

A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer

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Received: 7 July 2010 / Accepted: 10 September 2010 / Published online: 22 September 2010
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Abstract

Purpose Curcumin, a plant-derived natural polyphenol, could be a promising anti-cancer drug and shows synergic effects with cytotoxic agents. We evaluated the safety and feasibility of combination therapy using curcumin with gemcitabine-based chemotherapy.

Methods Gemcitabine-resistant patients with pancreatic cancer received 8 g oral curcumin daily in combination

with gemcitabine-based chemotherapy. The primary endpoint was safety for phase I and feasibility of oral curcumin for phase II study.

Results Twenty-one patients were enrolled. No dose-limiting toxicities were observed in the phase I study and oral curcumin 8 g/day was selected as the recommended dose for the phase II study. No patients were withdrawn from this study because of the intolerability of curcumin, which met the primary endpoint of the phase II study, and the median compliance rate of oral curcumin was 100% (Range 79–100%). Median survival time after initiation of curcumin was 161 days (95% confidence interval 109–223 days) and 1-year survival rate was 19% (4.4–41.4%). Plasma curcumin levels ranged from 29 to 412 ng/ml in five patients tested.

Conclusions Combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy was safe and feasible in patients with pancreatic cancer and warrants further investigation into its efficacy.

Keywords Curcumin · Gemcitabine · Pancreatic cancer

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Introduction

Pancreatic cancer is one of the most lethal malignancies worldwide [9, 15]. Although surgery remains the only modality to potentially cure this disease, most patients are diagnosed too late for curative resection. Even after potentially curative resection, this disease relapses in more than 80% of patients, and incidence rates are almost coincident with mortality rates [18]. Over the past decade, gemcitabine has been widely used as a standard therapy for advanced pancreatic cancer. Gemcitabine has been proved to improve the median survival time and quality of life in

advanced pancreatic cancer patients [4]; however, the prognosis of this disease remains dismal, and the development of more effective therapy is urgently needed. Because pancreatic cancer patients often suffer from symptoms related to the cancer itself (e.g. fatigue, appetite loss, pain), it is also very important to maintain a balance between efficacy and quality of life in palliative chemotherapy for pancreatic cancer.

Curcumin is derived from turmeric (*Curcuma longa*) and is a natural polyphenol. Curcumin has long been used as a food, coloring agent, and traditional medicine. More and more data support the idea that this chemical could be a promising anti-cancer drug for a variety of tumors [6, 10, 19, 23]. Preclinical studies demonstrated curcumin potentiates anti-tumor activity of gemcitabine against pancreatic cancer [2, 14]. Human studies of curcumin have shown that this agent can be administered safely at doses of up to 12 g/day [5, 21] and some clinical benefit in patients with pancreatic cancer [7]. Thus, synergic effects of curcumin on gemcitabine in preclinical studies and safety of curcumin monotherapy in clinical studies have been reported; however, at the time of planning, this clinical trial in 2008, the safety and feasibility of curcumin in combination with gemcitabine-based chemotherapy had not been reported in a human study. Because the clinical condition of pancreatic cancer patients who failed gemcitabine-based chemotherapy was generally poor, we needed to evaluate whether these patients could tolerate a large amount of daily oral curcumin in combination with gemcitabine-based chemotherapy. Therefore, we conducted this phase I/II study to determine the safety and feasibility of oral curcumin in combination with gemcitabine-based chemotherapy in patients with pancreatic cancer.

Patients and methods

Eligibility criteria

Patients with advanced pancreatic cancer who showed disease progression during gemcitabine-based chemotherapy and had no other effective treatment option were eligible if they met the following criteria: histological or radiological confirmation; age ≥ 20 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; bone marrow function (neutrophil count $\geq 1,500/\text{mm}^3$ and platelet count $\geq 100,000/\text{mm}^3$), liver function (total bilirubin ≤ 3 times the upper limit of normal (ULN) and aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤ 5 times ULN) and renal function (creatinine ≤ 1.5 mg/dL); adequate oral intake; and provision of written informed consent. A criterion of neutrophil count/platelet count was amended to $\geq 1,000/\text{mm}^3/\geq 50,000/\text{mm}^3$,

respectively, after confirming the safety of curcumin in the phase I study. Exclusion criteria included history of severe drug allergy, pregnancy or lactation, and other severe comorbid diseases.

This phase I/II study was conducted in two institutions in Japan. The protocol was approved by the institutional review board at each institution and registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (ID 000001386). Patient registration and data management were conducted in an independent data center at Translational Research Center, Kyoto University Hospital. All procedures were performed in accordance with the 1964 Declaration of Helsinki.

Curcumin

Curcuminoids were courteously provided by the Sabinsa Corporation (Piscataway, NJ, USA) in microbead form. The mixture of curcuminoids (C³ complex) consisted of curcumin (73%), demethoxycurcumin (22%), and bisdemethoxycurcumin (4%), which was confirmed by high-performance liquid chromatography tandem mass spectrometry (HPLC–MS/MS) as reported previously [3, 7, 21, 26].

Treatment

As an initial dose level, oral curcumin daily with a dose of 8 g was chosen according to the previous human studies [5, 7, 21]. Oral curcumin was added to the gemcitabine-based chemotherapy (19 patients received gemcitabine/S-1 combination therapy, and two patients received gemcitabine monotherapy). The standard schedule of gemcitabine/S-1 combination therapy consisted of intravenous administration of gemcitabine at a dose of 1,000 mg/m² on days 1 and 8 and 60 mg/m² of S-1 orally for 14 consecutive days every 3 weeks [29]. Patients were allowed to take 8 g of curcumin separately at their own convenience. The same dose and schedule of gemcitabine-based chemotherapy were applied as used before enrollment onto this study. After the initiation of curcumin intake, the dose and schedule of gemcitabine-based chemotherapy was adjusted at the discretion of individual physicians according to the adverse events observed in the previous cycle. Dose-limiting toxicity (DLT) for the phase I study was defined as follows: Grade 4 leucopenia; Grade 4 neutropenia; Grade 3 or more thrombocytopenia; non-hematological toxicity of Grade 3 or more (except for the abnormal blood test); patient refusal due to the intolerability of curcumin intake. Dose de-escalation to 6 g/day was pre-planned if more than one DLT among three assessable patients or more than two DLTs among six assessable patients were observed. No dose escalation was planned. Chemotherapy was

suspended until recovery if neutrophil count was $<1,000/\text{mm}^3$, platelet count was $<70,000/\text{mm}^3$, total bilirubin was $>3.0\text{ mg/dL}$, AST/ALT was $>150\text{ U/L}$, creatinine was $>1.5\text{ mg/dL}$, stomatitis/diarrhea was Grade 2 or higher, skin rash was Grade 3 or higher, or there was a fever ($>38^\circ\text{C}$) due to infection. During the suspension of gemcitabine-based chemotherapy, curcumin intake was also suspended. The study treatment was continued until intolerance of curcumin intake, unacceptable toxicity related to treatment, patient refusal, or discontinuation of gemcitabine-based chemotherapy because of deterioration of general condition due to disease progression.

Pretreatment and follow-up evaluation

Pretreatment evaluation included obtaining the patient's medical history and performing a physical examination, imaging using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), a complete blood cell count, and serum biochemical tests. Physical examinations and blood tests were scheduled on the day of gemcitabine administration. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured every month. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0 [25].

Sample preparation and measurement of plasma curcumin levels by HPLC–MS/MS

Despite the use of doses of curcumin as high as 8 g/day , previous studies reported that very little free curcumin is found in patient plasma samples [21]. Instead, curcumin is present in plasma in conjugated (glucuronide and sulfate) forms, which necessitates appropriate enzymatic hydrolysis of the plasma before detection of free curcumin [7, 26]. In the present study, we measured plasma curcumin levels in five patients who provided written informed consent for blood draws for this purpose. A 0.1 mL aliquot of each plasma sample was transferred to a 10-mL glass tube, and then 0.11 mL of 0.1 M sodium acetate buffer ($\text{pH } 5.0$) containing $1,000\text{ U } \beta\text{-glucuronidase}$ was added. The resulting solutions were incubated to hydrolyze the curcumin conjugates at 37°C for 1 h . After $10\text{ }\mu\text{L}$ of Internal Standard (IS) working solution (500 ng/mL) was added, 0.5 mL of chloroform as extraction solvent was added. The sample was vortexed for 1 min followed by ultrasonic vibrations for 15 min and then centrifugation at $1,610\times g$ for 5 min . The organic layer was transferred to a 1-mL glass tube and evaporated to dryness using a centrifuge concentrator. The dried extract was reconstituted in $100\text{ }\mu\text{L}$ of 50% acetonitrile containing 0.05% formic acid (FA) and then centrifuged at $7,700\times g$ for 10 min . A $10\text{-}\mu\text{L}$ aliquot of

supernatant of reconstituted sample solution was injected into the chromatographic system.

The HPLC–MS/MS system consisted of a Prominence micro-LC system (Shimadzu, Kyoto, Japan) and an API 3200 tandem mass spectrometer (Applied Biosystems, Carlsbad, CA, USA) with (+) electrospray ionization (ESI). Samples were put through an Atlantis T3 ($2.1\times 150\text{ mm}$, $3\text{ }\mu\text{m}$) (Waters, Milford, USA) C-18 separation column using a gradient of binding solvent (0.05% FA/water) and elution solvent (0.05% FA/acetonitrile) at a flow rate of 0.2 mL/min and a column temperature of 40°C . Separation of samples was conducted by a 35-min linear gradient ($5\text{--}95\%$ elution solvent). The mass spectrometer was operated under multiple reaction monitoring (MRM) mode with collision energy of 23 eV for curcumin and 33 eV for mepronil. The transitions (precursor to product) monitored were $m/z\ 369\rightarrow 285$ for curcumin and $270\rightarrow 119$ for mepronil. Chromatograms were integrated using ANALYST software, version 1.5. Stock solutions of curcumin and mepronil were prepared at a concentration of $1,000\text{ ng/mL}$ in methanol. The stock solution of mepronil was further diluted with 55% methanol to prepare a calibration standard at a concentration of 100 ng/mL . The stock solution of curcumin was further diluted with 62% methanol to prepare a calibration standard at a concentration of 200 ng/mL . Curcumin solution (200 ng/mL) was diluted with 50% methanol to prepare the following standard solutions: 0.4 , 0.8 , 1.6 , 3.1 , 6.3 , 12.5 , 25.0 , 50.0 , and 100.0 ng/mL . These solutions were mixed with IS solution (100 ng/mL) at a ratio of $1:1$ to prepare IS-containing calibration samples of $0.2\text{--}100.0\text{ ng/mL}$ (curcumin) and 50 ng/mL (mepronil). Stock solution ($1,000\text{ ng/mL}$) of mepronil was further diluted with methanol to prepare the IS working solution at a concentration of 500 ng/mL .

Statistical analysis

The primary endpoint was safety for the phase I study and treatment completion rate (TCR) of oral curcumin daily for the phase II study. The data for patients enrolled in the phase I study ($n=3$) were pooled together for phase II analysis because there was no difference in curcumin dose between the phase I and phase II studies. TCR was defined as the percentage of patients after excluding those who were withdrawn from this study because of the intolerance of curcumin. The secondary endpoints for phase II were response rate, overall survival (OS), and compliance rate of curcumin. We considered if less than 50% of patients could tolerate combination therapy using curcumin, this therapy was not worth for further evaluation. If 80% or more patients could continue this therapy without any clinically relevant toxicity, this therapy was considered

to be worth for further evaluation of its efficacy. Therefore, a sample size of 21 patients for phase II was determined to reject the null hypothesis of a TCR of 50% under the expectations of 80% TCR with a significance level of 0.05 and a power of 80%. Among patients with measurable target lesions, the objective response rate was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [24]. OS was defined as the time from initiation of combination therapy using curcumin to death from any cause or the final follow-up, and OS rate was calculated using the Kaplan–Meier method. The final analysis was conducted in April 2010. All analyses were conducted on an intention-to-treat basis and were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Twenty-one patients were enrolled between September 2008 and August 2009. The patient characteristics are shown in Table 1. The median age was 67 years (range 44–79 years), and 13 patients (62%) were men. Seven of the 21 patients (33%) experienced recurrent disease after undergoing curative surgery, and three patients had a history of radiotherapy. All the patients had a history of receiving gemcitabine and S-1. Oral curcumin was added to gemcitabine/S-1 combination therapy in 19 patients (90%) and gemcitabine monotherapy in two patients (10%).

Table 1 Patient characteristics ($n = 21$)

Gender	
Male	13 (62.0%)
Female	8 (38.0%)
Age (years)	
Median	67
Range	44–79
Diagnosis	
Histological confirmation	19 (90.0%)
Imaging test	2 (10.0%)
Histology	
Adenocarcinoma	19 (100.0%)
History of anti-cancer drugs	
Gemcitabine	21 (100.0%)
S-1	21 (100.0%)
History of surgery	7 (33%)
History of radiotherapy	3 (14%)
Concomitant chemotherapy	
Gemcitabine/S-1	19 (90%)
Gemcitabine	2 (10%)

Toxicity

In the phase I study, safety of oral curcumin taken daily at dose of 8 g in combination with gemcitabine-based chemotherapy was evaluated. Since the first three assessable patients enrolled for the phase I study completed their first cycle without a DLT at 8 g/day, we selected this amount as the recommended dose for the following phase II study. Overall adverse events are summarized in Table 2. The most common Grades 3–4 hematological toxicity was neutropenia (38%) and Grades 3–4 non-hematological toxicity was fatigue (10%), both of which were likely to be attributed to the gemcitabine-based chemotherapy or disease progression and considered to be irrelevant to curcumin. Other Grades 3–4 non-hematological adverse events were drowsiness ($n = 1$), anorexia ($n = 1$), obstruction of the gastrointestinal tract ($n = 1$), and edema ($n = 1$), all of which were also attributed to disease progression.

Treatment completion rate and compliance rate of curcumin

No patients were withdrawn from this study because of the intolerability of curcumin, yielding a TCR of 100% (95% confidence interval (CI) 84–100%; $P < 0.001$ under the null hypothesis of a 50% TCR). At the time of final analysis in April 2010, three patients were still on protocol treatment, and the reasons for discontinuation of protocol

Table 2 Toxicity ($n = 21$)

	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 1–4
Fatigue	7	3	2	0	10	57
Anorexia	5	2	1	0	5	38
Diarrhea	4	0	0	0	0	19
Hand-foot rash	4	0	0	–	0	19
Stomatitis	3	0	0	0	0	14
Nausea	2	0	0	0	0	10
Vomiting	1	0	0	0	0	5
Leukocytes	1	5	7	0	33	62
Neutrophil	0	4	8	0	38	57
Hemoglobin	3	9	4	0	19	76
Platelets	4	3	2	0	10	43
Bilirubin	7	2	1	1	10	52
AST	14	0	0	0	0	67
ALT	7	2	0	0	0	43
Creatinine	3	1	0	0	0	19
Albumin	9	9	0	0	0	86
ALP	11	4	0	0	0	71
Others (≥Grade 3)	–	–	4	0	19	–

Table 3 Compliance rate ($n = 21$)

Compliance rate	
<0.70	0
≥0.70, <0.80	1
≥0.80, <0.90	1
≥0.90, <0.95	1
≥0.95, <1.00	4
1.00	14
Compliance rate ≥0.90	90%
(95% CI)	(70–99%)

treatment were disease progression ($n = 12$), adverse events unrelated to curcumin intake ($n = 3$), judgment of physician ($n = 1$), referral to another hospital ($n = 1$), patient's request unrelated to intolerability of curcumin ($n = 1$), and protocol violation ($n = 1$). Compliance rate of curcumin is summarized in Table 3. In spite of the high amount required to be taken, 19 patients (90%) were able to take more than 90% of the curcumin scheduled in this clinical trial.

Efficacy

Seventeen patients (81%) died during the study period. The median overall survival time was 161 days (95% CI 109–223 days) and 1-year survival rate was 19% (95% CI 4.4–41.4%) (Fig. 1). Among eighteen evaluable patients, no patients experienced a partial or complete response and five patients (28%) demonstrated stable disease according to RECIST.

Curcumin pharmacology

Plasma curcumin levels were measured in five patients. We measured curcumin levels following digestion of

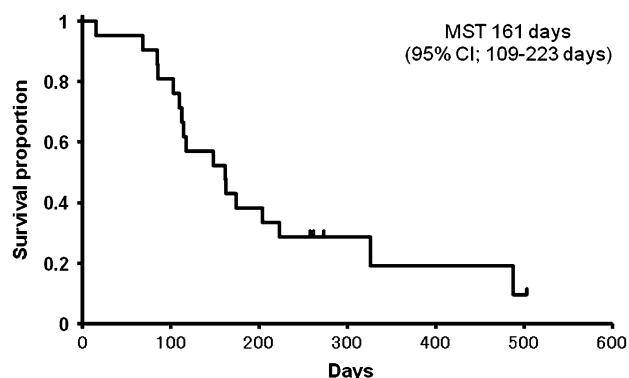


Fig. 1 Overall survival of patients with advanced pancreatic cancer treated with gemcitabine-based chemotherapy plus curcumin ($n = 21$). MST median survival time

Table 4 Plasma curcumin levels and patient information

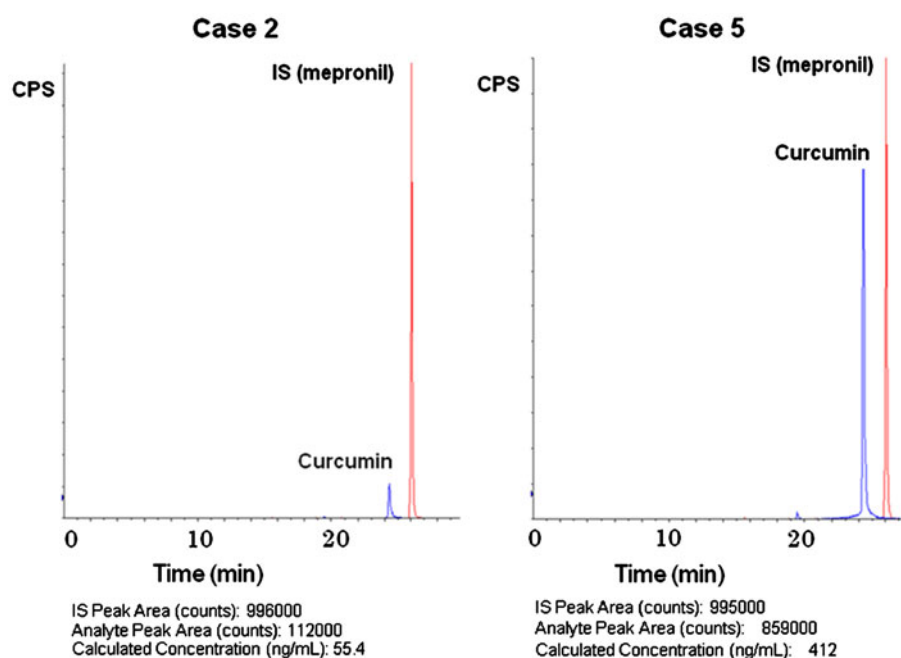
	Age (years)	Gender	Duration of curcumin intake (Months)	Plasma curcumin levels (ng/ml)	Time of blood draw after final curcumin intake (hours)
Case 1	69	Female	14	29	24
Case 2	75	Male	4	55	4
Case 3	67	Female	6	85	1
Case 4	75	Female	6	91	9
Case 5	70	Male	3	412	4

plasma with combined glucuronidase and sulfatase enzymes. The data on plasma curcumin levels and information about duration of curcumin intake and time of blood draw after final curcumin intake are summarized in Table 4. Representative data from HPLC chromatograms for two patients are shown in Fig. 2. Except for one patient who demonstrated a plasma curcumin level of 412 ng/ml (case 5), curcumin levels ranged from 29 to 91 ng/ml, which was comparable with the previous study [7, 21].

Discussion

Curcumin has been reported to modulate a variety of molecules which play an important role in cancer progression. One of the major targets of curcumin is NF- κ B, which regulates the expression of a number of genes involved in anti-apoptosis (Bcl-2, Bcl-xL), proliferation (cyclin D1, *c-myc*), angiogenesis (vascular endothelial growth factor (VEGF), interleukin-8), and invasion (matrix metalloproteinases) [1, 11, 13, 16]. Several preclinical studies have also reported the synergic effect of curcumin in combination with cytotoxic agents. Synergic inhibitory effects of curcumin and 5-fluorouracil on the growth of cancer cell lines have been demonstrated [8, 12]. Vinorelbine-mediated apoptosis is also enhanced by curcumin in squamous lung cancer cell line [20]. Kunnumakkara et al. [14] demonstrated that curcumin potentiates the anti-tumor effects of gemcitabine in pancreatic cancer and suppresses NF- κ B-regulated genes in vitro and in vivo; however, we have no data about the safety and feasibility of curcumin in combination with gemcitabine-based chemotherapy in human studies, and we conducted current study to evaluate whether pancreatic patients could tolerate large amount of daily oral curcumin in combination with gemcitabine-based chemotherapy. The toxicity profile of this study was comparable with that observed in pancreatic cancer patients treated with gemcitabine/S-1 combination therapy [29]. Therefore, we considered that adding oral curcumin to gemcitabine-based chemotherapy did not increase the risk of clinically relevant toxicity. No patients

Fig. 2 HPLC chromatograms showing plasma curcumin levels in two patients. Curcumin was identified in plasma after enzymatic hydrolysis. *IS* internal standard



were withdrawn from this study because of the intolerance of curcumin and a high compliance rate was achieved in spite of the poor clinical condition after failure of gemcitabine-based chemotherapy. In fact, the median compliance rate of oral curcumin was 100% (range 79–100%), as shown in Table 3, which strongly supported the minimal toxicity of this agent in cancer patients who were receiving concomitant chemotherapy. Furthermore, cumulative toxicity of curcumin was not observed in this study, and four patients could continue curcumin intake for more than 6 months without any significant toxicity, which supports the safety of this agent for long-term use. Since pancreatic cancer patients suffer from symptoms related to cancer itself, the low toxicity of this agent is a great advantage for its clinical application in cancer treatment. Some previous clinical studies indicated the risk of diarrhea with curcumin intake [10, 21]. In our study, among four cases of grade 1 diarrhea, two cases could have been attributed to curcumin, but this did not interrupt curcumin intake or gemcitabine-based chemotherapy. We speculated that allowing patients to take curcumin separately reduced the risk of osmotic diarrhea caused by large amounts of curcumin taken at once. Another possible explanation was that patients with pancreatic cancer often suffered from constipation due to peritonitis carcinomatosa or side effect of taking morphine, and these backgrounds might have attenuated the risk of diarrhea. In consistent with our current study, Bayet-Robert et al. [3] recently conducted phase I study of docetaxel plus curcumin in breast cancer patients and reported the safety of oral curcumin at a dose of 6 g/day for 7 consecutive days every 3 weeks.

As Oettle et al. [17] reported that median survival time after failure of first-line gemcitabine therapy was only 10 weeks in patients receiving best supportive care alone, the prognosis of pancreatic cancer patients who failed gemcitabine-based chemotherapy was very poor. Therefore, a median survival time of 161 days (95% CI 109–223 days) and a 1-year survival rate of 19% (95% CI 4.4–41.4%) in our current study were encouraging and warranted further investigation. Interestingly, several patients reported an improvement on cancer- or chemotherapy-related symptoms (e.g. fatigue, pain, constipation) after the initiation of curcumin intake. Unfortunately, the quality-of-life score was not included in the pre-specified endpoints in our current study, and these changes might be solely attributed to placebo effects; however, data from several basic studies support our current observation. Curcumin has been shown to improve depressive-like behaviors in mice with an increase in serotonin, noradrenaline, and dopamine levels in the brain [27, 28] or attenuate hyperalgesia in a mouse model of neuropathic pain [22]. It is very important to maintain quality of life in palliative chemotherapy for pancreatic cancer, and the improvement on cancer- or chemotherapy-related symptoms could increase the compliance to chemotherapy, which largely affects the efficacy of chemotherapy and overall survival. More clinical trials are needed to determine the efficacy of curcumin from viewpoint of quality of life in cancer patients.

Plasma curcumin levels were measured in five patients. Except for one patient, our current results were almost consistent with a previous study reporting that steady-state curcumin level ranged from 22 to 41 ng/ml [7]. The reason

for the high plasma curcumin level (412 ng/ml) that was observed in case 5 is unclear. One possible explanation is that constipation due to peritonitis carcinomatosa in this patient might have decreased the clearance of curcumin from the body, because curcumin is excreted mainly in the feces [21]. This may explain the high plasma curcumin level seen in this patient. Poor bioavailability is the major disadvantage of curcumin when considering its clinical application. Since basic studies have suggested that a microgram range of curcumin in target tissue is necessary to achieve anti-cancer effects, many researchers are focusing on improving the bioavailability of curcumin to get more benefit from this promising agent. Recently, pulverized curcumin was developed in Japan (Theravalues Corporation, Tokyo, Japan) to improve the agent's bioavailability. If we could achieve higher plasma curcumin levels, we could expect more benefits from curcumin in the treatment of cancer patients, and we are now planning clinical trials to evaluate the efficacy of this newly developed curcumin.

In conclusion, our data demonstrated that administration of oral curcumin in combination with gemcitabine-based chemotherapy is safe and well-tolerated in pancreatic cancer patients. More studies are now underway to establish the efficacy of this promising agent in cancer treatment.

Acknowledgments We thank Hiroe Tada and Miyuki Niimi for their contributions to data management, Emi Shimada, and Dr Vladimir Badmaev for their contributions to curcumin shipment. This work was supported by the Grant-in-Aid for Young Scientists (21790661) from the Japan Society for the Promotion of Science, Japanese Research Foundation for Clinical Pharmacology and Smoking Research Foundation.

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