/13.5	41.7/16.7	57.5/12.5	33.3/0.0	33.3/0.0	33.3/0.0
Rash	13.5/0.0	25.0/0.0	10.0/0.0	8.3/0.0	8.3/0.0	8.3/0.0
Hypertension	15.4/0.0	25.0/0.0	12.5/0.0	25.0/0.0	16.7/0.0	33.3/0.0
ALT elevation	40.4/7.7	41.7/8.3	40.0/7.5	37.5/8.3	41.7/8.3	33.3/8.3
Bilirubin elevation	21.2/5.8	16.7/0.0	22.5/7.5	25.0/.12.5	16.7/0.0	33.3/25.0
Decreased platelet count	21.2/7.7	33.3/16.7	17.5/5.0	29.2/4.2	33.3/0.0	25.0/8.3

*Significant difference ($P = 0.001$) between the ≥75-year-old and the <75-year-old patients in the 400 mg b.i.d. regimen (standard dosage).
The data represent any grade (%)/grade 3–4 (%) of ADRs.
ALT, alanine aminotransferase.

vs. <1 month, $P < 0.001$), AFP level and DCP levels (<1000 ng/mL vs. ≥1000 ng/mL, $P < 0.001$), and treatment response (complete response, partial response, and stable disease vs. progressive disease, $P < 0.001$). A multivariate analysis with a Cox proportional-hazards model identified five variables as prognostic factors for OS: age (<75 years vs. ≥75 years; hazard ratio [HR], 0.237; 95% CI, 0.072–0.784; $P = 0.018$), ECOG PS (score 0 vs. 1–2; HR, 4.090; 95% CI, 1.113–15.037; $P = 0.034$), AFP level (<1000 ng/mL vs. ≥1000 ng/mL; HR, 0.131; 95% CI, 0.044–0.390; $P < 0.001$), DCP level (<1000 ng/mL vs. ≥1000 ng/mL; HR, 0.166; 95% CI, 0.047–0.578; $P = 0.005$), and treatment duration (≥1 month vs. <1 month; HR, 4.412; 95% CI, 1.016–19.159; $P = 0.048$). Figure 1 shows Kaplan–Meier curves of OS for <75-year-old and ≥75 year-old patients.

There were no significant differences in the average OS and the median TTRP between the patients receiving the standard-dose regimen and those receiving the half dose regimen (6.6 months vs. 5.8 months, $P = 0.965$ for OS; 3.0 months and 2.8 months, $P = 0.600$ for TTRP, respectively). In the subgroup analysis of patients ≥75 years, the average OS and the median TTRP were comparable between the two dose regimens (5.3 months vs. 5.0 months, $P = 0.839$ for OS; 2.0 months vs. 2.8 months, $P = 0.138$ for TTRP, respectively).

DISCUSSION

OUR PREVIOUS REPORT[8] indicated that median treatment duration and incidence of ADRs were not statistically different with increasing age; however, age ≥75 years was an important prognostic factor for lower OS. To reevaluate the relationship between patient age and drug safety, we conducted a secondary analysis using the same cohort and found that sorafenib has modest

Table 3 Incidence of treatment discontinuation according to age and treatment regimens

Reasons for discontinuation	<75-year-olds			≥75-year-olds		
	Total	400 mg q.d. ($n = 12$)	400 mg b.i.d. ($n = 40$)	Total	400 mg q.d. ($n = 12$)	400 mg b.i.d. ($n = 12$)
ADRs	9 (17.3)	3 (25.0)	6 (15.0)*	8 (33.3)	3 (25.0)	5 (41.7)*
Radiologic tumor progression	22 (42.3)	4 (33.3)	18 (45.0)	8 (33.3)	4 (33.3)	4 (33.3)

*Significant difference ($P = 0.047$) between the <75-year-old and the ≥75-year-old patients in the 400 mg b.i.d. regimen (standard dosage).
The data represent the number of patients (percentage).
ADR, adverse drug reaction.

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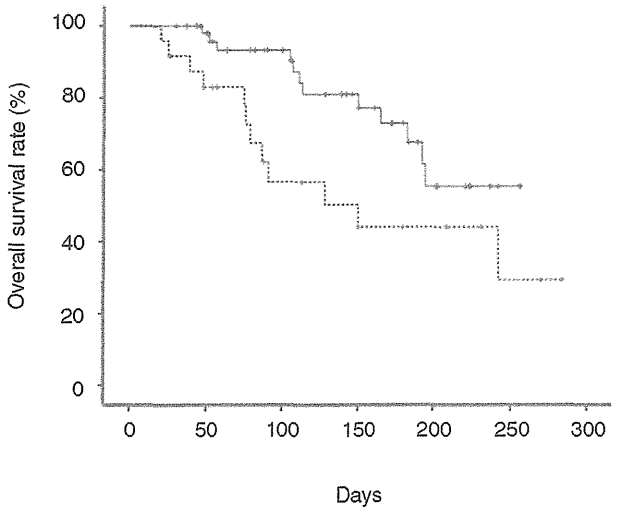

Figure 1 Kaplan–Meier estimates of overall survivals of the <75-year-old (solid line) and ≥75 year-old (broken line) patients. Univariate analysis revealed a significant difference ($P = 0.022$) between these age groups.

efficacy and tolerable ADRs in younger (<75 years) Japanese patients with advanced HCC; however, more than 40% of the elderly patients (≥75 years) who received the standard dosage (400 mg twice daily) discontinued the treatment because of ADRs. This is the first report indicating that older age is associated with a greater likelihood of discontinuation of sorafenib treatment and lower survival rate clinically.

The Raf/MAP kinase-ERK kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway is overexpressed in HCC.[12–14] Sorafenib is a small molecule that inhibits multiple tyrosine kinases including Raf kinase, platelet-derived growth factor (PDGF), VEGF receptor 2 and 3 kinases, and c-Kit receptor, and it uniquely targets the Raf/MEK/ERK pathway.[15] Sorafenib was generally well tolerated in global trials of non-Japanese younger populations[4–7] and a phase I trial of Japanese patients.[16] In the present study, we demonstrated a median OS of 8.1 months and a median TTRP of 2.6 months. These data are similar to those of an Asia-Pacific trial[5] but do not indicate the benefit of sorafenib reported in the SHARP trial.[4] These conflicting results may be derived from the poorer treatment compliance in the current study than in the SHARP trial: 76% of the sorafenib-group patients received more than 80% of the planned daily dose of sorafenib in the SHARP trial, whereas only 40% of our patients received more than 80% of the planned daily dose (data not shown). Our study population also had significantly short treatment duration (median, 1.7 months) due to ADRs. The percentage of patients with any ADRs in this study was >10% higher than that in the global trials.[4,5] Especially, higher percentages of patients had fatigue, anorexia, and diarrhea (59.2%, 34.2%, and 59.2%, respectively) than those in the SHARP trial (22%, 14%, and 39%, respectively) or Asia-Pacific trial (20.1%, 12.8%, and 25.5%, respectively). These differences in ADRs can be explained by the differences in the elderly populations of these three studies: the mean age in the current study (70.3 years) is older than those in the SHARP trial (64.9 years) and Asia-Pacific study (51.0 years). On the other hand, our data indicate that the incidence of sorafenib discontinuation because of ADRs is low in younger patients (<75 years) (15.4%) and comparable with the published data.[4]

There are several reports indicating that the elderly are at increased risk of ADRs when they receive various antiangiogenic drugs.[17,18] van der Veldt *et al.*[17] showed that age and gender are predictive factors for severe toxicity of sunitinib in patients with advanced renal cell cancer. Ramalingam *et al.*[18] showed that, in elderly patients with non-small-cell lung cancer, the addition of bevacizumab to standard chemotherapy did not improve the clinical outcome but results in increased toxicity and treatment-related deaths compared with patients aged <70 years. Therefore, we emphasize that when taking the antiangiogenic drugs, including sorafenib, for adjuvant or maintenance treatment in elderly patients with HCC, the special concern of the safety might be needed.

In the present study, the difference in the initial dose did not affect the OS and TTRP. A recent case report of a 74-year-male patient with advanced HCC described that the patient received the half-dose of sorafenib for 8 months and achieved a more than 16 months survival benefit without disease recurrence.[19] Therefore, further studies will be needed to determine whether a reduced-dose regimen of sorafenib truly imparts a survival benefit for patients with HCC comparable to the standard-dose regimen. At present, older age alone should not preclude the therapeutic option using standard-dose of sorafenib; however, such regimen might be cautious for elderly patients with other risk factors to avoid discontinuation of sorafenib due to ADRs.

The Cox proportional-hazards model indicated age (<75 years), ECOG PS (score 0), AFP level (<1000 ng/mL), DCP level (<1000 ng/mL), and treatment duration (≥1 month) as favorable prognostic factors for OS. In a global phase III trial of patients with renal cell carcinoma treated with sorafenib, multivariate analysis

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revealed that the ECOG PS score is an independent factor for OS, although this score was also an independent factor for OS in the placebo group.[20] The recent study in France has shown that in patients with advanced HCC administered sorafenib, the Child–Pugh class, BCLC stage, and ECOG PS score are prognostic factors for survival.[21] Therefore, the ECOG PS score at the start of sorafenib therapy may contribute a survival advantage in the treatment of advanced HCC.

Our study has some limitations, such as small sample size, retrospective design, which allowed for potential biases including selection, and recall bias. The retrospective nature of our analysis raises the potential limitation of accurate and complete documentation of ADRs. Despite these limitations, our data have some impact, especially in view of this first report of efficacy and safety profiles of sorafenib in Japanese older patients with HCC.

In conclusion, sorafenib has modest efficacy and acceptable toxicity profiles in younger (<75 years) Japanese patients with HCC; however, elderly patients experience some side effects with the standard dosage. A larger prospective study is necessary to determine the efficacy of sorafenib in this group of patients.

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Construction and Validation of a Prognostic Index for Patients With Metastatic Pancreatic Adenocarcinoma

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Objectives: To identify prognostic factors in patients with metastatic pancreatic adenocarcinoma.

Methods: The relationship between patient characteristics and outcome was examined by multivariate regression analyses of data from 409 consecutive patients with metastatic pancreatic adenocarcinoma who had been treated with a gemcitabine-containing regimen, and we stratified the patients into 3 risk groups according to the number of prognostic factors they had for a poor outcome. A validation data set obtained from 145 patients who had been treated with agents other than gemcitabine was analyzed. The prognostic index was applied the each of the patients.

Results: The multivariate regression analyses revealed that the presence of pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value significantly contributed to a shorter survival time. The patients were stratified into 3 groups according to their number of risk factors, and their outcomes of the 3 groups were significantly different. When the prognostic index was applied to the validation data set, the respective outcomes of the 3 groups were found to be significantly differed from each other.

Conclusions: Pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value are important prognostic factors for patients with metastatic pancreatic adenocarcinoma.

Key Words: pancreatic cancer, prognostic factor, validation, chemotherapy, multivariate analyses, prognostic index

(*Pancreas* 2011;40: 415–421)

Despite the major advances in cancer management that have been achieved in recent years, pancreatic adenocarcinoma (PC) remains a challenge to clinicians because of the difficulty of early diagnosis. Most PC patients have locally advanced or metastatic disease by the time the diagnosis is made. Even when resection is performed, the recurrence rate is extremely high, and nonsurgical treatments after recurrence have largely been ineffective.[1,2] Although gemcitabine (GEM) has been demonstrated to provide a modest clinical benefit and therefore become the standard chemotherapy for advanced PC,[3,4] the median survival time of patients with advanced disease remains only around 6 months. Many clinical trials of treatments with combinations GEM and other agents have been conducted to improve treatment efficacy in patients with advanced PC, and one of them, a combination of GEM and erlotinib, has resulted in longer survival than treatment with single-agent GEM.[5] However, because the difference in median overall survival between the 2 regimens was only 0.3 months and the incidence of adverse events with GEM plus erlotinib tended to be higher, this combination has been considered a treatment option for patients in good general condition, not an alternative to GEM monotherapy. Because various treatment options according to the patient's general condition and prognosis are expected to be developed in the future, if the survival time of patients with metastatic PC could be predicted before the start of the treatment, those with an extremely poor prognosis could be offered supportive care alone or more conservative treatment, such as GEM monotherapy and spared the adverse effects of combination chemotherapy. A validated prognostic index would identify subgroups of patients for specific treatments and predict survival, and identification of prognostic factors would be helpful in designing clinical trials of systemic chemotherapy and analyzing their results. Furthermore, clinical trials of various new treatments will be conducted in the future, and because some of the candidate drug combinations for new treatment regimens may contain GEM and others may not, establishment of an accurate prognostic index that can be applied to various treatment regimens is needed. Although many possible prognostic factors, such as performance status,[6 8] the serum carbohydrate antigen (CA 19-9) level,[9 14] and the serum C-reactive protein (CRP) level[11,13,15,16] have been identified in advanced PC, most were identified in small numbers of patients, and the results were not validated, possibly making the analyses underpowered and unreliable.

The purposes of this study were (1) to identify the most helpful, readily available prognostic factors for predicting the survival time of metastatic PC patients and (2) to construct and validate a practical and universal prognostic index for metastatic PC patients.

MATERIALS AND METHODS

Cases Used as the Basis for Construction of the Prognostic Index (Construction Set)

Data from 409 consecutive patients with metastatic PC who had received GEM-containing systemic chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between March 2001 and January 2007 were reviewed to construct the prognostic index. None of the patients had been treated for their cancer before chemotherapy, except that some of them had undergone by pancreatectomy. All patients had distant metastasis based on diagnostic imaging findings obtained by various modalities, including chest radiography, ultrasonography, and computed tomography. The diagnosis of adenocarcinoma was confirmed pathologically in every case by examination of the surgical specimen or a fine-needle aspiration biopsy specimen. Whenever possible, peritoneal or pleural fluid cytodiagnosis was performed in patients with an intraperitoneal or intrapleural fluid collection. Percutaneous transhepatic or endoscopic retrograde biliary drainage was performed in all patients who had

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Received for publication March 25, 2010; accepted October 15, 2010.

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TABLE 1. Patient Characteristics

			Construction Set		Validation Set	*P*
Age		Median (range)	64 (21–81)		59.5 (39–75)	0.0005*
Sex	Male	n (%)	241 (59)		98 (68)	0.10†
	Female	n (%)	168 (41)		47 (32)	
Performance status	0–1	n (%)	395 (97)		138 (95)	0.40†
	2–3	n (%)	14 (3)		7 (5)	
Prior pancreatectomy	(+)	n (%)	66 (16)		16 (11)	0.24†
Abdominal and/or back pain‡	(+)	n (%)	138 (34)		62 (43)	0.074†
Diabetes mellitus	(+)	n (%)	171 (42)		46 (31)	0.037†
Location of primary tumor	Uncus and head	n (%)	191 (47)		48 (33)	0.01†
	Body or tail	n (%)	217 (53)		94 (65)	
Liver metastasis	(+)	n (%)	297 (73)		111 (77)	0.39†
Lymph node metastasis	(+)	n (%)	124 (30)		49 (34)	0.44†
Lung metastasis	(+)	n (%)	68 (17)		22 (15)	0.76†
Peritoneal dissemination	(+)	n (%)	88 (22)		37 (26)	0.40†
Pleural metastasis	(+)	n (%)	28 (7)		4 (3)	0.10†
Bone metastasis	(+)	n (%)	8 (2)		2 (1)	0.92†
Leukocytes count, /mL	(3900–6300)§	Median (range)	6100 (2100–35,500)		6800 (3400–18,000)	0.015*
Hemoglobin level, g/dL	(11.3–14.9)§	Median (range)	12.3 (6.7–16.1)		12.2 (8.6–15.9)	0.50*
Platelets count, /mL	(12.5–37.5)§	Median (range)	22.3 (9.2–57.4)		22.5 (9.5–47.1)	0.55*
Albumin level, g/dL	(3.7–5.2)§	Median (range)	3.7 (2.2–4.9)		3.7 (2.2–4.7)	0.50*
Total bilirubin level, mg/dL	(0.3–1.2)§	Median (range)	0.7 (0.2–3.1)		0.7 (0.3–3.2)	0.92*
AST level, IU/L	(13–33)§	Median (range)	27 (10–196)		26 (10–204)	0.46*
ALT level, IU/L	(6–27)§	Median (range)	29 (5–465)		28 (7–366)	0.90*
LDH level, IU/L	(119–229)§	Median (range)	188 (19–2311)		162 (15–2192)	0.001*
CRP level, mg/dL	(−0.1)§	Median (range)	0.6 (0.0–20.6)		0.8 (0–17.8)	0.15*
CEA level, ng/mL	(−5.0)§	Median (range)	6 (0.6–2090)		6.9 (0.4–9990)	0.55*
CA19-9 level, U/mL	(−37)§	Median (range)	1857 (1–1620,000)		3022 (1–1,857,600)	0.088*
Treatment		n (%)	GEM alone 302 (74)	Irinotecan	16 (11)	
		n (%)	GEM + S-1 41 (10)	Docetaxel	6 (4)	
		n (%)	GEM + 5-FU 27 (7)	S-1	29 (20)	
		n (%)	GEM + CDDP 39 (10)	UFT	22 (15)	
		n (%)		5-FU + CDDP	31 (21)	
		n (%)		MTX + 5-FU	41 (28)	

*Mann-Whitney *U* test.

†χ^2 test.

‡Abdominal and/or back pain: treated with opioid.

§Reference range.

CDDP indicates cisplatin; FU, fluorouracil; MTX, methotrexate.

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obstructive jaundice before chemotherapy. All patients provided written informed consent before the start of treatment.

Factors Analyzed

The following 24 variables were selected for analysis in this study based on the results of previous investigations[12,13,15,17 23] and/or our own clinical experience: (1) age, sex, prior pancreatectomy, Eastern Cooperative Oncology Group performance status, abdominal and/or back pain treated with an opioid, diabetes mellitus, leukocyte count, hemoglobin level, platelet count, and serum level of albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin, CRP, as host-related variables, and (2) location of the primary tumor, liver metastasis, lymph node metastasis, lung metastasis, peritoneal dissemination, pleural metastasis, bone metastasis, serum level of carbohydrate antigen 19-9 (CA19-9), and CEA, as tumor-related variables. All data were obtained immediately before the start of systemic chemotherapy. Nodules more than 1 cm in diameter and/or a conspicuous volume of effusion in the abdominal or thoracic cavity observed by ultrasonography or computed tomography and cytologically proven malignant effusions were considered evidence of peritoneal dissemination or pleural metastasis in this study.

Cases Used as a Basis for Validation of the Prognostic Index (Validation Set)

A data set from 145 patients who participated in clinical trials of anticancer agents other than GEM at the National Cancer Center Hospital between August 1991 and January 2004 was used to validate the prognostic index. The treatment regimens were docetaxel,[24] irinotecan,[25] S-1,[26] UFT,[27] 5-fluorouracil + cisplatin,[28] and methotrexate + 5-fluorouracil.[29]

TABLE 2. Univariate Analysis

Categorical Variables			Continuous Variables		
	Median Survival Time, d	*P*		Coefficient (β)	*P*
Sex					
Male	209		Age, yr	−0.005	0.3542
Female	188	0.3543	Leukocytes count, /mL	7.59	<0.0001
Performance status					
0–1	207		Hemoglobin level, g/dL	−1.59	<0.0001
2–3	102	0.138	Platelets count, /mL	0.021	0.001
Prior pancreatectomy					
+	298		Albumin, g/dL	−0.867	<0.0001
−	191	<0.0001	Total bilirubin level, mg/dL	−0.088	0.3902
Abdominal and/or back pain*					
+	144		AST level, IU/l	0.008	<0.0001
−	238	<0.0001	ALT level, IU/L	0.003	0.0095
Diabetes mellitus					
+	201		LDH level, U/L	0.003	<0.0001
−	198	0.9802	CRP level, mg/dL	0.129	<0.0001
Location of primary tumor					
Uncus or head	200		CEA level, ng/mL	0.001	<0.0001
Body or tail	204	0.9885	CA19-9 level, U/mL	1.296	0.0004
Liver metastasis					
+	186				
−	243	<0.0001			
Lymph node metastasis					
+	167				
−	219	0.0584			
Lung metastasis					
+	224				
−	196	0.5835			
Peritoneal dissemination					
+	156				
−	219	0.0063			
Pleural metastasis					
+	198				
−	200	0.5435			
Bone metastasis					
+	113				
−	204	0.0336			

*Abdominal and/or back pain: treated with an opioid.

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Statistical Analysis

Survival rates were calculated by the method of Kaplan and Meier.[30] All deaths regardless of cause were considered events. The stratified log-rank test was used to compare survival curves, and censored data were taken into account.[31]

Univariate Analysis

A univariate analysis was conducted to select candidate factors to adopt in the multivariable analysis. For categorical data, factors were divided into 2 categories, and the log-rank test was applied. Because dichotomizing continuous variable data, such as the serum biochemical and hematological data, by using arbitrary cutoff points might have resulted in major biases, we used the Cox proportional hazards model, which enables selection of candidate factors without dichotomization.[32,33] Differences with a $P < 0.01$ were considered significant.

Multivariate Analysis

The variables identified as having prognostic significance in the univariate analyses were included in the subsequent multivariate analysis. To construct a simple and practical prognostic index for routine clinical use, all factors were divided into 2 categories. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cutoff value to maximize both the sensitivity and the specificity of continuous variables. Each ROC curve was constructed as a predictor of death at 6.6 months, which was the median survival time of the cases in the construction set. The Cox proportional hazards model was used to identify the variables that made the most significant contribution to survival. Differences with a $P < 0.01$ were considered significant. All P values were 2 sided. All analyses were performed by using Dr SPSS statistical software (SPSS Inc, Chicago, Ill).

The numbers of risk factors present were used to construct the prognostic index. Patients were stratified into 3 risk groups on the basis of the number of risk factors present.

RESULTS

Patient Characteristics

There were 241 men and 168 women in the construction set. Their median age was 64 years (range, 21–81 years), and the performance status of 395 patients was 0 to 1. Liver metastasis had been diagnosed in 297 patients, and peritoneal dissemination had been diagnosed in 88 patients (Table 1). The treatment regimens were GEM alone in 302 patients, GEM + cisplatin, 39, GEM + 5-flurorouracil, 27, and GEM + S-1, 41.

Survival

As of the date of the survival analysis, 404 patients had died, and the median survival time and 1-year survival rate were 6.6 months and 22%, respectively.

Univariate Analysis

The following 14 of the 24 pretreatment variables evaluated were identified as significantly associated with shorter survival time (Table 2): absence of prior pancreatectomy ($P < 0.0001$), presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver metastasis ($P < 0.0001$), presence of peritoneal dissemination ($P = 0.0063$), elevated leukocyte count ($P < 0.0001$), elevated platelet count ($P = 0.001$), elevated serum AST level ($P < 0.0001$), elevated serum ALT level ($P < 0.0095$), elevated serum LDH level ($P < 0.0001$), elevated serum CRP level ($P < 0.0001$), elevated serum CA19-9 level ($P = 0.0004$), elevated serum CEA level ($P < 0.0001$), low hemoglobin level ($P < 0.0001$), and low serum albumin level ($P < 0.0001$).

Multivariate Analysis

The 14 variables found to be of prognostic significance in the univariate analysis were included in the subsequent multivariate Cox regression model. Receiver operating characteristic curve analysis was used to determine the cutoff point for continuous variables. Finally, to simplify the prognostic index, some cutoff values were approximated, thus: leukocyte count, from 7200/mL to 7000/mL; hemoglobin level, from 11.9 to 12 g/dL; platelet count, from $27.8 \times 10^4/\mu L$ to $28 \times 10^4/\mu L$; serum CRP level, from 0.9 to 1.0 mg/dL; serum CA19-9 level, from 3414 to 3000 U/mL; and serum CEA level, from 6.7 to 7 ng/mL. Originally simple values, such as serum albumin level (3.7 g/dL), serum AST level (22 IU/L), serum ALT level (28 IU/L), and serum LDH level (190U/L) were not approximated. Only 4 of the previously mentioned factors, presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver

TABLE 3. Multivariate Analysis

		Coefficient (β)	Hazards Ratio	99%CI	*P*
Prior pancreatectomy	−	0.297	1.346	0.906–2.000	0.530
Abdominal and/or back pain*	+	0.526	1.692	1.262–2.271	<0.0001
Liver metastasis	+	0.353	1.423	1.015–1.995	0.0071
Peritoneal dissemination	+	0.563	1.756	1.238–2.492	<0.0001
Leukocyte count	>7000 (/μL)	0.058	1.060	0.775–1.449	0.6313
Hemoglobin level	<12 (g/dL)	0.244	1.277	0.949–1.717	0.0337
Platelet count	>28 ($\times 10^4/\mu L$)	0.269	1.309	0.954–1.796	0.0285
Albumin level	<3.7 (g/dL)	0.124	1.132	0.841–1.523	0.2826
AST level	>22 (IU/L)	0.078	1.081	0.731–1.599	0.6089
ALT level	>28 (IU/L)	0.212	1.236	0.858–1.781	0.1352
LDH level	>190 (U/L)	0.259	1.295	0.951–1.764	0.0309
CRP level	>1 (mg/dL)	0.432	1.540	1.117–2.124	0.0005
CEA level	>7 (U/mL)	0.205	1.227	0.924–1.631	0.0634
CA19-9 level	>3000 (ng/mL)	0.101	1.106	0.825–1.482	0.3762

CI indicates confidence interval.

*Abdominal and/or back pain: treated with an opioid.

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TABLE 4. Prognostic Index of Patients With Metastatic PC Receiving Systemic Chemotherapy

Risk Factors	
• Abdominal and/or back pain treated with an opioid	Present
• Liver metastasis	Present
• Peritoneal dissemination	Present
• Serum CRP level	>1 (mg/dL)
Risk groups	
No. risk factors	
0	Low risk
1–2	Intermediate risk
3–4	High risk

metastasis ($P = 0.008$), presence of peritoneal dissemination ($P < 0.0001$), and elevation of the serum CRP level to greater than 1.0 mg/dL ($P < 0.0007$), were identified as independent prognostic factors (Table 3).

Risk Groups Based on the Regression Model

To be able to apply the indicated prognostic factors to clinical routine use, patients were stratified into 3 risk groups according to their number of the negative prognostic factors (Table 4): a low-risk group of 47 patients with 0 risk factors, an intermediate-risk group of 276 patients with 1 to 2 risk factors, and a high-risk group of 86 patients with 3 to 4 risk factors. The survival curves of these groups are shown in Figure 1. There were significant differences between survival time in the 3 groups (median survival time: low-risk group, 11.0 months; intermediate-risk group, 7.3 months; and high-risk group, 3.2 months; $P = 0.0001$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

Validation of the Prognostic Index

The prognostic index was applied to each of the 145 cases used for validation. The patient's characteristics were similar to those of the cases in the construction set (Table 1), but the proportion of patients with diabetes mellitus and the proportion of patients whose primary tumor was in the uncus or the head were lower in the validation set. In addition, median age was younger, the median leukocyte count was higher, and the LDH value was lower in the validation set than those in the construction set. Of the 145 patients in the validation set, 141 had died. The median survival time of the 145 patients was 4.8 months, and their 1-year survival rate was 12%. We calculated the prognostic index of the 145 patients and then stratified them into 3 risk groups as described previously and compared the distribution of survival times among the 3 risk groups. Figure 2 shows a comparison of the survival curves of the 3 risk groups. There were significant differences in survival time among the 3 groups (median survival time: low-risk group, 8.6 months; intermediate-risk group, 5.2 months; and high-risk group, 2.3 months; $P = 0.03$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

DISCUSSION

In this study, we attempted to identify prognostic factors in patients with metastatic PC who had received systemic chemotherapy, and 14 of the 24 potential prognostic factors assessed were identified as significant predictors of survival by the univariate analysis. However, only 4 factors, abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and elevated serum CRP level, were found to have independent prognostic value by the multivariate analysis.

Abdominal and/or back pain is one of the most common symptoms of PC patients. Previous studies have shown correlations between pancreatic tumor size, invasion of the anterior pancreatic capsule, and lymph node metastasis and the pain intensity of patients with operable tumors.[23,34] Several studies have also shown a significant impact of preoperative pain has on the outcome after resection.[34 36] However, the pain of patients with unresectable, more advanced PC may be attributable to invasion of the retroperitoneum or extrapancreatic nerve plexus

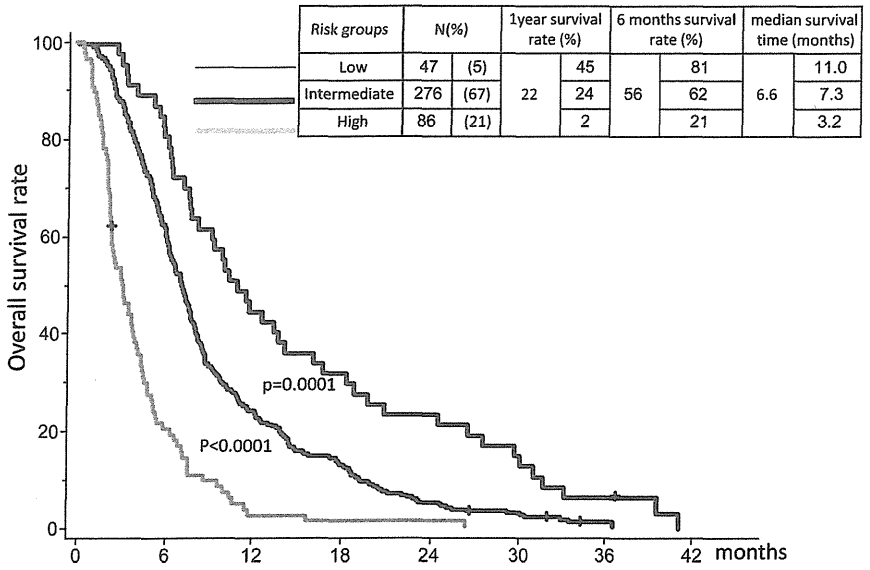

FIGURE 1. Comparison of the survival curves of patients who have received GEM-containing systemic chemotherapy and stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.0001$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.

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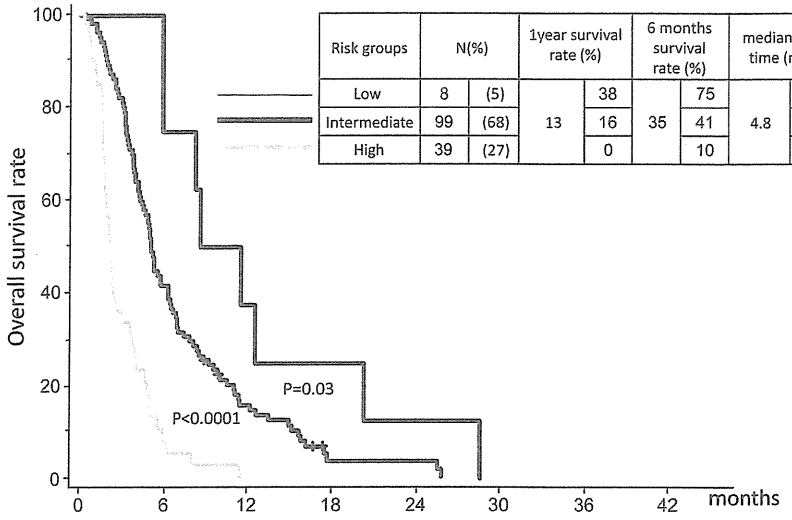

Risk groups	N(%)		1year survival rate (%)		6 months survival rate (%)		median survival time (months)	
Low	8	(5)	13	38	35	75	4.8	8.6
Intermediate	99	(68)		16		41		5.2
High	39	(27)		0		10		2.3

FIGURE 2. Comparison of the survival curves of patients used for validation stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.03$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.

because such advanced tumors sometimes destroy nerves more extensively than resectable tumors.

Peritoneal dissemination[37,38] and liver metastasis[39 41] have long been considered to tend to result in a fatal clinical course. Patients with peritoneal dissemination exhibit the clinical manifestations of bowel obstruction, ascites, and abdominal pain. Such complications often cause malnutrition and general deterioration. Patients with liver metastasis often have jaundice or lapse into a hepatic coma. Moreover, the dose and the schedule of chemotherapy sometimes have to be modified for patients with peritoneal dissemination or liver dysfunction because the adverse effects of chemotherapy are more severe in such patients. A previous study found that peritoneal dissemination predicts limited the effectiveness of chemotherapy in advanced PC.[42]

An elevated CRP level[13,16] has been demonstrated to be of prognostic significance in patients with PC and a variety of other gastrointestinal neoplasms.[43 45] Proinflammatory cytokines, including interleukin 6, are key signals in promoting hepatic CRP production, and there is evidence that they play a role in the genesis of cancer-associated cachexia,[46 48] which shortens the survival time of patients with metastatic PC.

Although previous studies have shown that performance status is one of the most important prognostic factors in patients with advanced PC,[13,49,50] it was not identified as a significant predictor of survival in this study. One of the main reasons for not having identified it as a significant predictor may be that proportion of patients with a performance status of 2 to 3 was extremely small in this study, only 3%.

Many models for clinical outcome prediction have been described in the medical literature, but most never find their way into clinical practice. One reason for their failure to be adopted in clinical practice may be that they have not been validated by external data and therefore lack universality and credibility. To our knowledge, this is the first report of not only construction but also validation of a practical prognostic index for patients with metastatic PC.

Some of the factors assessed in this study were continuous variables, and continuous variables are often converted into categorical variables by grouping the values into 2 or more categories. However, there is also the risk of major bias when the choice of the cutoff value is data driven, and the use of different cutoff points across multiple studies hinders direct comparisons. Dichotomizing continuous variables, on the other hand, is a reasonable method of constructing simple and practical tools for routine clinical use. To achieve a balance between convenience and credibility, we applied the Cox regression model to continuous variables in the univariate analysis to select candidates for the multivariable analysis. We then identified objective cutoff values by ROC curve analysis for the candidates, divided continuous variables into 2 categories, and applied the multivariate analysis.

Because we used a data set of patients treated with a GEM-containing regimen to construct the prognostic index and a data set of patients treated with anticancer agents other than GEM to validate it, this prognostic index may be helpful in designing clinical trials of systemic chemotherapy even if the investigational regimen does not contain GEM.

In conclusion, the presence of abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and serum CRP elevation to 1.0 mg/dL or greater were identified as significant prognostic factors in patients with metastatic PC who had received systemic chemotherapy. Accurate prediction of survival may be achieved by applying a prognostic index incorporating these 4 factors. This index facilitates stratification of patients with metastatic PC into 3 risk groups. Our index is expected to be useful for selecting treatment strategies; patients with an extremely poor prognosis could be offered supportive care alone or more conservative treatment. Furthermore, it is also expected to be useful for designing future clinical trials for patients with metastatic PC.

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Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer

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Received September 27, 2010; Accepted January 4, 2011

DOI: 10.3892/ol.2011.254

Abstract. Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI) has become a standard regimen for advanced or recurrent colorectal cancer. Numerous studies have reported that long-term use of FOLFOX or FOLFIRI leads to better survival for these patients. Thus, control of the toxicity of these drugs may be crucial to prolonging survival. Fucoidan is one of the major sulfated polysaccharides of brown seaweeds and exhibits a wide range of biological activities. In the present study, we analyzed the effect of fucoidan on suppressing the toxicity of anti-cancer drugs. A total of 20 patients with unresectable advanced or recurrent colorectal cancer scheduled to undergo treatment with FOLFOX or FOLFIRI were randomly allocated into a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). Results showed that fucoidan regulated the occurrence of fatigue during chemotherapy. Chemotherapy with fucoidan was continued for a longer period than chemotherapy without fucoidan. Additionally, the survival of patients with fucoidan treatment was longer than that of patients without fucoidan, although the difference was not significant. Thus, fucoidan may enable the continuous administration of chemotherapeutic drugs for patients with unresectable advanced or recurrent colorectal cancer, and as a result, the prognosis of such patients is prolonged.

Introduction

To prolong the survival of patients with unresectable advanced or recurrent colorectal cancer, it is essential to continue effective chemotherapy for as long as possible. Since the introduction of oxaliplatin for use in Japan in April 2005, combination chemotherapy with oxaliplatin plus 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) has become the standard regimen for advanced or recurrent colorectal cancer, and a high response rate has been reported (1-3). However, FOLFOX and FOLFIRI are associated with severe toxicity, such as nausea, vomiting, stomatitis, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia and liver dysfunction. A number of patients discontinue these effective chemotherapies due to toxicity. Thus, the prognosis of patients with unresectable advanced or recurrent colorectal cancer remains low despite advances in chemotherapeutic drugs.

To reduce the toxicity of chemotherapeutic drugs, various types of drugs or dietary supplements have been introduced (4-6). Among these supplements, fucoidan has been reported to exhibit anti-inflammatory, antiviral and anti-tumor activities (7-9). Fucoidan is a sulfated polysaccharide found mainly in various species of brown seaweeds such as kombu, wakame, mozuku and hijiki. Subsequently, fucoidan has become the focus of substantial pharmaceutical research.

The present study investigated whether fucoidan reduces the toxicity of chemotherapeutic drugs in patients with unresectable advanced or recurrent colorectal cancer.

Materials and methods

Patients. Between April 2008 and June 2009, 20 patients were diagnosed with unresectable advanced or recurrent colorectal cancer and were scheduled to undergo FOLFOX or FOLFIRI chemotherapy at our hospital. The Eastern Cooperative Oncology Group performance status of these patients was 0 or 1, and they had adequate bone marrow (platelet count ≥100,000/l, white blood cell count ≥4,000/l, granulocyte count ≥1500/l, hemoglobin level of ≥10.0 mg/dl), renal (serum creatinine concentration ≤2.0 mg/dl), and hepatic (serum bilirubin level ≤2.0 mg/dl) functions. Adjuvant chemotherapy using 5-FU plus LV was administered to 9 of the 20 patients prior to enrollment in this study. The Ethics Committee of Tottori University approved treatment with fucoidan to reduce the toxicity of chemotherapeutic drugs in 2008 (approval no. 1223).

Informed consent was obtained from the 20 patients, who were randomly allocated to a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). The patients were followed up until July 2010. The patient details are shown in Table I.

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Key words: fucoidan, colorectal cancer, chemotherapy, fatigue

Table I. Patient characteristics.

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Age (mean ± SD, years)	71.3±7.5	69.6±8.8	0.762
Male/Female	6/4	7/3	0.639
ECOG			0.653
PS 0/1	5/5	4/6	
Tumor			0.653
Primary/Recurrent	4/6	5/5	
Primary tumor			0.639
Colon/Rectum	6/4	7/3	
Previous chemotherapy			0.653
Yes/No	4/6	5/5	
Site of disease			0.953
Liver	5	4	
Lung	2	2	
Pelvis	1	1	
Peritoneum	1	1	
Lymph node	1	1	
Primary tumor	0	1	

ECOG, The Eastern Cooperative Oncology Group; PS, performance status.

Chemotherapy. A number of versions of FOLFOX therapy exist, of which modified FOLFOX6 (mFOLFOX6) allows for more convenient administration and has been adopted by various medical institutions in association with popularization of outpatient chemotherapy. Thus, mFOLFOX6 has been the first-line therapy for patients with unresectable advanced or recurrent colorectal cancer at our hospital (10). A 2-h intravenous infusion of oxaliplatin (85 mg/m^2) plus l-LV (200 mg/m^2) was followed by a bolus intravenous injection of 5-FU (400 mg/m^2), after which 5-FU (2,400 mg/m^2) was administered by continuous infusion for 46 h. However, 4 of the 20 patients requested FOLFIRI as first-line therapy. In the FOLFIRI regimen, on day 1, 180 mg/m^2 of irinotecan and 200 mg/m^2 of l-LV were administered as a 2-h infusion, prior to a 400 mg/m^2 5-FU intravenous bolus injection. Subsequently, 2,400 mg/m^2 of 5-FU was administered as a 46-h continuous infusion. The duration of one cycle of mFOLFOX6 was the same as that of FOLFIRI (2 weeks). Details of the chemotherapy regimens have been previously described (10).

Fucoidan treatment. Fucoidan is a sulfated polysaccharide that is extracted from brown seaweed, such as mozuku. In the present study, a high-molecular-weight product of fucoidan was used, which was derived from *Cladosiphon okamuranus* (Okinawamozuku) by Marine Products Kimuraya Co., Ltd. (Tottori, Japan). In the fucoidan group, each patient received 150 ml/day of liquid that contained 4.05 g fucoidan for 6 months from the initial day of chemotherapy.

Table II. Major adverse events.[a]

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Leukocytopenia	1	0	0.305
Neutropenia	3	4	0.639
Anemia	2	1	0.531
Thrombocytopenia	0	2	0.136
Nausea	1	1	1.000
Diarrhea	1	2	0.531
Stomatitis	3	1	0.264
Fatigue	1	6	0.019
Peripheral neuropathy	3	5	0.361
Liver dysfunction	0	2	0.136

[a]Adverse events ≥2.

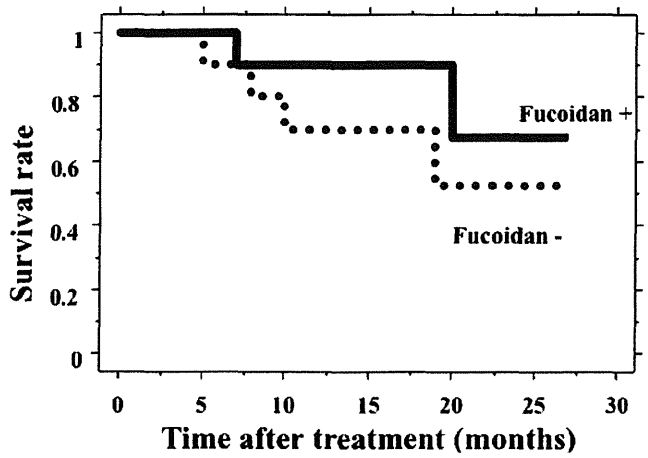

Figure 1. Survival curves of advanced or recurrent colorectal cancer patients. Solid line, survival curve of 10 patients who received fucoidan treatment. Dotted line, survival curve of 10 patients who did not receive fucoidan treatment. The difference was not significant (P=0.314).

Clinical assessment. All toxicities, with the exception of peripheral neuropathy, were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) (11). Peripheral neuropathy was graded according to the specific grading system (12). Hematological variables and clinical status were recorded every 2 weeks during the chemotherapy period. The drug dose level was reduced in the case of severe or persistent toxicity according to our protocol (10). In the case of persistent grade 3 toxicity or when grade 4 toxicity was recorded, chemotherapy was terminated.

Endpoints. The incidence and severity of adverse events were assessed as the primary endpoints, and patient survival, measured from the date of the first treatment until the patient succumbed to the disease, was assessed as the secondary endpoints.

Statistical analysis. The Chi-square test for independence, Fisher's exact probability test and the Mann-Whitney U test were used to compare patient characteristics, treatment status,

adverse events and the anti-tumor effect. The survival rates of the two groups were estimated by the Kaplan-Meier method, and the statistical differences between survival curves were examined by the log-rank test. $P<0.05$ was considered to be statistically significant.

Results

It was noted that fucoidan exhibited no side effects, such as allergic dermatitis. All 20 patients completed the 6 months of fucoidan therapy safely. Additionally, no patients succumbed due to chemotherapeutic toxicity. A total of 307 cycles of mFOLFOX6 or FOLFIRI were administered during the study, with a median of 15.4 cycles per patient (range 7-38). The average number of treatment cycles (19.9) in the fucoidan group was significantly greater than that in the control group (10.8 cycles, $P=0.016$).

The observed toxicities of the chemotherapeutic drugs are listed in Table II. No patients presented with severe toxicity (grade 4) in either group. The occurrences of diarrhea and neurotoxicity were not suppressed by fucoidan. Myelosuppression was found to be similar in the fucoidan and control groups. In contrast, general fatigue was detected in 60% of the control group, but was significantly suppressed to 10% in the fucoidan group (Table II).

Patients were followed up at our hospital. The median follow-up period of the 20 patients was 15 months (range 5-27). During the follow-up period, 6 patients (2 in the fucoidan group and 4 in the control group) succumbed due to colorectal cancer progression. The survival of the 10 patients receiving fucoidan treatment was longer than that of the 10 patients in the control group, but the difference was not significant ($P=0.314$, Fig. 1).

Discussion

Fucoidan is one of the major sulfated polysaccharides of brown seaweeds, and it has a wide range of biological activities. Choi *et al* (13) found that fucoidan protects gastric mucosa from inflammatory cytokine-mediated oxidative damage in rats. Hayashi *et al* (7) reported that fucoidan reduces CCl_4-induced acute and chronic liver failure with hepatic fibrosis. The anti-inflammatory activity of fucoidan was demonstrated in rats (14), and fucoidan conferred no toxicity in rats at high doses (15). Thus, fucoidan is anticipated to improve human health, and has been widely distributed as a foodstuff but not as a drug. However, the detailed mechanism of action of fucoidan remains to be verified, and its effects in humans have yet to be determined.

In the present study, we analyzed whether fucoidan protects patients from the toxicity of anti-cancer drugs. Nausea, vomiting, diarrhea, general fatigue and bone marrow suppression are well-known common adverse effects of anti-cancer drugs. Peripheral neuropathy is specific for oxaliplatin. We found that fucoidan suppressed the occurrence of general fatigue in colorectal cancer patients during chemotherapy. It has been demonstrated that fatigue reduces the individual resources of patients, affects their nutritional status, increases morbidity and can have a negative impact on the dose intensity of cancer therapy (16). Iop *et al* (16) reported that fatigue, which was graded using NCI CTC, was detected in almost 30% of patients receiving chemotherapy. In the present study, grade 2 and 3 fatigue was detected in 60% of colorectal cancer patients during chemotherapy. The use of antidepressants may also play a role in the treatment of fatigue, and a number of patients are administered chemical supplements of unproven efficacy. However, no published data exist to confirm this hypothesis. In our study, patients who received fucoidan were able to endure prolonged chemotherapy without fatigue. However, fucoidan did not have an impact on other adverse effects of anti-cancer drugs. The mechanisms that explain chemotherapy-induced fatigue remain to be determined, and no general treatment is currently available to alleviate the symptoms.

Fucoidan has also been found to play a significant role in tumor suppression (17-20). Yamasaki-Miyamoto *et al* (8) and Hyun *et al* (21) showed that fucoidan activates caspase-8 or extracellular signal-regulated kinase and induces apoptosis in tumor cells. These pro-apoptotic effects of fucoidan have not been detected in normal cells. However, no indisputable evidence exists that fucoidan prolongs the survival of cancer patients, even in animal models with human tumor implants. In the present study, although the number of patients was limited and the results were not statistically significant, the prognosis of patients with unresectable advanced or recurrent colorectal cancer was more favorable upon treatment with fucoidan than without. This may be explained by the fact that fucoidan prolonged the duration of the chemotherapy by suppressing the toxicity of the anti-cancer drugs or through an anti-cancer effect of fucoidan itself. Therefore, large controlled studies are required to evaluate the therapeutic effect of fucoidan for unresectable advanced or recurrent colorectal cancer.

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