Table 1. Patient characteristics

	D arm		DG arm	
	No. of patients	%	No. of patients	%
Patients enrolled	65		65	
Age, years				
Median	62		60	
Range	34–75		34–74	
Gender				
Male	48	73.8	51	78.5
Female	17	26.2	14	21.5
ECOG PS				
0	20	30.8	21	32.3
1	45	69.2	44	67.7
Histology				
Squamous	19	29.2	22	33.8
Adenocarcinoma	40	61.5	40	61.5
Large cell	4	6.2	3	4.6
Others	2	3.1	0	0
Best response of prior chemotherapy				
CR	2	3.1	0	0
PR	38	58.5	40	61.5
SD	20	30.8	19	29.2
PD	5	7.7	6	9.2

D, docetaxel; DG, docetaxel plus gemcitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

gemcitabine, respectively. Sixteen patients treated with docetaxel (25.0%) and 11 patients with docetaxel plus gemcitabine (16.9%) developed febrile neutropenia. All required antibiotic treatment and G-CSF; however, no patient died. One patient in the docetaxel plus gemcitabine arm developed anaphylatic shock immediately after administration of docetaxel at the second cycle. Grades 2–4 ALT elevation was more frequent with docetaxel plus gemcitabine than with docetaxel (20.0% versus 4.7%). Grades 2–4 non-neutropenic infection occurred more often with docetaxel plus gemcitabine than with docetaxel (21.5% versus 15.6%). Grades 2–4 ILD was more frequent with docetaxel plus gemcitabine than with docetaxel (16.9% versus 1.6%). Other toxic effects were relatively mild (Table 2). Overall, docetaxel plus gemcitabine was more toxic than docetaxel, however, well tolerated except for ILD in docetaxel plus gemcitabine arm.

treatment efficacy

The overall response rate for docetaxel alone was 6.8% [95% confidence interval (CI) 1.9% to 16.5%] and 7.0% for docetaxel plus gemcitabine (95% CI 2.0% to 17.0%). There was no significant difference between treatment arms ($P = 0.71$; Fisher's exact test).

At the time of this analysis, 50 docetaxel patients (76.9%) and 48 docetaxel plus gemcitabine patients (73.8%) had died. The median survival time was 10.1 months for docetaxel alone and 10.3 months for docetaxel plus gemcitabine (one-sided $P = 0.36$ stratified log-rank test; Figure 2A). The respective 1-year survival rate was 43.1% (95% CI 31.0% to 55.1%) for docetaxel and 46.0% (95% CI 33.8% to 58.1%) for docetaxel plus gemcitabine.

The median PFS time was 2.1 and 2.8 months for docetaxel and docetaxel plus gemcitabine, respectively (one-sided $P = 0.028$ stratified log-rank test; Figure 2B).

Table 2. Hematological and non-hematological toxicity

	D arm ($n = 64$) NCI-CTC grade					DG arm ($n = 65$) NCI-CTC grade				
Hematological	0–1	2	3	4	3–4%	0–1	2	3	4	3–4%
Anemia	27	35	2	0	3.1	21	32	9	3	18.5
Leukopenia	9	14	29	12	64.1	11	12	32	10	64.6
Neutropenia	7	2	15	40	85.9	8	4	19	34	81.5
Thrombocytopenia	64	0	0	0	0	43	14	8	0	12.3
Non-hematological	0–1	2	3	4	2–4%	0–1	2	3	4	2–4%
Allergic reaction	64	0	0	0	0	59	5	1	0	9.2
Alopecia	45	18	–	–	28.1	49	14	–	–	21.5
ALT	61	2	1	0	4.7	52	10	3	0	20.0
Diarrhea	61	3	0	0	4.7	60	3	2	0	7.7
Edema	63	1	0	0	1.6	64	1	0	0	1.5
Fatigue	56	5	2	1	12.5	56	7	1	1	13.8
Febrile neutropenia	48	–	16	0	25.0	54	–	11	0	16.9
Infection with grades 3–4 neutropenia	59	–	5	0	7.8	56	–	9	0	13.8
Infection without neutropenia	54	8	2	0	15.6	51	4	9	1	21.5
Nausea	55	7	2	–	14.1	55	6	4	–	15.4
Neuropathy	62	2	0	0	3.1	62	2	0	1	4.6
Pneumonitis (ILD)	63	1	0	0	1.6	54	3	7	1	16.9
Stomatitis	61	3	0	0	4.7	60	5	0	0	7.7

D, docetaxel; DG, docetaxel plus gemcitabine; NCI-CTC, National Cancer Institute—Cancer Common Toxicity Criteria; ALT, alanine aminotransferase; ILD, interstitial lung disease.

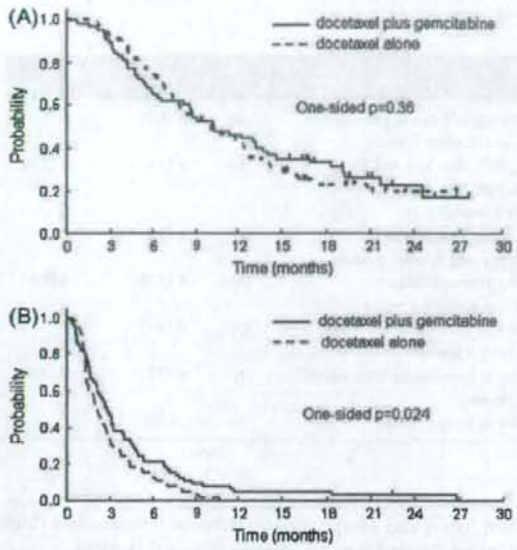

Figure 2. Overall survival (A) and progression-free survival (B) by treatment arm.

disease-related symptom assessment

Patients' compliance with disease-related symptom assessment was 100% at baseline and 95.4% at 6 weeks later. Compliance rates were not different between the arms ($P = 1.00$). LCS data were missing in four surveys due to death or severe impairment of the patient's general condition; this accounted for 1.5% of the total number of surveys scheduled. Mean LCS at baseline and 6 weeks were shown in Table 3. There were no significant differences in the LCS changes from baseline to 6 weeks between docetaxel and docetaxel plus gemcitabine arms ($P = 0.61$).

discussion

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths due to ILD in the docetaxel plus gemcitabine arm. Our findings seem to indicate that the combination of docetaxel and gemcitabine may be associated with a higher incidence of pulmonary adverse events compared with docetaxel alone, especially in patients with previously treated NSCLC.

Pulmonary toxicity following chemotherapeutic agents, including ILD, has been well recognized for many years. In most cases, this toxicity is mild and self-limiting. However, the mechanism of developing drug-induced ILD is uncertain, and risk factors for developing this disorder have not been identified. In terms of combination therapy with docetaxel and gemcitabine for advanced NSCLC, there were few reports about the incidences of ILD at the time this study was planned. A phase I study of patients with transitional cell carcinoma evaluated thrice-weekly doses of docetaxel given on day 1 plus gemcitabine given on days 1 and 15 and showed that pulmonary toxicity occurred in three of five patients and was

Table 3. Disease-related symptom assessment

Lung Cancer Subscale	D arm	DG arm
Baseline		
Number	$n = 65$	$n = 65$
Mean ± SD	19.0 ± 5.48	19.7 ± 5.25
6 weeks later		
Number	$n = 62$	$n = 62$
Mean ± SD	18.1 ± 5.56	18.9 ± 5.05
Difference		
Mean ± SD	−1.11 ± 3.81	−0.99 ± 4.49

D, docetaxel; DG, docetaxel plus gemcitabine; SD, standard deviation.

the cause of death in one [25]. Recently, some reports have been published about the high incidence of ILD due to the combination regimen of docetaxel and gemcitabine in patients with NSCLC [13, 26, 27], including the present study (Table 4). In Japanese population, ILD is a very complex issue in treatment of patients with lung cancer. Epidermal growth factor tyrosine kinase inhibitor gefitinib is developing ILD significantly in Japanese patients with NSCLC [28]. It is uncertain why ILD is developing more in Japanese patients with NSCLC than the Western patients. Ethnic difference may be one of the explanations for this occurrence. The combination of gemcitabine and docetaxel is associated with a high incidence of severe pulmonary toxicity. The regimen should not be used outside a clinical trial.

The median survival times of 10.1 and 10.3 months and estimated 1-year survival rates of 43.1% and 46.0% with docetaxel alone and docetaxel plus gemcitabine, respectively, suggest that adding gemcitabine to docetaxel did not provide any increased efficacy in patients with previously treated NSCLC. Interestingly, the combination regimen of docetaxel plus gemcitabine significantly improved the median PFS time ($P = 0.028$). Possible reasons for failing to detect a significant difference between survival curves may include an insufficient occurrence of documented events as a result of the study population comprising patients with relatively good prognosis, in addition to a high proportion of patients subsequently receiving third-line therapy. During this study, gefitinib treatment was commonly used for patients with recurrent NSCLC in Japan [29]. Asian ethnicity is a well-known predictive factor for a response for gefitinib [30].

Two randomized phase II trials compared docetaxel alone with docetaxel plus irinotecan in second-line chemotherapy for NSCLC [31, 32]. No significant treatment differences in survival were observed in either trial; however, the trials were phase II study and were not powered or designed to compare survival. This study was not powered to compare survival when it was terminated early due to the unexpected high incidence of ILD in the docetaxel plus gemcitabine arm. However, based on previous studies, as well as the present results, combination chemotherapy with docetaxel and another chemotherapeutic agent has not improved survival in patients with previously treated NSCLC.

In conclusion, docetaxel alone is still the standard second-line treatment for advanced NSCLC. The combination of docetaxel and gemcitabine was too toxic to obtain any survival

Table 4. Reports of interstitial lung disease due to docetaxel plus gemcitabine regimen

Author	Year	Study type	Treatment schedule	n	Grades 3–4 ILD (%)	TRD (%)
Rebattu et al. [13]	2001	Phase I/II	Docetaxel (60, 75, 85, 100 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	49	3 (6.1)	0
Kouroussis et al. [25]	2004	Phase I	Docetaxel (30, 35, 40 mg/m^2), days 1, 8 and 15; gemcitabine (700, 800, 900, 1000 mg/m^2), days 1, 8 and 15, every 4 weeks	26	6 (23)	2 (7.7)
Matsui et al. [21]	2005	Phase I/II	Docetaxel (50, 60 mg/m^2) day 1 or 8; gemcitabine (800, 1000 mg/m^2), days 1 and 8, every 3 weeks	59	3 (5.1)	0
Pujor et al. [27]	2005	Phase III	Docetaxel (85 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	155	8 (5.2)	1 (0.6)
			Cisplatin (100 mg/m^2) day 1; vinorelbine (30 mg/m^2), days 1, 8, 15 and 22, every 4 weeks	156	1 (0.6)	0
Takeda (present study)	2008	Phase III	Docetaxel (60 mg/m^2) day 8; gemcitabine (800 mg/m^2), days 1 and 8, every 3 weeks	65	8 (12.3)	3 (4.6)
			Docetaxel (60 mg/m^2) day 1, every 3 weeks	64	0 (0)	0

ILD, interstitial lung disease; TRD, treatment-related death.

benefit in patients with recurrent advanced NSCLC. The development of less toxic and more effective chemotherapeutic agents, including molecular targeted drugs, is warranted for the second-line treatment of NSCLC.

funding

Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

acknowledgements

We thank Ms Mieko Imai for data management, Mr Takashi Asakawa, Dr Naoki Ishizuka for statistical analyses in the interim monitoring, and Dr Haruhiko Fukuda for valuable contributions to this study. This study is registered with UMIN-CTR [http://www.umin.ac.jp/ctr/index.htm umin.ac.jp/ctr], identification number C000000027].

appendix

The following institutions participated in the study: Hokkaido Cancer Center (Sapporo), Ibaragi Prefectural Central Hospital (Kasama), Tochigi Cancer Center (Utsunomiya), Nishigunma National Hospital (Shibukawa), Gunma Prefectural Cancer Center Hospital (Ohta), Saitama Cancer Center Hospital (Ina), National Cancer Center Hospital East (Kashiwa), National Cancer Center Hospital (Tokyo), International Medical Center of Japan (Tokyo), Cancer Institute Hospital (Tokyo), Toranomon Hospital (Tokyo), Kanagawa Cancer Center Hospital (Yokohama), Yokohama Municipal Hospital (Yokohama), Niigata Cancer Center Niigata Hospital (Niigata), Gifu Municipal Hospital (Gifu), Aichi Cancer Center Hospital (Nagoya), Nagoya National Hospital (Nagoya), Prefectural Aichi Hospital (Okazaki), Osaka City University Medical School (Osaka), Kinki University School of Medicine (Osaka-Sayama), Osaka Medical Center for Cancer and Cardiovascular Disease (Osaka), Osaka Prefectural Medical Center for Respiratory and Allergic disease (Habikino), Kinki-Chuo Chest Medical Center (Sakai), Toneyama National Hospital (Toyonaka), Osaka Prefectural General Hospital (Osaka), Osaka City General Hospital (Osaka), Kobe City General Hospital (Kobe), Hyogo Collage of Medicine (Nishinomiya), Hyogo Cancer Center (Akashi), Shikoku Cancer Center Hospital (Matsuyama), Kyusyu University Hospital (Fukuoka), and Kumamoto Regional Medical Center (Kumamoto).

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doi:10.1093/annonc/mdn705 | 7

Phase I and II pharmacokinetic and pharmacodynamic study of the proteasome inhibitor bortezomib in Japanese patients with relapsed or refractory multiple myeloma

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(Received July 22, 2007/Revised September 6, 2007/Accepted September 9, 2007/Online publication October 29, 2007)

The purpose of this phase I and II study was to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of bortezomib in Japanese patients with relapsed or refractory multiple myeloma. This was a dose-escalation study designed to determine the recommended dose for Japanese patients (phase I) and to investigate the antitumor activity and safety (phase II) of bortezomib administered on days 1, 4, 8, and 11 every 21 days. Thirty-four patients were enrolled. A dose-limiting toxicity was febrile neutropenia, which occurred in one of six patients in the highest-dose cohort in phase I and led to the selection of 1.3 mg/m^2 as the recommended dose. Adverse events ≥ grade 3 were rare except for hematological toxicities, although there was one fatal case of interstitial lung disease. The overall response rate was 30% (95% confidence interval, 16–49%). Pharmacokinetic evaluation showed a biexponential decline, characterized by a rapid distribution followed by a longer elimination, after dose administration, whereas the area under the concentration–time curve increased proportionately with the dose. Bortezomib was effective in Japanese patients with relapsed or refractory multiple myeloma. A favorable tolerability profile was also seen, although the potential for pulmonary toxicity should be monitored closely. The pharmacokinetic and pharmacodynamic profiles of bortezomib in the present study warrant further investigations, including more relevant administration schedules. (*Cancer Sci* 2008; 99: 140–144)

Multiple myeloma, one of the B-cell lymphatic tumors, is a malignant hematopoietic tumor with poor prognosis for which a cure cannot ever be expected. The peak age of onset is high at 65–70 years, and its onset in patients younger than 40 years is rare. The median survival of patients with multiple myeloma is approximately 6–12 months if untreated, but it is prolonged to approximately 3 years with the administration of chemotherapy; the 5-year survival rate has been reported to be approximately 25% and the 10-year survival rate is <5%.[1,2] As initial therapy for multiple myeloma, melphalan + prednisolone therapy and vincristine + doxorubicin + dexamethasone therapy have been used as global standards.[3,4] High-dose chemotherapy combined with autologous hematopoietic stem-cell transplantation is reported to be significantly superior to multiagent chemotherapy in terms of response rate and progression-free survival,[5] and is considered to be a standard therapy primarily for patients who are 65 years old or younger. However, no consensus has been reached on the standard therapy for relapsed or chemotherapy-refractory multiple myeloma patients.[6–8] Multiple myeloma is an intractable disease with poor prognosis that continues to relapse, and the duration to relapse becomes shorter in patients who repeatedly receive treatment. There are no available treatment options in which durable efficacy can be expected after relapse, and therefore effective therapeutic choices with new mechanisms of action have been long awaited.

Bortezomib is a novel small molecule that is a potent selective and reversible inhibitor of the proteasome, and has been approved for the treatment of recurrent or refractory multiple myeloma in the USA and Europe. The pharmacokinetics (PK) of bortezomib were reported in a phase I study in which it was administered in combination with gemcitabine twice weekly for 2 weeks followed by a 10-day rest period,[9] and in another phase I study in which it was administered once weekly for 4 weeks followed by a 13-day rest period.[10] Both studies were conducted in patients with advanced solid tumors and not patients with multiple myeloma. Therefore, the present phase I and II study was designed to assess the PK and pharmacodynamic (PD) effects of bortezomib in multiple myeloma patients, particularly in a Japanese population. In addition, efficacy and safety were evaluated to determine the recommended dose (RD).

Patients and Methods

Eligibility. The main eligibility criteria were: confirmed multiple myeloma according to the South-west Oncology Group diagnostic criteria;[11] had received at least previous standard front-line therapy (including melphalan and predonisone, vincristine, doxorubicin, and dexamethasone chemotherapy, and high-dose chemotherapy with autologous stem cell transplantation); had documentation of relapse or refractoriness to the last line of therapy and required therapy because of progressive disease at enrolment. Progressive disease was defined as at least one of the following: more than 25% increase in monoclonal immunoglobulin in the serum or urine; development of new osteolytic lesions or soft tissue tumors, or worsening of existing lesions; hypercalcemia (corrected serum calcium value of >11.5 mg/dL); relapse from complete response (CR); the presence of measurable disease lesions; Karnofsky performance status ≥ 60; 20–74 years of age; adequate bone marrow function (absolute neutrophil count ≥ 1000/mm^3, platelets ≥ 75 000/mm^3, and hemoglobin ≥ 8 g/dL).

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doi: 10.1111/j.1349-7006.2007.00638.x

hepatic function (aspartate aminotransferase and alanine aminotransferase levels ≤2.5 times the upper limit of institutional normal range, total bilirubin ≤1.5 times the upper limit of institutional normal range), renal function (creatinine clearance ≥ 30 mL/min), and cardiac function (left ventricular ejection fraction ≥ 55% by echocardiography without New York Heart Association class III to IV congestive heart failure) in the previous 2 weeks; and had received no systemic chemotherapy or radiotherapy in the previous 4 weeks. This study was approved by the Institutional Review Board of each participating hospital. All patients gave written informed consent and the study was conducted in accordance with Good Clinical Practice for Trials of Drugs and the Declaration of Helsinki.

Study design. The RD was determined based on the occurrence of dose-limiting toxicity (DLT) in Japanese patients and in the dose-escalating phase I of the study. The safety and efficacy of bortezomib at the RD were assessed in phase II. In phase I, three patients were enrolled in the 0.7 mg/m^2-dose group, and six patients each in the 1.0 and 1.3 mg/m^2-dose groups. DLT was defined as ≥grade 3 non-hematological toxicity or grade 4 hematological toxicity for which the relation to bortezomib could not be ruled out. The RD was defined as a dose level with a DLT incidence closest to but lower than the estimated (expected) value of 30%. Bortezomib was administered for up to six cycles.

Drug administration. Bortezomib, supplied by Janssen Pharmaceutical (Tokyo, Japan) in vials containing 3.5 mg, was administered by intravenous push over 3–5 s on days 1, 4, 8, and 11, followed by a 10-day rest period, with this 3-week period comprising one cycle. There was an interval of at least 72 h between doses.

Response and safety assessments. Patients were monitored for response after every two treatment cycles by quantitation of serum immunoglobulins, serum protein electrophoresis and immunofixation (IF), and collection of a 24-h urine specimen for total protein, electrophoresis, and IF. Response was evaluated using the European Group for Blood and Marrow Transplantation criteria,[12] after cycles 2, 4, and 6.

Adverse events were assessed and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 from the first dose until 28 days after the last dose of bortezomib.

Pharmacokinetic and pharmacodynamic analysis. Plasma bortezomib concentrations and blood 20S proteasome activity were measured in phase I. Blood samples were collected before each dose, at 5, 15, and 30 min, and 1, 2, 4, 6, 8, 12, 24, and 48 h after treatment on days 1 and 11. The measurement of plasma bortezomib concentration was conducted at Advion BioSciences (Ithaca, NY, USA) using liquid chromatography/tandem mass spectrometry (LC/MS/MS).[13] The measurement of blood 20S proteasome activity was conducted at Millennium Pharmaceuticals (Cambridge, MA, USA) using the synthetic fluorescence substrate method validated for the chymotrypsin-like activity/trypsin-like activity ratio.[14]

Results

Patients and dose escalation. The study was conducted from May 2004 to January 2006, and 34 patients were enrolled. Patient characteristics are shown in Table 1. All patients had secretory-type myeloma, and the breakdown was 20 patients (59%) with IgG type, eight patients (24%) with IgA type, three patients (9%) with light-chain type, and three patients (9%) with IgA and light-chain type. Most patients had received prior therapy with steroids, alkylating agents, and/or vinca alkaloids. Ten patients (29%) had received stem cell transplantation including high-dose therapy. The median number of lines of prior therapy was two (range: one to eight). Osteolytic lesions were observed in 30 patients (88%) and soft-tissue tumors were observed in seven (21%). The median number of treatment cycles was four (range: one to six), and the median duration of treatment was 79 days (range: 1–152 days). Ten patients (29%) completed all six cycles. The reasons for discontinuation of therapy in 25 patients were progressive disease in 11 patients, patient's own request in six patients, serious adverse events in four patients, DLT in two patients, and others in three patients. Three patients were enrolled in the 0.7 mg/m^2 group and six in the 1.0 mg/m^2 group, and no DLT were observed at any dose level. In the 1.3 mg/m^2 group, DLT (grade 3 febrile neutropenia) occurred in one of the six patients. Therefore, 1.3 mg/m^2 was determined to be the RD in subsequent phase II, in which 18 patients were enrolled.

Table 1. Patient characteristics

Patient characteristic	n	%
Patients	34	
Sex		
Female	12	35
Male	22	65
Age (years)		
Median	60	
Range	34–72	
Durie-Salmon stage		
I	0	
II	15	44
III	19	56
Time since diagnosis (years)		
Median	3.4	
Range	1.0–13.7	
Karnofsky performance status		
100	15	44
90–80	18	53
70–60	1	3
Serum interleukin-6 (pg/mL)		
Mean	4.2	
Range	0.5–30.2	
Cytogenetics		
Karyotype abnormal	4	12
del(13)(q14)	7	21
t(11; 14)	4	12
Prior therapy		
Chemotherapy	34	100
Steroids	34	100
Alkylating agents	33	97
Vinca alkaloids	27	79
Anthracyclines	22	65
Thalidomide	8	24
Interferon	7	21
Radiation therapy	6	18
Autologous hematopoietic stem cell transplantation	10	29

Adverse events. The safety analysis dataset consisted of all patients who received at least one dose of bortezomib (34 patients). Adverse events observed in ≥20% of patients are shown in Table 2. The events observed at a high frequency (≥50%) were lymphopenia, neutropenia, leukopenia, thrombocytopenia, anemia, asthenia, diarrhea, constipation, nausea, anorexia, and pyrexia. At least one ≥grade 3 adverse event was observed in 88% of the patients. Major ≥grade 3 adverse events were hematological toxicities including lymphopenia, neutropenia, leukopenia, thrombocytopenia, and anemia. Grade 4 hematological toxicities included neutropenia in six patients (18%), three of which experienced this adverse event during cycle 1. At least grade 3 non-hematological toxicities occurred in fewer than 10%, and no DLT during cycle 1 were observed. Grade 4 non-hematological toxicities included hematuria, blood amylase

Table 2. All adverse events occurring in at least 20% of patients ($n = 34$)

Dose (mg/m²)	0.7		1.0		1.3		All			
No. of Patients	($n = 3$)		($n = 6$)		($n = 25$)		($n = 34$)		Total	%
NCI-CTC grade	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4		
Adverse event										
Hematologic										
Lymphopenia	3	0	4	2	8	17	15	19	34	100
Neutropenia	1	1	2	4	7	16	10	21	31	91
Leukopenia	2	0	6	0	11	12	19	12	31	91
Thrombocytopenia	1	0	4	0	12	11	17	11	28	82
Anemia	2	0	2	3	10	8	14	11	25	74
Nonhematological										
Asthenia[†]	3	0	3	0	15	0	21	0	21	62
Diarrhea	1	0	2	0	15	1	18	1	19	56
Constipation	2	0	3	0	14	0	19	0	19	56
Nausea	2	0	2	0	14	0	18	0	18	53
Anorexia	3	0	2	0	14	0	18	0	18	53
Pyrexia	0	0	4	0	14	0	18	0	18	53
Peripheral neuropathy[‡]	0	0	3	0	12	1	15	1	16	47
AST increased	1	0	1	0	11	2	13	2	15	44
LDH increased	1	0	1	0	12	1	14	1	15	44
Vomiting	1	0	0	0	9	1	10	1	11	32
Rash	0	0	1	0	10	0	11	0	11	32
ALP increased	0	0	2	0	8	0	10	0	10	29
Headache	0	0	1	0	8	0	9	0	9	27
ALT increased	1	0	1	0	7	0	9	0	9	27
Hyperglycaemia	0	0	2	0	5	0	7	0	7	21
Hyponatremia	1	0	0	1	5	0	6	1	7	21
Renal impairment	1	0	1	0	5	0	7	0	7	21
CRP increased	0	0	1	0	6	0	7	0	7	21
Weight decreased	0	0	0	0	7	0	7	0	7	21

[†]Including fatigue and malaise. [‡]Including peripheral sensory neuropathy, peripheral motor neuropathy, and hypoesthesia. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

increase, and blood uric acid increase in one patient (3%) each. Hematuria was attributed to prostate cancer and judged as not related to bortezomib. The underlying disease was considered to be involved in the blood uric acid increase; this event was judged unlikely to be related to bortezomib. At the occurrence of grade 4 blood amylase increase, blood amylase isozymes were pancreatic-type in 86% and salivary-type in 14%. There were no gastrointestinal symptoms, such as abdominal pain, associated with amylase increase. Abdominal echography revealed no finding suggesting pancreatitis or pancreatolithiasis, and the relevant events recovered 5 days after the onset. The causality of the grade 4 blood amylase increase with bortezomib was evaluated as 'probable', and therefore treatment was continued at a reduced dose from 1.3 to 1.0 mg/m².

One case of interstitial lung disease (ILD) that resulted in a fatal outcome was observed in phase II. The patient with grade 5 ILD had developed the event on day 10 in cycle 2 after receiving seven doses of bortezomib in total. Pyrexia, non-productive cough, hypoxia, and dyspnea were observed as early symptoms, and antibiotics, antimicrobials, steroid pulse therapy, and oxygen inhalation were initiated to treat it. However, respiratory failure worsened, so the patient was put on a ventilator, and the study was discontinued. After the onset of ILD, bronchoalveolar lavage was conducted, but the causative pathogen could not be identified. The available examinations for β-D-glucan, cytomegalovirus antigenemia, influenza virus, and urinary antigen of *Legionella* were found to be negative. The diagnosis from the pathological findings was diffuse alveolar damage. A retrospective analysis of the pretreatment computed tomography (CT) images indicated that the patient had subtle interstitial shadows in the basal region of both lungs. In response, the protocol was amended to exclude patients with abnormal pretreatment bilateral interstitial shadows on CT. No cases of fatal pulmonary toxicity were observed thereafter.

Efficacy. Thirty-three patients were evaluable for efficacy, excluding one ineligible patient who had another malignancy (prostate cancer). Objective responses were observed in 10 of 33 patients (30%; 95% confidence interval 16–49%), including five IF-positive complete responses (CR^{IF+}) and five partial responses. Of the 10 responders, five patients had one line of prior therapy, two patients had three lines of prior therapy, and three patients had four or more lines of prior therapy. It is noteworthy that one patient who had received eight lines of prior therapy, including high-dose chemotherapy with autologous stem-cell transplantation, showed CR^{IF+}. Of the 10 patients who had received prior autologous hematopoietic stem cell transplantation, two patients showed CR^{IF+}, and three patients showed PR. With respect to osteolytic lesions, which is one of the efficacy endpoints, partial regression in five patients, partial disappearance in one patient, and regression of soft-tissue tumors in two patients were observed.

Pharmacokinetics and pharmacodynamics. The mean plasma bortezomib concentration–time profiles on days 1 and 11 obtained from 16 patients enrolled in phase I are shown in Fig. 1a. PK parameters obtained using non-compartmental analysis are shown in Table 3. The plasma bortezomib concentration–time

doi: 10.1111/j.1349-7006.2007.00638.x

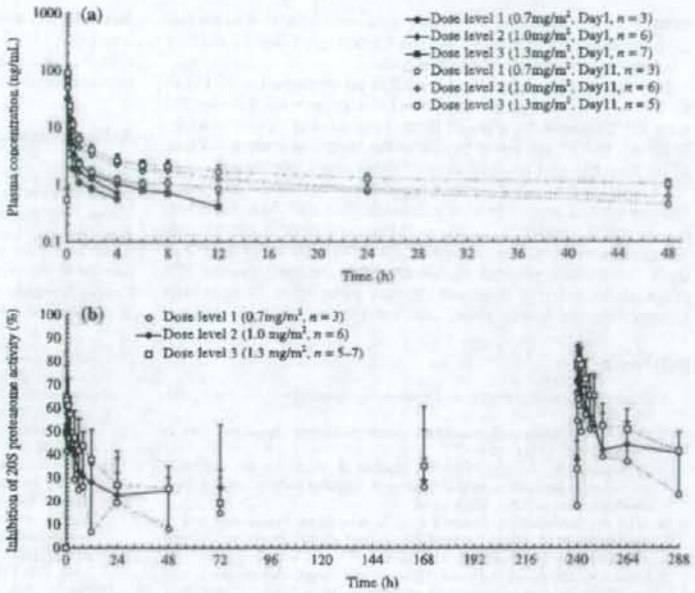

Fig. 1. (a) Plasma bortezomib concentrations (mean + SD). (b) Inhibition of blood 20S proteasome activity (mean + SD).

Table 3. Pharmacokinetic parameters (non-compartmental analysis)

Parameter	Day	Dose (mg/m²)		
		0.7 ($n = 3$)	1.0 ($n = 6$)	1.3 ($n = 5$–7)[1]
C_0 (ng/mL)	1	73.75 ± 7.89	144.92 ± 179.31	185.84 ± 57.65
	11	130.68 ± 71.97	147.19 ± 72.33	187.03 ± 54.31
AUC	1	14.04 ± 0.70	28.58 ± 24.86	46.50 ± 19.89
(ng · h/mL)	11	112.01 ± 47.74	108.39 ± 52.32	186.60 ± 49.79
Half life (h)	1	3.31 ± 0.88	6.81 ± 8.81	16.11 ± 20.75
	11	64.59 ± 30.29	32.46 ± 12.91	57.39 ± 24.92
Clearance	1	83.35 ± 10.52	105.41 ± 75.66	51.97 ± 18.99
(L/h)	11	11.77 ± 4.67	19.63 ± 14.50	12.10 ± 3.73
V_z (L)	1	406.92 ± 154.03	520.08 ± 349.87	894.41 ± 682.35
	11	978.51 ± 263.13	731.69 ± 242.35	957.81 ± 350.40
V_{ss} (L)	1	186.46 ± 85.02	288.90 ± 260.74	507.75 ± 558.30
	11	812.60 ± 202.03	540.03 ± 218.72	763.81 ± 271.64
C_0 ratio	11/1	1.789 ± 0.973	1.848 ± 1.133	1.103 ± 0.249
AUC ratio	11/1	7.940 ± 3.247	5.363 ± 2.970	5.142 ± 0.543

[1]Day 1, $n = 7$; day 11, $n = 5$. Values are mean ± SD. AUC, area under the concentration–time curve from time zero to infinity; AUC ratio, AUC on day 11/AUC on day 1; C_0, plasma concentration at the end of administration; C_0 ratio, C_0 on day 11/C_0 on day 1; V_z, the apparent volume of distribution during the terminal phase; V_{ss}, the apparent volume of distribution at steady state.

profiles showed a biphasic elimination profile, characterized by rapid distribution followed by a longer elimination at all dose levels. At any dose level, the elimination half-life ($t_{1/2}$) on day 11 was prolonged, and systemic clearance (CL) was lower compared with day 1. Therefore, delayed elimination of bortezomib from plasma associated with repeated administrations was observed, and the plasma bortezomib concentration after administration (C_0, estimated value) and area under the plasma concentration–time curve (AUC) showed higher values on day 11 compared with day 1. AUC showed dose dependency, whereas C_0 did not.

The inhibition of blood 20S proteasome activity is shown in Fig. 1b. The 20S proteasome inhibition recovered over time at all dose levels, but was prolonged compared with the temporal decrease in plasma bortezomib concentration, and the inhibition was still observed before treatment on days 4, 8, and 11.

Discussion

In the present study, bortezomib was generally well tolerated in the 25 Japanese patients whose treatments were started at the RD of 1.3 mg/m². Hematological toxicities, gastrointestinal toxicities, and peripheral neuropathies observed in our patients were similar to those reported for patients in clinical studies from the USA and Europe.[15,16] Most could be managed without interventions or with the usual symptomatic therapy. Grade 4 neutropenia was observed in 18% of patients, but treatment could be continued with dose reduction. The response rate obtained in the present study was comparable to that reported by Richardson *et al.* in a pivotal phase III study.[16] In addition, patients who had received heavy prior therapy also showed a consistent response. Therefore, 1.3 mg/m² is considered appropriate as an initial dose of bortezomib in Japanese patients. There was a fatal pulmonary disorder event (ILD) in one patient treated with the 1.3 mg/m² dose in which a causal relationship with bortezomib could not be ruled out. Hence, special care should be taken prior to initiating treatment with bortezomib to evaluate patients (e.g. chest X-ray or chest CT scan) and during and after bortezomib treatment if they develop subjective symptoms such as dyspnea, cough, and fever.

The assessment of PK and PD in multiple myeloma patients treated with bortezomib twice weekly for 2 weeks was conducted for the first time in Japanese patients. A decrease in CL associated with increased exposures and subsequently longer $t_{1/2}$ values were observed after repeated administration and dose escalation. The relatively large volume of distribution suggests that bortezomib may be distributed extensively into the extravascular tissues. It can be postulated that CL values on day 1 are apparent values observed due to rapid tissue distribution, whereas

saturation of proteasome binding sites and tissue distribution occur after multiple dosing, and the CL value on day 11 may be a better representation of the true value.

It was also found that the blood 20S proteasome inhibition at each dose level recovered over time, but was prolonged compared with the temporal decrease in plasma bortezomib concentration. Similarly to CL, this could be due to the large distribution volume of bortezomib and its slow return from tissues to plasma.

Delayed elimination and enhanced proteasome inhibition were observed with repeated administration and dose increase, but no clear tendency in the incidence or degree of adverse reactions was observed. However, the PD results of the present study in Japanese patients demonstrate that the inhibition of 20S proteasome activity does not recover even after 72 h, which is specified as a minimum interval for bortezomib dosing. Accordingly, when bortezomib is used in clinical practice, it is important to determine the optimal dosage and determine whether it is appropriate to administer bortezomib while considering the balance between safety and efficacy.

Acknowledgments

We thank all of the investigators, physicians, nurses, and clinical research coordinators at Tokai University School of Medicine, National Cancer Center Hospital, Aichi Cancer Center, and National Cancer Center Hospital East. We give recognition to Dr A. Togawa (Kofu National Hospital, Kofu, Japan), Dr Y. Sasaki (Saitama Medical University, Saitama, Japan), and Dr K. Hatake (Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan) for their strict review of the clinical data as members of the Independent Data Monitoring Committee.

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doi: 10.1111/j.1349-7006.2007.00638.x

Phase I and pharmacokinetic study of sorafenib, an oral multikinase inhibitor, in Japanese patients with advanced refractory solid tumors

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(Received February 25, 2008/Accepted March 23, 2008/Online publication May 12, 2008)

Sorafenib is a novel oral multikinase inhibitor that targets Raf serine/threonine and receptor tyrosine kinases, and inhibits tumor cell proliferation and angiogenesis. We have conducted a phase I study of sorafenib to determine the safety, tolerability, pharmacokinetics, and potential efficacy of this agent in 31 Japanese patients with advanced refractory solid tumors. Sorafenib (100–600 mg) was given as a single dose followed by a 7-day wash-out period, and then administrated twice daily (bid). The most frequent drug-related adverse events were rash/desquamation (61%), hand–foot skin reactions (39%), diarrhea (36%), and elevations of serum lipase (36%) and amylase (26%) levels. Dose-limiting toxicities (DLTs) were grade 3 diarrhea at 200 mg bid and grade 3 fatigue at 600 mg bid. Grade 3 and 4 pancreatic enzyme elevations were observed at 200–600 mg bid, but they were not deemed dose-limiting because they were asymptomatic and were not associated with pancreatitis or chronic damage to the pancreas. The AUC and C_{max} of sorafenib increased linearly with dose up to 400 mg bid. Partial responses were observed in one of 10 patients with non-small cell lung cancer and one of three patients with renal cell carcinoma. In conclusion, sorafenib 400 mg bid was well tolerated in Japanese patients with advanced refractory solid tumors. The recommended dose for future clinical trials is 400 mg bid. (*Cancer Sci* 2008; 99: 1492–1498)

Recent research on the molecular mechanisms controlling tumor cell proliferation, invasion, and metastasis has identified several novel targets for cancer therapeutics. The mitogen-activated protein kinase (MAPK) signaling pathways, which mediate transduction of extracellular signals to the nucleus via a cascade of phosphorylation events through Ras/Raf/MEK/ERK, are often dysregulated in human tumors. Dominant negative mutants of Raf or ERK inhibit both the primary and metastatic growth of human tumor xenografts *in vivo*. Thus, activation of Raf kinase is considered to be an important mechanism by which human cancer develops. Therefore, the critical components of MAPK signaling pathways, including Raf kinase, represent potential targets for anticancer treatment.[1–4]

Tumor angiogenesis, the proliferation of a vascular network to supply tumors with nutrients and oxygen, is necessary for tumors to maintain growth and to spread. It is supported by angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF bind the VEGF receptor (VEGFR) on endothelial cells and the PDGF receptor (PDGFR) on smooth muscle cells, which are both receptor tyrosine kinases, respectively. Thus, the receptors themselves and their signaling pathways are also potential therapeutic targets for cancer.[5,6]

Sorafenib (BAY 43-9006) is an orally available small molecule that displays inhibitory activity against multiple kinases including c-Raf-1 and B-Raf. Inhibition of Raf activity is followed by interference with the activation of ERK, thereby inhibiting cell proliferation, differentiation, and transformation.[7,8] In addition, sorafenib inhibits receptor tyrosine kinases including VEGFR-2 and PDGFR, thereby inhibiting angiogenesis. Inhibition of both tumor cell proliferation and angiogenesis is considered to contribute to the potent antitumor activity of sorafenib. In studies of various human tumors, sorafenib exhibited a dose-dependent inhibition of tumor growth associated with apoptosis in xenograft models.[7,8]

Various types of clinical development programs for sorafenib are now on-going worldwide. In the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), sorafenib significantly prolonged progression-free survival as well as overall survival in patients with advanced renal cell cancer.[9] Sorafenib has recently been approved for advanced renal cell carcinoma and hepatocellular carcinoma in the USA, Europe, and other countries.

The phase I study reported here was planned to determine the safety, dose-limiting toxicities (DLTs), maximum-tolerated dose (MTD), and pharmacokinetics of sorafenib in Japanese patients with refractory advanced solid tumors. Pharmacodynamics was also studied using flow cytometric analysis of ERK-phosphorylation in patients' peripheral blood mononuclear cells (PBMCs), as well as plasma adrenomedullin levels. Furthermore, disease activity was evaluated by fluorodeoxyglucose-positron emission tomography (FDG-PET).

Materials and Methods

Patient selection. Study eligibility criteria included histologically or cytologically confirmed advanced solid cancer, which was refractory to standard therapy or for which no effective therapy was available, patient age ≥ 20 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, estimated life expectancy ≥ 12 weeks, and adequate organ function. Main exclusion criteria were as follows: chronic heart failure (New York Heart Association Grade III or IV), active cardiac diseases, history of HIV infection or chronic hepatitis B or C, active infections, tumor involving the central nervous system, history of seizure, concurrent malignancy, other anticancer therapy within 4 weeks (6 weeks for mitomycin C or nitrosourea, 2 weeks for hormonal therapy, and 3 weeks for radiotherapy), and surgery within 4 weeks prior to this study. Patients treated with CYP3A4 inhibitors or inducers were also excluded because of possible drug interactions with sorafenib and confounding effects

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doi: 10.1111/j.1349-7006.2008.00837.x

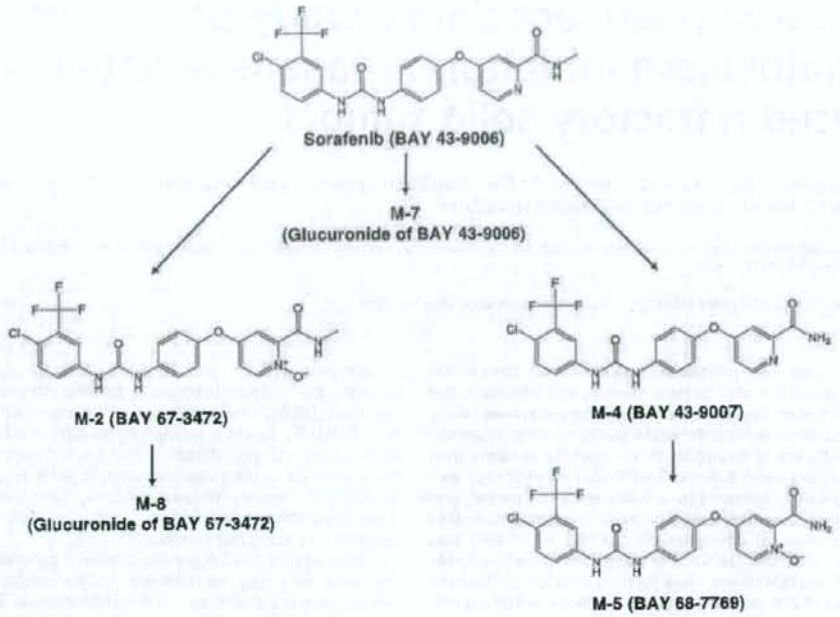

Fig. 1. Metabolism map of sorafenib and its metabolites.

on the pharmacokinetics results. The study was approved by the Institutional Review Board of the National Cancer Center and all patients gave written informed consent before entry onto the study.

Study design. A single dose of sorafenib was given orally, followed by a 7-day wash-out, and then administration of sorafenib continued twice daily until the occurrence of unacceptable toxicity, withdrawn consent, disease progression, or death.

In this study, the initial dose was 100 mg, which was based on observations in phase I studies performed in foreign countries as well as on preclinical studies. In both dogs and rats, exposures to between 53.5 and 67.1 mg h/L was associated with moderate toxicity. Assuming that oral bioavailability is similar in humans, a single 100 mg dose of sorafenib would be expected to yield a systemic exposure of 5.8 mg h/L. Therefore, 100 mg sorafenib was considered to be a safe starting dose for this phase I study, thereafter escalated to 200, 400, and 600 mg bid.

For each dose level, a cohort of three patients was treated. In the absence of observed DLTs during the first 4 weeks of continuous administration bid, a further cohort of three patients was enrolled to the next higher dose. If one of the first three patients experienced DLTs, three additional patients were treated at that same dose level. The dose was then escalated when no DLTs was observed in the three additional patients.

Definition of dose-limiting toxicity. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, with DLTs being defined as grade 3 or 4 non-hematological toxicity (except anorexia and manageable nausea and vomiting), grade 4 neutropenia lasting for ≥7 days, febrile neutropenia, or thrombocytopenia <25 000/mm^3.

Grade 4 elevations of pancreatic enzymes were observed in 200 mg bid cohorts, but ultrasound investigation, magnetic resonance imaging, and computed tomography did not show any evidence of pancreas damage or pancreatitis. Therefore, after the safety of 200 mg bid was confirmed, the definition of DLT was amended to exclude clinically insignificant elevations of pancreatic enzymes and the definition of DLT for serum pancreatic enzymes was amended accordingly. DLTs were deemed dose-limiting only when they were grade 4 for >4 days, associated with clinical/imaging findings of pancreatitis, or considered to be life-threatening or result in chronic damage to the pancreas.

Patient evaluation. Physical examination and hematological/biochemical laboratory evaluation were performed weekly for the first 4 weeks of continuous dosing and every 2 weeks thereafter. Laboratory evaluation was also performed on day 4 of the continuous dosing. Tumor measurements were performed at the baseline, and repeated every 8 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST).[10] Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Pharmacokinetics. For the measurement of plasma concentrations of sorafenib and its metabolites, blood samples (5 mL aliquots) were drawn prior to drug administration, as well as 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h after the single dose administration. For the continuous dosing period, blood was sampled prior to the first dosing on days 1, 4, 7, 10, 14, 21, and 28, along with 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h after the first dose on day 14 at 100, 200, 400, and 600 mg bid. The same full sampling was performed on day 28 at 100 and 200 mg bid, while blood was sampled prior to and 12 h after the morning administration at 400 and 600 mg bid. Urine voided up to 48 h after the single administration was collected.

Concentrations of sorafenib and its metabolites in plasma and urine were determined at Bayer HealthCare (Berlin, Germany) using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS-MS) methods.[11] The method was validated within a working range of 0.0100–12.0 mg/L (sorafenib) and 0.0100–2.5 mg/L (metabolite M2; M4; M5; Fig. 1). Mean interassay precision and accuracy for sorafenib quantification ranged from 0.4% to 4.9% and from 91.2% to 96.5%, respectively. Plasma pharmacokinetic parameters, area under the curve

Table 1. Patient characteristics

Number of patients (female/male)	31 (10/21)
Median age (range)	63 (32–72)
ECOG performance status	
0	8
1	23
Cancer type	
Non-small cell lung	10
Colorectal	6
Renal	3
Gastric	2
Others	10
Prior therapy	
Chemotherapy	30
Radiotherapy	11
Surgery	29

ECOG, Eastern Cooperative Oncology Group.

Table 2. Incidence of drug-related adverse events by worst grade

Adverse event	All grades *n* (%)	Grade 3 *n* (%)	Grede 4 *n* (%)
Hypertension	4 (13%)	1 (3.2%)	0
Fatigue	3 (10%)	1 (3.2%)	0
Fever	3 (10%)	0	0
Alopecia	8 (26%)	0	0
Dry skin	7 (23%)	0	0
Hand–foot skin reaction	12 (39%)	0	–
Rash/desquamation	19 (61%)	0	–
Pruritus	5 (16%)	0	0
Anorexia	8 (26%)	0	0
Diarrhea	11 (36%)	1 (3.2%)	0
Nausea	3 (10%)	0	0
Vomiting	3 (10%)	0	0
Lipase	11 (36%)	2 (6.5%)	5 (16%)
Amylase	8 (26%)	2 (6.5%)	1 (3.2%)
Alkaline phosphatase (ALP)	3 (10%)	1 (3.2%)	0
Alanine amino transferase (ALT)	3 (10%)	1 (3.2%)	1 (3.2%)
Aspartic aminotransferase (AST)	3 (10%)	1 (3.2%)	2 (6.5%)
Abdominal pain	5 (16%)	0	0
Leukocytopenia	4 (13%)	4 (13%)	0

(AUC), maximum concentration (C_{max}), and elimination half-life ($t_{1/2}$) for sorafenib were calculated by non-compartment analysis using the KINCALC program (Bayer HealthCare).

Pharmacodynamics. As a specific marker for the Ras signaling pathway, phosphorylated ERK (pERK) in peripheral blood mononuclear cells (PBMC) was quantified. Peripheral blood samples with EDTA anticoagulant were taken at the baseline and on day 28 of the continuous treatments. PBMCs were prepared from blood, stimulated by phorbol myristate acetate (PMA), and fixed in 4% formaldehyde. pERK in PBMCs was stained using an antipERK and fluorescein isothiocyanate-conjugated secondary antibody. The cells were resuspended in phosphate-buffered saline and flow cytometry was performed.[12] The plasma concentration of adrenomedullin was measured by immunoradiometric assay at the baseline and on day 28 of the continuous dosing. FDG-PET was performed before treatment, 1, 2, and 3 months after the initiation of treatment, and every 2 months thereafter. The maximum standardized uptake values (SUV_{max}) were recorded. The relationship between trough concentrations of sorafenib on day 28 *versus* SUV_{max} 1 month after the start of continuous dosing was investigated by using an inhibitory Emax model:

Table 3. Incidence of common drug-related adverse events by dose levels

Adverse event	100 mg *n* = 3	200 mg *n* = 15	400 mg *n* = 6	600 mg *n* = 7
Hypertension	0	2 (13%)	1 (17%)	1 (14%)
Fatigue	0	1 (6.7%)	1 (17%)	1 (14%)
Alopecia	0	3 (20%)	3 (50%)	2 (29%)
Dry skin	0	4 (27%)	3 (50%)	0
Hand–foot skin reaction	0	3 (20%)	3 (50%)	6 (86%)
Rash/desquamation	2 (67%)	8 (53%)	6 (100%)	3 (43%)
Pruritus	0	1 (13%)	2 (33%)	2 (29%)
Anorexia	1 (33%)	4 (27%)	1 (17%)	2 (29%)
Diarrhea	0	6 (40%)	3 (50%)	2 (29%)
Lipase	0	4 (27%)	3 (50%)	4 (57%)
Amylase	0	3 (20%)	3 (50%)	2 (29%)

$$E = E_{max} \times (1 - C/[C + EC_{50}])$$

where E is the percentage of SUVmax relative to the baseline, E_{max} is the maximum effect expressed as a percentage of baseline, C is trough concentration, and EC_{50} is the concentration yielding 50% of E_{max}.

Results

Patient characteristics. A total of 31 patients were enrolled in this study: 10 males and 21 females. The median age was 63 years with a range of 32–72 years. The baseline demographics for all patients are shown in Table 1. The commonest cancers were non-small cell lung (10 patients) and colorectal (six patients) cancers. Six of 10 patients with lung cancer had adenocarcinoma. All patients had an ECOG performance status of 0 or 1. Thirty patients had been pretreated with chemotherapy, 29 had had surgery, and 11 radiotherapy. Four patients discontinued treatment during the initial 4-week continuous dosing period (cycle 1) because of disease progression in three and withdrawal of consent in one case. All 31 patients were assessable for safety.

Dose escalations and dose-limiting toxicity. DLTs were not observed in any of the cohort of three patients at 100 mg bid. A total of 15 patients were enrolled at the 200 mg bid dose level, 12 of whom could be evaluated for DLTs (two patients did not complete cycle 1 due to progressive disease and withdrawal of consent in the other). One of these 12 patients presented with grade 3 diarrhea, classified as a DLT. In addition, two patients had grade 3/4 elevations of pancreatic enzymes including grade 4 lipase and grade 3/4 amylase. However, examination of these patients with pancreatic enzyme elevations using ultrasound, magnetic resonance imaging, and computed tomography did not show any evidence of pancreatitis, and the lipase level began to decrease before sorafenib was stopped. After the safety of 200 mg bid had been thus confirmed, the next dose of 400 mg bid was investigated. Six patients in the 400 mg bid cohorts experienced no DLTs, although two had grade 4 lipase elevations which were not associated with pancreatitis. Next, seven patients at 600 mg bid were studied. One patient was taken off the study because of early disease progression. One of the remaining six patients experienced dose-limiting grade 3 fatigue. In addition to this observation, hand–foot skin reactions were observed in five patients at 600 mg bid. Therefore, 400 mg bid sorafenib was established as the MTD and is recommended for future clinical studies.

Safety. Thirty patients experienced drug-related adverse events (Tables 2,3), the most frequent of which were dermatological (77%), gastrointestinal (58%), or elevations of lipase (36%) or amylase (26%). The most common dermatological adverse

doi: 10.1111/j.1349-7006.2008.00837.x

Table 4. Plasma pharmacokinetic parameters of sorafenib

Dose (mg bid)	day 1						day 14			day 28	
	AUC (mg h/L)	AUC_{0-12} (mg h/L)	C_{max} (mg/L)	T_{max} (h)	$T_{1/2}$ (h)	CL/f (L/h)	AUC_{0-12} (mg h/L)	C_{max} (mg/L)	C_{trough} (mg/L)	AUC_{0-12} (mg h/L)	C_{max} (mg/L)
100 ($n = 3$)	9.4	3.3	0.43	4	27.1	10.6	9.4	1.04	0.70	12.3	1.42
	(39)	(42)	(41)	(3–8)[†]	(39)	(39)	(21)	(30)	(43)	(27)	(35)
200 ($n = 15$)	24.3	5.1	0.74	4	24.4	8.2	20.2[‡]	2.64[‡]	1.38[§]	21.1[¶]	2.43[¶]
	(100)	(110)	(107)	(3–24)[†]	(58)	(100)	(37)	(49)	(588)	(49)	(52)
400 ($n = 6$)	35.4	7.0	1.21	8	25.5	11.3	36.7	4.91	3.75	n/a	n/a
	(195)	(173)	(201)	(3–24)[†]	(40)	(195)	(73)	(76)	(104)		
600 ($n = 7$)	40.5**	9.7	1.41	6	30.4[††]	14.8[††]	33.8[††]	4.42[††]	4.29[††]	n/a	n/a
	(67)	(81)	(70)	(4–23)	(34)	(67)	(43)	(55)	(62)		

Data are expressed as geometric mean or median, and percent coefficient of variance is expressed in parentheses.
[†]range; [‡]$n = 10$, [§]$n = 11$, [¶]$n = 8$, [††]$n = 9$, [‡‡]$n = 6$ (Calculated by using the half of lower limit of quantification for one patient with C_{trough} lower than the lower limit of quantification)
AUC, area under the curve; n/a, not available.

events were rash/desquamation (61%), hand–foot skin reaction (39%), alopecia (26%), dry skin (23%), and pruritus (16%; Table 2). However, these were mild, beginning mostly 2–8 weeks after the start of sorafenib treatment and resolving with the application of local therapies without requiring a change of sorafenib dosing of any patients. No grade 3/4 dermatological toxicities were observed. The incidence of hand–foot skin reaction tended to be dose-dependent (Table 3).

The most common gastrointestinal adverse event was diarrhea (35%). It was mostly mild to moderate and easily managed with oral loperamide. However, grade 3 diarrhea (a DLT) occurred in one patient at the 200 mg bid dose level.

Elevation of lipase or amylase was not observed at the 100 mg bid dose level (Table 3). Of the 15 patients treated with 200 mg bid, four showed elevated lipase (27%) and three elevated amylase (20%). Two of these patients had grade 4 elevated lipase, but no indications of pancreatitis were observed by diagnostic imaging. Three of six patients (50%) in the 400 mg bid group and four of seven (57%) in the 600 mg bid group had elevated levels of pancreatic enzymes, which returned to normal without requiring interruption of sorafenib administration. Serum levels of amylase and lipase began increasing on days 4–7, and then decreased again back to normal levels within 3–10 days with/without stopping administration of sorafenib. No patients had symptoms of pancreatitis. Ultrasound, computed tomography, and magnetic resonance imaging of the pancreas showed no evidence of acute pancreatitis.

Hypertension was observed in four patients, with one occurrence of grade 3 at the 600 mg bid dose level. A causal relationship with the use of the study drug could not be ruled out. These events mostly began 1–7 weeks after the initial sorafenib treatment and returned to normal during continuous treatment thereafter. Treatment-related abnormalities in hepatic parameters, such as ALT and AST elevations, were reported in two patients as serious adverse events, and drug administration had to be discontinued. Fatigue was reported in three patients including one case of dose-limiting grade 3.

Pharmacokinetics. Pharmacokinetics data sets after the initial single dosing were obtained in a total of 31 patients. Thereafter, 25 patients were eligible for pharmacokinetics analysis on day 14 during the continuous dosing; six were excluded because of discontinuation of drug administration. The pharmacokinetic parameters of sorafenib are shown in Table 4. Drug absorption was moderate after the single administration, with time to maximum plasma concentration (T_{max}) 3–24 h (mean, 8 h) after administration. Plasma half-life ($T_{1/2}$) was found to be 24–30 h (mean, 25.5 h). Although considerable interpatient variability was observed, the geometric means of AUC, AUC_{0-12} as well as the maximum and trough concentrations increased dose dependently from 100 mg to 400 mg after administration of a single dose and at steady state (day 14). At 600 mg bid, drug exposure seemed to be increased less than proportionally to the dose escalation. Plasma trough concentrations at 400 mg bid (3.75 mg/L) exceeded the IC_{50} for inhibition of tumor cell proliferation *in vitro* (ranging between 0.057 and 2.5 mg/L).[8]

Major metabolites of sorafenib M-2, M-4, and M-5 were detected in plasma, but the AUC_{0-12} of each metabolite was less than 13% of the sum of all measured compounds (Table 5). Similar to sorafenib, the AUC_{0-12} and C_{max} of these metabolites were increased by dose escalations from 100 to 400 mg bid, but were not further increased at 600 mg bid. Sorafenib and M-2 were not detectable in urine, while the glucuronidated metabolites, M-7 and M-8, were excreted in the urine at up to 4% of the administered dose of sorafenib (Table 6).

Pharmacodynamics. ERK is an essential component of MAPK signaling pathways and a downstream factor of Raf kinase, which is a target molecule of sorafenib.[7,8] Adrenomedullin is a bioactive peptide and known to be expressed/secreted by human tumors.[13,14] In preclinical studies, expression of adrenomedullin decreased in tumors as the plasma concentration of sorafenib increased. Thus, phosphorylation of ERK and plasma adrenomedullin levels may be a candidate biomarker of sorafenib efficacy. Nevertheless, in the present study, large interindividual variations were observed in changes of pERK-positive cells in PBMCs and also in plasma adrenomedullin levels, and no obvious trend was recognizable for these parameters (Table 7).

Twenty-three patients underwent repeated examination by FDG-PET, with the median value of SUV_{max} decreasing significantly from 16.2 (range, 3.0–80.3) at the baseline to 11.2 (3.0–57.8) at the first examination after the start of treatment ($P = 0.0007$ by Wilcoxon signed-rank test). The median percent change from baseline for each patient was –25% (–54% to 25%). SUV_{max} was decreased from baseline in 19 patients, with a 25% or greater decrease being observed in 11 patients. A higher trough concentration of sorafenib on day 28 was associated with larger reduction in SUV_{max} (Fig. 2). This relationship could be described by an E_{max} model with $E_{max} = 130.1$ (SE, 21.0)% and $EC_{50} = 4.8$ (2.4) mg/L.

Antitumor activity. Twenty-nine patients were evaluated for tumor response according to RECIST criteria. Overall duration of treatment was prolonged as the dose was increased. PR was observed in two patients (total, 7%). In a 69-year-old patient with renal cell carcinoma previously treated with interferon-α2b, PR was achieved 1 month after the start of continuous dosing

Table 5. Plasma pharmacokinetic parameters of metabolites

Dose (mg bid)	M-2 (BAY 67-3472)			M-4 (BAY 43-9007)			M-5 (BAY 68-7769)		
	AUC_{0-12} (mg h/L)	Ratio (%)	C_{max} (mg/L)	AUC_{0-12} (mg h/L)	Ratio (%)	C_{max} (mg/L)	AUC_{0-12} (mg h/L)	Ratio (%)	C_{max} (mg/L)
100 ($n = 3$)	0.63	6.07	0.07	0.16	1.54	0.02	0.21[†]	2.04[†]	0.02[†]
	(57)	(74)	(45)	(40)	(25)	(23)	(54)	(78)	(71)
200 ($n = 10$)	2.47	10.01	0.31	0.70	2.83	0.11	0.83[‡]	3.13[‡]	0.10[‡]
	(79)	(55)	(71)	(179)	(124)	(95)	(50)	(63)	(55)
400 ($n = 6$)	5.84	11.7	0.73	1.89	3.81	0.24	1.79	3.60	0.22
	(269)	(63)	(285)	(324)	(81)	(353)	(563)	(144)	(573)
600 ($n = 6$)	5.44	12.2	0.66	1.81	4.09	0.23	1.48	3.34	0.18
	(140)	(58)	(150)	(139)	(61)	(153)	(185)	(84)	(205)

Data are expressed as geometric mean, and percent coefficient of variance is expressed in parentheses.
Ratio of each metabolite to the sum of AUC_{0-12} of sorafenib, M-2, M-4, and M-5.
[†]$n = 2$; [‡]$n = 9$.
AUC, area under the curve.

Table 6. Urinary excretion of sorafenib and metabolites 48 h after single administration of sorafenib

Dose (mg bid)	Sorafaneib (BAY 43-9006) (%)	M-2 (BAY 67-3472) (%)	M-7 (BAY 43-9006G) (%)	M-8 (BAY 67-3472G) (%)
100	ND	ND	4.15 (34)[†]	0.09 (0)[†]
200	ND	ND	1.97 (55)[§]	0.08 (99)[§]
400	ND	ND	1.66 (64)[¶]	0.11 (99)[¶]
600	ND	ND	1.70 (66)[¶]	0.09 (120)[¶]

Percent coefficient of variance is expressed in parentheses.
BAY 43-9006G: BAY 43-9006 glucuronide, BAY 67-3472G: BAY 67-3472 glucuronide.
[†]$n = 3$, [‡]$n = 2$, [§]$n = 2$, [‖]$n = 9$, [¶]$n = 5$, [#]$n = 4$.
ND, not detected.

Table 7. Plasma pharmacodynamics of sorafenib on day 28 of cycle 1

	100 mg ($n = 3$)	200 mg ($n = 12$)	400 mg ($n = 6$)	600 mg ($n = 5$)
pERK+ (%)	44.8 (10.3)	43.6 (15.4)	64.1 (29.6)	57.5 (12.4%)
Adrenomedullin (fmol/mL)	2.18 (0.62)[†]	1.90 (0.67)	2.97 (1.67)	2.23 (0.61)

Standard deviation is in parentheses.
pERK+ (phosphorylated ERK+) is expressed as percentage of positive cells in peripheral blood mononuclear cells.
[†]$n = 2$.

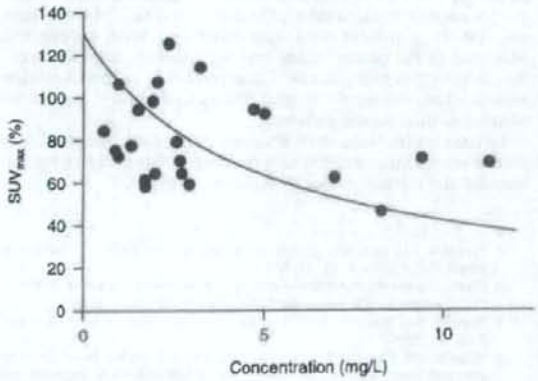

Fig. 2. Relationship between the trough concentration of sorafenib and the maximum standardized uptake value (SUV_{max}) relative to the baseline.

(600 mg bid) and was maintained over 8 months. In another patient with non-small cell lung cancer (NSCLC) who had been treated with cisplatin, vinorelbine, docetaxel, and gefitinib, tumor size gradually decreased and PR was achieved 11 months after the start of continuous dosing (200 mg bid), and was maintained for more than 20 months. Treatment was discontinued when a second cancer (small cell lung cancer) developed, which was surgically resected and treated with cisplatin and etoposide. The original NSCLC did not grow during the treatment course for a period exceeding 30 months. In addition to the PR, a total of 14 patients (48%) experienced SD. Four of 10 patients with non-small cell lung cancer achieved SD for more than 6 months.

Discussion

The results of this study showed a favorable safety profile of sorafenib in Japanese patients with advanced refractory solid tumors. The most common drug-related toxicities including rash/desquamation, hand–foot skin reactions, and diarrhea, and elevations of serum pancreatic enzyme levels were mostly mild to moderate. Dose-limiting toxicities in this study were diarrhea and fatigue.

doi: 10.1111/j.1349-7006.2008.00837.x

Dermatological adverse events were frequently observed. The most common drug-related events were rash/desquamation (61%) and hand–foot skin reactions (39%), which were grade 2 or milder although their incidence was increased with dose escalation from 400 to 600 mg bid (Table 3). Another type of common toxicity was gastrointestinal, such as diarrhea and anorexia. Diarrhea was reported in 11 patients (36%) and one of them experienced a grade 3 dose-limiting event. Previous phase I studies in Europe and the United States in patients with advanced refractory solid tumors (100–800 mg bid) showed similar drug-related adverse events.[15–19] The most frequently reported adverse events in four studies were fatigue (40%), anorexia (35%), diarrhea (34%), rash/desquamation (27%), and hand–foot skin reactions (25%). Similarly, the incidence rates of these drug-related adverse events were higher in the 600 mg group. Diarrhea and fatigue were also dose-limiting toxicities in those studies, and the most common drug-related events were dermatological and gastrointestinal toxicities, which were comparable between Japanese and non-Japanese patients.[15–19] Similar to the previous phase I studies, the results of this study suggests that it is appropriate to recommend 400 mg bid for phase II studies in Japan.

Elevated lipase (36%) and amylase (26%) levels were also common drug-related adverse events, and seven patients (23%) experienced grade 3 or worse. The incidences seemed to be dose-dependent, suggesting that it was related to sorafenib. In a preclinical study, histological changes in the pancreas were observed. Such elevations have been rarely reported in previous clinical studies of sorafenib performed in other countries, where pancreatic enzyme levels were not routinely measured. Lack of symptoms and the transient nature of this toxicity could have led to underestimation in previous studies. The elevation of lipase was also reported in patients treated with sunitinib, a receptor tyrosine kinase inhibitor,[20] which inhibits VEGFR-2, PDGFR, Flt-3, and c-KIT.[21,22] The mechanism of the elevation of pancreatic enzymes may be related to kinase inhibition or to some chemical property, rather than to inhibition of angiogenesis, because patients treated with bevacizumab, an anti-VEGF antibody, did not experience this.[23,24] Importantly, elevations of pancreatic enzyme levels did not cause any clinically relevant events. They were transient, and did not interrupt the sorafenib administration schedule in most patients in the present study. However, as pancreatitis was reported in other clinical trials of sorafenib,[25] physicians treating patients with this drug need to recognize the possibility of occurrence of pancreatitis, although the diagnosis of pancreatitis should not be made solely on the basis of elevation of pancreatic enzymes.

The results of pharmacokinetic analysis suggested that the AUCs of sorafenib and metabolites were related to dose within the range of 100–400 mg bid, but with no further increase at 600 mg. Although the N-oxide of sorafenib (M-2) is the main drug metabolite in plasma, sorafenib exists in plasma mostly in an unchanged form. The ratio of the metabolite to the sum of the unchanged drug and three metabolites was 6–12%, which was lower than the 17% measured in healthy volunteers who received [^{14}C]-sorafenib.[11] The difference might be related to variation in subjects, methodology, and the dose.

Preclinical data suggested that sorafenib is metabolized by CYP3A4. However, coadministration of ketoconazole, a CYP3A4 inhibitor, did not change the concentration of sorafenib in healthy volunteers. In this case, the formation of the main metabolite decreased, suggesting other metabolic pathways, such as glucuronidation.[11] This is the first report that has investigated urinary excretion of sorafenib and metabolites in cancer patients. It was found that glucuronidated sorafenib and other glucuronidated metabolites but not sorafenib itself were in fact excreted in the urine. The amount of metabolites excreted in urine was 2–4%. Following oral administration of [^{14}C]-sorafenib to healthy volunteers, 19% of the dose was excreted as glucuronides in urine, and 77% in feces (50% as unchanged drug).[11] A gain, variation in subjects, methodology, and the dose might explain the difference in the amount of drug excreted in urine. Consistent with the results of previous phase I studies in non-Japanese patients, considerable interpatient variability in relation to the pharmacokinetics of sorafenib was observed in Japanese patients as well.[15] Although drug exposures in Japanese patients were slightly lower than in non-Japanese patients,[15] available data suggest that no dosage adjustment due to ethnicity will be necessary.

We assessed pharmacodynamics in patients treated with sorafenib. ERK is a downstream kinase of Raf kinase, and when sorafenib inhibits Raf kinase, the phosphorylation levels of ERK may also be decreased.[8] Previous clinical studies indicated a significant reduction of pERK levels with increasing sorafenib dose.[18] In the present study, pERK-positive cells within PBMCs were not found to change at any of the dose tested. In addition, adrenomedullin was suggested to be a biomarker of sorafenib in preclinical studies, but no significant changes were observed in our clinical study. In contrast, FDG-PET analysis, performed one month after the start of continuous dosing, showed that treatment with sorafenib decreased disease activity in 83% of patients. Furthermore, reduction in FDG uptake was associated with drug exposure. These observations imply that FDG-PET may be used as a surrogate endpoint. Validity of FDG-PET in evaluating the activity of molecular targeted drugs needs to be further investigated.

Preliminary efficacy data in this study indicated one confirmed PR in a patient with renal cell carcinoma. Angiogenesis is suggested as an essential factor in the progression and metastasis of the disease.[26] The anti-VEGF antibody bevacizumab inhibits VEGF signalings and has demonstrated antitumor activity against renal cell carcinoma. Sorafenib targets VEGFR-2 and PDGFR and inhibits angiogenesis. The efficacy of sorafenib for renal cell carcinoma has been demonstrated in a clinical phase III study (TARGET), in which it significantly prolonged progression-free survival and overall survival.[9] In addition, one PR in a patient with non-small cell lung cancer was observed in the present study and SD for more than 24 weeks was achieved in four patients. These responses support a clinical benefit of sorafenib and suggest that further clinical studies are warranted in Japanese patients.

In conclusion, sorafenib was generally well tolerated, and continuous administration at a dose of 400 mg bid is recommended for further studies in Japanese patients.

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doi: 10.1111/j.1349-7006.2008.00837.x

Jpn J Clin Oncol 2009;39(2)116–123
doi:10.1093/jjco/hyn135

Phase I Dose-escalation and Pharmacokinetic Trial of Lapatinib (GW572016), a Selective Oral Dual Inhibitor of ErbB-1 and -2 Tyrosine Kinases, in Japanese Patients with Solid Tumors

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Received August 24, 2008; accepted October 30, 2008; published online December 3, 2008

Objective: The Phase I dose-escalation study was conducted to evaluate the safety and pharmacokinetics of lapatinib (GW572016), a dual ErbB-1 and -2 inhibitor, in Japanese patients with solid tumors that generally express ErbB-1 and/or overexpress ErbB-2.
Methods: Patients received oral lapatinib once daily until disease progression or in an event of unacceptable toxicity.
Results: Twenty-four patients received lapatinib at dose levels of 900, 1200, 1600 and 1800 mg/day; six subjects enrolled to each dose level. The majority of drug-related adverse events was mild (Grade 1–2); the most common events were diarrhea (16 of 24; 67%), rash (13 of 24; 54%) and dry skin (8 of 24; 33%). No Grade 4 adverse event was observed. There were four Grade 3 drug-related adverse events in three patients (i.e. two events of diarrhea at 1600 and 1800 mg/day each and γ-glutamyl transpeptidase increase at 1800 mg/day). The maximum tolerated dose was 1800 mg/day. The pharmacokinetic profile of lapatinib in Japanese patients was comparable to that of western subjects.
Conclusions: Lapatinib was well tolerated at doses of 900–1600 mg/day in Japanese solid tumor patients. Overall, our findings were similar to those of overseas studies.

Key words: ErbB-1 – ErbB-2 – lapatinib – phase I – tyrosine kinase inhibitor

INTRODUCTION

Dysregulation of the human epidermal growth factor (ErbB) family of cell surface receptors has been noted in several solid tumors. Binding of extracellular ligand to ErbB receptors activates multiple intracellular signaling pathways that can promote tumor growth through processes, such as cell proliferation, differentiation and inhibition of apoptosis. ErbB-1 and ErbB-2 are implicated in the pathogenesis of several cancers (1), and their overexpression in epithelial tumors—including those of the lung, breast, head and neck, colon, stomach, ovary and prostate—often correlates with poor prognosis (2,3).

ErbB receptors present two rational targets for inhibition: blockade of the extracellular ligand-binding domain by monoclonal antibodies and inhibition of the intracellular tyrosine kinase domain by small molecules (4). Several anticancer agents target specific ErbB isoforms. For example, the small molecule tyrosine kinase inhibitors gefitinib (Iressa®) and erlotinib (Tarceva®) and the monoclonal antibody cetuximab (Erbitux®) all target ErbB-1 (5–7), and thus, they are indicated for the treatment of non-small cell lung cancer (NSCLC) and colorectal cancer (8,9). Furthermore, a monoclonal antibody directed against ErbB-2 (trastuzumab, Herceptin®) has been approved for patients with ErbB-2-overexpressing breast cancer (10). Sensitivity to some of these agents is strongly associated with the expression levels of ErbB-1 and -2 (2,3).

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Since it has been suggested that tumors with ErbB-1 expression and ErbB-2 overexpression are more aggressive than those without expression of the receptors (11–13), it has been proposed that dual inhibition of ErbB-1 and -2 could be a useful approach in patients with overexpression of these receptors. Lapatinib (GW572016) is a potent, orally active, small molecule dual inhibitor of ErbB-1 and -2. Lapatinib markedly reduces autophosphorylation of ErbB-1 and -2, and inhibits activation of Erk1/2 and AKT, the downstream effectors of cell proliferation and cell survival, respectively (14–17). Lapatinib inhibits tumor cell proliferation in various human tumor cell lines expressing ErbB-1 and overexpressing ErbB-2, as well as in tumor xenograft models (14–17).

Preclinical study of lapatinib revealed the agent to be well tolerated with an effective half-life of ~24 h, suggesting once-daily oral administration to be feasible (18). Clinical studies of the safety and efficacy of lapatinib in cancer patients are underway.

This was the first Japanese Phase I study of lapatinib in patients with solid tumors. This study was primarily designed to assess the safety of repeated oral doses of lapatinib in these patients and to investigate pharmacokinetics to see if they are comparable with those in western patients.

PATIENTS AND METHODS

Study Design

This was a non-randomized, open-label, multicenter, dose-escalation Phase I study conducted at two sites in Japan—Kinki University Hospital, Osaka and National Cancer Center Hospital East, Chiba.

The primary objectives were to assess the safety of repeated oral doses of lapatinib, to determine the maximum tolerated dose (MTD) in patients with solid tumors, to evaluate the pharmacokinetics (PK) of repeated oral doses of lapatinib and to compare the data from overseas studies and based on these data, to find the clinically recommended dose of lapatinib in Japanese patients enrolled in further studies.

Patient Eligibility

Adult patients aged 20–74 years with histologically or cytologically confirmed solid tumors that are generally known to express EGFR and/or overexpress ErbB-2 (including colorectal cancer, gastric cancer, NSCLC and breast cancer) were eligible for inclusion, provided that they had failed standard therapies or there were no other appropriate therapies available (19–40). Patients had to have normal function of major organs and adequate bone marrow, hepatic and renal functions defined as hemoglobin $\geq$9 g/dl, neutrophil count $\geq$1500/mm^3 and platelets $\geq$100 000/mm^3, AST and ALT $\leq$2.5 of upper limit of normal (ULN) and bilirubin $\leq$1.5 of ULN, and serum creatinine $\leq$1.5 of ULN, respectively. Left ventricular ejection fraction by echocardiography had to be $\geq$50% and in all patients an appropriate length of time since cessation of previous therapy was required (chemotherapy, radiotherapy, surgery or investigational products other than anticancer drugs, $\geq$4 weeks; nitrosourea compounds or mitomycin C, $\geq$6 weeks; biologic response modifiers or hormone therapy, $\geq$2 weeks). Patients were also to have an Eastern Cooperative Oncology Group performance status (PS) 0–2 and life expectancy $\geq$3 months after the start of lapatinib treatment.

Exclusion criteria were serious complications (Grade $\geq$3 according to the National Cancer Institute common toxicity criteria, NCI-CTC, version 2); pleural effusion, ascites and/or pericardial effusion requiring drainage by puncture, intracavital administration, or any other relevant treatment; systematic steroid use for $\geq$50 days or possible need for long-term use of systemic steroids; multiple active cancers; symptomatic brain metastases; malabsorption and/or total resection of the stomach or small intestine; corneal disorder; history of drug allergy; breast feeding; previous trastuzumab-induced impaired cardiac function; and previous acute pulmonary disorder or interstitial pneumonia induced by gefitinib.

All patients gave written informed consent before the start of study. The protocol was approved by the institutional review board of each study site. The study was conducted according to the World Medical Association Declaration of Helsinki (41) and Japanese good clinical practice guidelines (42).

Treatment

Based on the findings of overseas Phase I study (43), and in order to compare PK profiles with an overseas parallel Phase I study (44), patients were assigned to receive lapatinib 900, 1200 or 1600 mg/day for 21 consecutive days. Lapatinib was taken orally once daily with water after a light low-fat breakfast, except on Days 1 and 21 when it was administered in fasting state.

The dose levels started at 900 mg/day and increased to 1200 and 1600 mg/day, then increased by 200-mg increments until MTD was reached. MTD was defined as the dose at which dose-limiting toxicity (DLT), i.e. a drug-related adverse event of NCI-CTC Grade $\geq$3, occurred within 21 days after the initiation of dosage in two or more patients at each dose level with six subjects. When DLT was observed, the next dose for the patients was to be postponed, and could not restart until NCI-CTC grade became $\leq$2 within 14 days. In such cases, when NCI-CTC became Grade 2 or below, the dose was to be restarted at the previous dose level. When NCI-CTC did not reach Grade 2 or below after dose delays of 14 days, the treatment for the patients was to be discontinued. These dose delays and reductions were allowed to be performed only once.

Although appropriate supportive care and symptomatic treatment were allowed, prophylactic use (including

antiemetics) was not permitted between screening and Day 21 of the treatment period. Anticancer therapy of any kind, medications that may affect the absorption or metabolism of lapatinib, and other investigational drugs were prohibited throughout the study. Also, to prevent PK interactions, patients were instructed to avoid grapefruit, grapefruit juice and St John's Wort (*Hypericum perforatum*) throughout the study.

Safety Assessments

Assessments including clinical laboratory tests, vital signs, PS and body weight were performed at screening, at baseline (i.e. within 3 days before the first dose), on Days 7, 14 and 21, every 4 weeks thereafter, on cessation of treatment, and on the last day of observation (i.e. 28 days after the final dose or immediately before the start of next anticancer therapy). Chest X-ray, 12-lead electrocardiogram and echocardiography were performed at screening, once between Days 14 and 21, and on the last observation day. Toxicity was graded according to the NCI-CTC version 2.

Pharmacokinetic Analysis

For PK evaluation, 3-ml blood samples were collected at 1 h pre-dosing and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after dosing on Days 1 and 21 and at pre-dosing on Days 7 and 14. Urine samples were collected before dosing on Day 1 and 0–24 h after dosing on Days 1 and 21.

Serum concentrations of lapatinib were measured by liquid chromatography tandem mass spectrometry with a lower limit of quantitation of 1 ng/ml.

The calculated PK parameters were maximum serum concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration–time curve from 0 to 24 h (AUC_{0-24}) and terminal half-life ($t_{1/2}$). Renal clearance was calculated from urine concentrations of lapatinib.

Efficacy Assessments

For efficacy assessment [i.e. tumor response as determined by X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and/or other objective measurements according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (45)], evaluations were performed at screening (i.e. 4 weeks before the first dose of lapatinib), once during Days 14–21, every 4 weeks thereafter, and on the last day of observation. Target and non-target lesions were assessed in the same manner before and after dosing. Consistency of efficacy evaluation by the study investigators was assessed by extramural review committee.

RESULTS

Patients

Twenty-four patients were enrolled; all had received prior chemotherapy. Table 1 shows their baseline characteristics. The median age was 60 years (range, 37–73), and they had a median PS of 1. NSCLC was the main tumor type. Six patients at four dose levels, 900, 1200, 1600 and 1800 mg/day each, received lapatinib. Eight patients received lapatinib for >3 months and four for >6 months.

All patients completed the initial 21-day treatment period, although one of the patients had dose reduction (overall compliance, 90.5%) due to the onset of a Grade 3 drug-related adverse event (diarrhea) during this period. Four patients (three at 1200 mg dose level and one at 1600 mg dose level) withdrew from study due to disease progression and four (one each at 900 and 1600 mg dose level and two at 1800 mg dose level) were withdrawn at their own request. Mean durations of study treatment in the 900, 1200, 1600 and 1800 mg groups were 131, 68.2, 117 and 49.3 days, respectively. No patient withdrew due to adverse events.

Safety

All 24 patients were eligible for safety analysis. Table 2 lists the drug-related adverse events experienced by ≥20% of

Table 1. Baseline characteristics of patients

Characteristic	Dose (mg/day)				Total ($n = 24$)
	900 ($n = 6$)	1200 ($n = 6$)	1600 ($n = 6$)	1800 ($n = 6$)	
Sex					
Male	5	2	3	4	14
Female	1	4	3	2	10
Tumor type					
Non-small cell lung cancer	5	3	1	4	13
Adenocarcinoma	2	1	1	3	7
Squamous cell carcinoma	2	1	0	1	4
Other	1	1	0	0	2
Colorectal cancer	1	1	2	1	5
Breast cancer	0	0	2	0	2
Others	0	2	1	1	4
Performance status[a]					
0	2	1	2	3	8
1	4	5	3	3	15
2	0	0	1	0	1

[a]Eastern Cooperative Oncology Group performance status.

Table 2. No. of patients with drug-related adverse events that occurred in ≥20% of patients receiving lapatinib

	Dose (mg/day)[a]												No. of patients (%)
	900			1200			1600			1800			
Common terminology criteria grade	1	2	3	1	2	3	1	2	3	1	2	3	
Any adverse events	3	3	0	4	2	0	1	4	1	2	2	2	24 (100)
Gastrointestinal	1	1	0	4	0	0	2	3	1	3	1	2	18 (75)
Diarrhea	1	1	0	4	0	0	2	1	1	3	1	2	16 (67)
Stomatitis	0	0	0	1	0	0	1	2	0	1	0	0	5 (21)
Skin	4	2	0	3	1	0	4	2	0	4	2	0	22 (92)
Rash	1	0	0	4	0	0	1	2	0	3	2	0	13 (54)
Dry skin	5	0	0	2	0	0	1	0	0	0	0	0	8 (33)
Seborrheic dermatitis	3	1	0	0	0	0	0	0	0	1	0	0	5 (21)
Paronychia	0	1	0	0	1	0	2	0	0	1	0	0	5 (21)
Metabolism and nutrition	1	0	0	1	0	0	2	0	0	4	0	0	8 (33)
Anorexia	0	0	0	1	0	0	1	0	0	3	0	0	5 (21)
Investigations	2	1	0	3	2	0	3	1	0	3	1	1	17 (71)
Decreased lymphocyte count	0	1	0	1	1	0	0	1	0	1	0	0	5 (21)

[a]Six patients at each dose level.

patients at each dose level. The majority of events was mild (Grade 1–2); the most common events were skin reactions (mostly rash and dry skin) observed in 22 patients (92%) and gastrointestinal disorders (mostly diarrhea) in 18 patients (75%). The most severe drug-related adverse events were Grade 3 diarrhea observed in one patient at 1600 mg dose level and two patients at 1800 mg dose level. One of these also had Grade 3 γ-GTP increase. All diarrhea resolved with routine symptomatic treatment during or after withdrawal of lapatinib therapy, γ-GTP increase resolved without further treatment after completion of lapatinib therapy.

Grade 1/2 drug-related nausea and vomiting were experienced only by patients at higher dose levels of lapatinib [1/6 (17%) at 1600 mg/day and 3/6 (50%) at 1800 mg/day], with Grade 2 symptoms only seen at the 1800 mg dose level.

For other adverse events, no clear drug relation was found. The most frequent events included decreased body weight and serum alkaline phosphatase increase, each observed in 10 patients (42%). Grade 1 drug-related decreases in left ventricular ejection fraction were found in three of the six patients at the 1200 mg dose level. No clinically relevant changes in vital signs, 12-lead electrocardiogram or echocardiography were noted.

Hypoxemia and pneumonia were reported at the 900-mg dose level in another patient with NSCLC on Day 35. After hypoxemia occurred, the patient continued to receive study drug medication until Day 40. We attributed hypoxemia to bronchostenosis caused by the primary disease. Oxygen inhalation and erythromycin were given and hypoxemia improved while the pneumonia was resolved on Day 41 before the patient died from progression of primary disease 3 months after the events were resolved. Chest X-rays and CT findings for this patient were inconsistent with those for interstitial pneumonia associated with other tyrosine kinase inhibitors; therefore a drug relation with lapatinib was denied.

Maximum Tolerated Dose

Dose escalation was stopped at 1800 mg/day, where two patients experienced DLT (Grade 3 diarrhea). One of these patients also experienced Grade 3 γ-GTP increase. Thus, 1800 mg/day was determined as the MTD.

Pharmacokinetics

Table 3 shows the PK parameters derived from data on 23 patients (data from one patient received lapatinib for only 19 days and are not included).

Serum concentrations of lapatinib at each dose level on Days 1 and 21 are shown in Fig. 1. Repeated doses of lapatinib (900–1800 mg/day) for 21 days resulted in dose-related increases in mean C_{max} (range, 1715–3111 ng/ml) and mean AUC_{0-24} (range, 25 680–51 099 ng·h/ml) (Table 3). Large inter-patient variations were found in mean C_{max} and mean AUC_{0-24}. After a single dose of lapatinib, t_{max} was ~4 h, although values varied greatly among patients. After 21 days of treatment, t_{max} values were similar to those observed after the single dosing on Day 1.