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ORIGINAL ARTICLE

Phase I dose-finding and pharmacokinetic study of the oral epidermal growth factor receptor tyrosine kinase inhibitor Ro50-8231 (erlotinib) in Japanese patients with solid tumors

Noboru Yamamoto · Atsushi Horiike · Yasuhito Fujisaka · Haruyasu Murakami · Tatsu Shimoyama · Yasuhide Yamada · Tomohide Tamura

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Abstract
Purpose The objectives of this phase I dose-finding study of erlotinib were to investigate the toxicity profile, to confirm the acceptable toxicity of doses up to 150 mg/day, and to assess the pharmacokinetic (PK) profile and antitumor activity in Japanese patients with solid tumors.
Patients and methods Patients with solid tumors not amenable to standard forms of treatment were included. Treatment cycle 1 consisted of single-dose administration on day 1, withdrawal on day 2, continuous daily administration from days 3–23, and withdrawal from days 24–30. Subsequent cycles (28 days) used continuous daily administration. The dose of erlotinib was escalated from 50 mg/day to 150 mg/day in 50-mg increments. PK evaluation was performed in all patients during cycle 1.
Results Fifteen patients, aged 38–70 (median; 57) years with non-small-cell lung ($n = 11$), colorectal ($n = 3$) or head and neck ($n = 1$) cancer were enrolled. The major toxicities were rash, diarrhea and liver dysfunctions, which were generally mild and easily manageable. The good tolerability of erlotinib up to the dose of 150 mg/day was confirmed. One patient developed grade 5 treatment-related interstitial pneumonitis. Four of 11 evaluable patients achieved partial responses; all four had non-small-cell lung cancer (NSCLC). The peak plasma concentration of erlotinib, and the area under the concentration-time curve increased proportionally to the dose, suggesting linear PK.
Conclusion The recommended dose of erlotinib in Japanese patients is 150 mg/day. Further trials in Japanese NSCLC patients are warranted.

Keywords Phase I study · EGFR · Tyrosine kinase inhibitor · Ro50-8231 · Erlotinib · Tarceva

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N. Yamamoto · A. Horiike · Y. Fujisaka · H. Murakami · T. Shimoyama · Y. Yamada · T. Tamura (✉)
Division of Internal Medicine, National Cancer Center Hospital, 5-1-1, Tsukiji Chuo-ku, Tokyo 104-0045, Japan
e-mail: ttamura@ncc.go.jp

Introduction

The epidermal growth factor receptor (EGFR) is a transmembrane receptor that has been shown to play an important role in the growth and survival of many solid tumors. Ligand-activated EGFR-dependent signaling is involved in cell proliferation, apoptosis, angiogenesis, invasion, and metastasis [5, 12, 21, 26]. Targeting EGFR has already been recognized as a promising molecular approach in cancer therapy.

Ro50-8231 (erlotinib, Tarceva®) is an orally available, quinazoline-based, highly selective, reversible inhibitor of EGFR tyrosine-kinase activity. This agent competes with adenosine triphosphate for binding to the intracellular tyrosine-kinase domain of EGFR, thus inhibiting receptor phosphorylation. In preclinical studies, the 50% inhibitory concentration of erlotinib was 2 nM, and substantial antitumor activity was demonstrated against human colorectal, head and neck, non-small-cell lung, and pancreatic tumor cells [1, 4, 9]. Following promising preclinical studies, erlotinib was investigated in 40 patients with advanced solid tumors [10]. In this initial US-based phase I study, the major toxicities with once-daily erlotinib were diarrhea, rash, mucositis, headache, and hyperbilirubinemia. The incidence and severity of diarrhea and skin rash were related to the dose of erlotinib and determined as dose-limiting toxicities (DLTs). DLTs were noted at 200 mg/day and, therefore,

150 mg/day was selected as the recommended dose for further studies [10].

Based on the results of the initial US phase I study, we conducted a phase I study of erlotinib in Japanese patients with solid tumors. The objectives of this study were (1) to assess the toxicity profile of erlotinib, including DLTs, (2) to confirm the acceptable tolerability of erlotinib up to a dose of 150 mg/day, (3) to assess the pharmacokinetic (PK) profile of erlotinib, and (4) to assess antitumor activity.

Patients and methods

Patient eligibility

Patients were eligible if they had histologically or cytologically confirmed malignant solid tumors that were resistant to standard therapies, or for which there was no effective treatment. The tumor types selected were among those known to commonly overexpress EGFR, but patients were not selected on the basis of individual EGFR status. Eligibility criteria also included the following: age 20–74 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; life expectancy greater than 3 months; no previous chemotherapy, radiation therapy, or surgery within 4 weeks before treatment with erlotinib (6 weeks for previous treatment with nitrosoureas or mitomycin); adequate bone marrow, hepatic and pulmonary functions (absolute neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin $\geq$ 9.0 g/dl, total serum bilirubin $\leq$ 1.5 mg/dl, aspartate aminotransferase [AST] $\leq$ 100 IU/l, alanine aminotransferase [ALT] $\leq$ 100 IU/l, serum creatinine $\leq$ 1.5 mg/dl, arterial oxygen pressure [PaO_2] $\geq$ 70 torr). Exclusion criteria included: pregnancy or lactation; symptomatic brain metastasis; previous treatment with other EGFR tyrosine-kinase inhibitors or trastuzumab; a history of hypersensitivity reactions to any drugs; pleural effusion and ascites that required drainage; malabsorption syndrome or any other disorder that would affect gastrointestinal absorption; hepatic B or C virus or human immunodeficiency virus infection; serious pre-existing medical conditions such as uncontrolled infections, severe heart disease, uncontrolled diabetes and psychogenic disorders; concomitant use of a contact lens or active corneal disease.

Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center, and conducted in accordance with Japanese Good Clinical Practice guidelines.

Drug administration

Erlotinib was supplied by Chugai Pharmaceutical Co. Ltd. (Tokyo, Japan) as 25, 100 and 150 mg tablets. The agent was administered orally with 200 ml of water in the morning, 1 h before breakfast. Subjects fasted for at least 2 h before and 1 h after administration. The initial treatment cycle consisted of single dose administration on day 1, withdrawal on day 2, continuous daily administration from day 3 to day 23 (21 days), and withdrawal from day 24 to day 30 (7 days). Both withdrawal periods were planned for PK assessment. From the second cycle onwards, erlotinib was administered daily without intervals. Cycles were repeated every 4 weeks (Fig. 1).

Dose escalation procedure

Based on the results of the previously reported US study [10], the starting dose of erlotinib was determined as 50 mg, escalating in 50 mg increments up to 150 mg. Three patients were entered at the initial dose level. If dose limiting toxicity (DLT) was observed in one-third of the patients at this dose level, an additional three patients were entered at the same dose level. Six patients were entered at the second (100 mg) and third (150 mg) dose levels. The dose level at which at least two patients experienced DLTs was defined as the maximum tolerated dose (MTD). The definition of DLT was as follows: (1) grade 3/4 hematologic toxicity, (2) grade 3/4 non-hematologic toxicity excluding skin toxicity, AST/ALT elevation and hyperbilirubinemia, (3) grade 4 skin toxicity, (4) grade 4 AST/ALT elevation or grade 3 AST/ALT elevation lasting more than 7 days, (5) hyperbilirubinemia (>3.5 mg/dl or 2.5–3.5 mg/dl lasting more than 7 days).

Pretreatment assessment and follow-up studies

Complete clinical assessments, including physical examination, ECOG PS, blood pressure, weight, electrocardiogram, chest X-ray, and routine laboratory tests were evaluated in all patients before study entry and prior to each subsequent treatment cycle. Routine laboratory tests included a complete blood count and differential testing of electrolytes, total serum protein, albumin, total serum bilirubin, AST, ALT, alkaline phosphatase, lactic dehydrogenase, gamma-glutamyl transferase, serum creatinine, uric

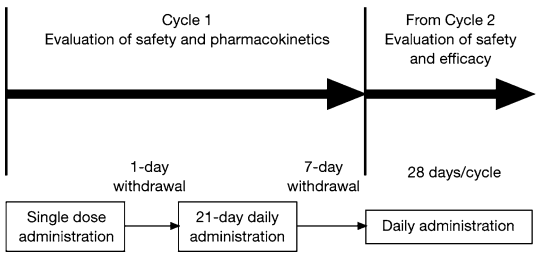

Fig. 1 Treatment schema

acid, cholesterol, glucose, PaO_2, adequate tumor markers and urinalysis. With the exception of PaO_2, tumor markers and urinalysis, these laboratory tests were repeated on days 1, 3, 10, 17, 24 and 31, and then weekly. PaO_2 was obtained as occasion demanded. Tumor markers and urinalysis were determined before each treatment cycle and biweekly, respectively. Toxicities were evaluated according to the National Cancer Institute common toxicity criteria (NCI-CTC, version 2.0). Tumor responses were evaluated according to RECIST (response evaluation criteria in solid tumors) criteria [23].

Pharmacokinetics

PK evaluation was performed in all patients during the initial cycle of treatment. Heparinized venous blood samples (5 ml) were taken: before treatment and 1, 2, 4, 6, 8, 10, 24, 34 and 48 h after treatment on day 1; before treatment on days 4, 10, and 17; before treatment on the last treatment day (day 23) of cycle 1, and 1, 2, 4, 6, 8, 10, 24, 34 and 48 h after this treatment administration. Blood samples were immediately centrifuged at 1,500 rpm for 10 min, and plasma was aliquoted and stored at $\leq -70°C$ in polyethylene tubes until analysis. The plasma concentrations of erlotinib and its O-desmethylated metabolite (OSI-420) were measured by reverse-phase high-performance liquid chromatography using ultraviolet absorbance detection, as described previously [14].

Individual plasma erlotinib and OSI-420 concentration data were analyzed by non-compartmental methods analysis using the WINNonlin software program version 1.5 (Pharsight Corporation, CA, USA). Derived PK parameters included the maximum plasma drug 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 to infinity ($AUC_{0-inf.}$), terminal half-life ($t_{1/2}$) and the oral clearance (Cl/*F*). To assess the drug accumulation by daily administration, the accumulation index (*R*) was calculated according to the following formula: $R = 1/(1-\exp^{-Ket})$, where Ke is the elimination rate constant and *t* is the administration interval.

Results

Patient characteristics

Fifteen patients were enrolled between April 2002 and October 2002. Patient characteristics are listed in Table 1. There were 11 males and four females with a median age of 57 (range, 38–70) years. The predominant tumor type was non-small-cell lung cancer (NSCLC). A total of 78 cycles (28 days/cycle) of erlotinib were administered, and the median number of cycles administered per patient was three (range, 1–19). All 15 patients were included in the toxicity evaluation, and 11 patients were evaluable for efficacy according to the RECIST criteria. Of the four patients not evaluable (NE) for efficacy, one was excluded due to interstitial lung disease (ILD). This patient received erlotinib 100 mg/day, and was withdrawn from the study due to the development of interstitial pneumonitis after 8 days of treatment during cycle 1. Of the remaining three patients, one was regarded as NE because the previously documented brain metastasis was not scanned during the screening period (even though the evaluable supraclavicular lymph node metastasis remained stable through seven cycles of treatment). The other two patients chose to stop treatment. Their target lesions had progressed by about 6–15% after the first cycle of treatment, but their tumor responses met neither SD nor PD according to RECIST criteria, and therefore were classed as NE.

Table 1 Patient characteristics

Characteristic		No. of patients
Total no. of patients		15
Male/female		11/4
Age (years); median (range)		
Median	57	
Range	38–70	
ECOG performance status		
0		3
1		12
Tumor type		
NSCLC		11
Colorectal		3
Head and neck		1
Prior treatment		
Surgery		5
Radiotherapy		4
Chemotherapy		14
No. of prior chemotherapy regimens		
0		1
1		8
2		3
3		2
4		1

NSCLC non-small-cell lung cancer

Toxicity

The major toxicities in the first cycle and in all cycles combined are listed in Tables 2 and 3, respectively. Rash and diarrhea were the principal toxicities associated with

Table 2 Major toxicities in the first cycle

Erlotinib dose (mg/day)	50			100			150			All			Total	%
No. of patients	3			6			6			15				
NCI-CTC grade	1	2	≥3	1	2	≥3	1	2	≥3	1	2	≥3		
Leukopenia	1	0	0	0	0	0	0	0	0	1	0	0	1	6.7
Neutropenia	0	0	0	2	0	0	0	0	0	2	0	0	2	13.3
Anemia	1	0	0	0	0	0	1	1	0	2	1	0	3	20.0
Skin rash	1	1	0	4	1	0	1	5	0	6	7	0	13	86.7
Diarrhea	1	0	0	2	0	0	5	0	0	8	0	0	8	53.3
Stomatitis	0	0	0	1	0	0	2	1	0	3	1	0	4	26.7
Keratitis	0	0	0	1	0	0	1	0	0	2	0	0	2	13.3
Pneumonitis	0	0	0	0	0	1*	0	0	0	0	0	1*	1	6.7

* Grade 5

Table 3 Major toxicities in all cycles

Erlotinib dose (mg/day)	50			100			150			All			Total	%
No. of patients	3			6			6			15				
NCI-CTC grade	1	2	≥3	1	2	≥3	1	2	≥3	1	2	≥3		
Leukopenia	1	0	0	2	0	0	1	0	0	4	0	0	4	26.7
Neutropenia	0	0	0	3	0	0	0	0	0	3	0	0	3	20.0
Anemia	1	0	0	2	0	0	3	1	0	6	1	0	7	46.7
Skin rash	1	1	0	4	1	0	1	5	0	6	7	0	13	86.7
Diarrhea	2	0	0	4	0	0	4	1	0	10	1	0	11	73.3
Stomatitis	0	0	0	2	0	0	2	1	0	4	1	0	5	33.3
Keratitis	0	0	0	3	0	0	2	0	0	5	0	0	5	33.3
ALT increased	1	0	0	3	2	0	3	2	0	7	4	0	11	73.3
AST increased	2	0	0	3	1	0	3	0	0	8	1	0	9	60.0
Total protein decreased	1	0	0	4	0	0	3	0	0	8	0	0	8	53.3
Pneumonitis	0	0	0	0	0	1*	0	0	0	0	0	1*	1	6.7

ALT alanine aminotransferase, *AST* aspartate aminotransferase

* Grade 5

erlotinib. Hematologic toxicities were generally mild (grade 1–2) in severity.

Rash was experienced by 13 (86.7%) of 15 assessable patients, and mostly consisted of rash and seborrhea. The onset of these skin toxicities generally occurred between days 10–14 of cycle 1, and persisted with continued erlotinib treatment. The rash was less than or equal to grade 2 in severity and almost asymptomatic. Supportive treatment with various dermatologic medications, including riboflavin, vitamin B6 and minocyclin did not resolve or relieve these skin effects, although they were clinically tolerable. Although the skin manifestations were qualitatively similar in all affected patients, they occured more frequently with the higher doses of erlotinib.

Diarrhea was observed in 11 (73.3%) of 15 patients (Table 3). The onset of diarrhea generally occurred during the initial treatment cycle. This toxicity was generally mild (grade 1–2) in severity, and watery diarrhea was not observed. The diarrhea was generally manageable, and responded to treatment with a lactobacillus preparation; loperamide was not required.

ALT and AST elevations, were observed in 11 (73.3%) and 9 (60.0%) of 15 patients (Table 3), respectively. However, these toxicities were mild (grade 1–2) in severity, and improved without any medication during treatment with erlotinib. Stomatitis and keratitis, including corneal erosion, were generally mild, and did not seem to be dose-related.

Grade 5 pulmonary toxicity was observed in one patient at the 100 mg/day dose level. The patient was a 68-year-old male with PS 1, who was diagnosed with advanced NSCLC, and had previously suffered from tuberculosis and had chronic emphysema. Before study entry, this patient had received 5 cycles of first-line cisplatin and irinotecan chemotherapy. He complained of dyspnea, and a chest X-ray and computed tomography scan on the eighth day of erlotinib treatment showed a ground-glass appearance in the left lung, suggestive of interstitial pneumonitis. The bronchoalveolar lavage fluid did not suggest the presence of any infections such as fungus, *Pneumocystis carinii*,. Neither steroid hormone (60 mg/day of predonisolone) nor pulse steroid therapy (1,000 mg/day of methylprednisolone for 3 days) improved his pulmonary condition, and he died on day 34 of treatment. An autopsy was performed and the pathologic findings demonstrated severe emphysematous changes, with alveolar destruction and pyogenic bronchopneumonia with infiltration of inflammatory cells, as well as disease progression. Although the pathological findings did not support drug-induced interstitial pneumonitis, the clinical observations indicated suspected drug- induced interstitial pneumonitis that could have exacerbated respiratory failure.

Up to a dose level of 150 mg/day, one DLT was observed (grade 5 pulmonary toxicity at a dose of 100 mg/day); other toxicities were considered acceptable. Therefore, the MTD was not reached, and the acceptable tolerability of erlotinib doses up to 150 mg/day was confirmed. The dose level of erlotinib 150 mg/day was, therefore, determined as the recommended dose.

Antitumor activity

Eleven of 15 patients were evaluable for anti-tumor response (Table 4). Four patients (all NSCLC) achieved a partial response and three achieved stable disease (all NSCLC). Of the four responders, three were male former smokers (>50 pack years) and one was a female never-smoker; all had tumours with adenocarcinoma histology.

Table 4 Objective tumor response and duration

No.	Dose level (mg/day)	Age	Sex	PS	Smoking status	Tumor type	Histology	Response	Response duration (days)
01	50	56	M	1	Smoker[a]	NSCLC	Large-cell carcinoma	NE	
02	50	52	M	1	Smoker[a]	NSCLC	Adenocarcinoma	PD	
03	50	60	F	1	Never smoker	Colorectal	Adenocarcinoma	PD	
04	100	62	M	1	Smoker[a]	NSCLC	Adenocarcinoma	PR	85
05	100	57	M	1	Smoker[a]	NSCLC	Adenocarcinoma	SD	87
06	100	38	M	1	Smoker[a]	NSCLC	Adenocarcinoma	NE	
07	100	68	M	1	Smoker[a]	NSCLC	Undifferentiated	NE	
08	100	50	F	1	Never smoker	NSCLC	Adenocarcinoma	PR	>283[b]
09	100	60	F	0	Never smoker	NSCLC	Adenocarcinoma	SD	197
10	150	48	M	1	Smoker[a]	Colorectal	Adenocarcinoma	NE	
11	150	53	M	0	Smoker[a]	NSCLC	Undifferentiated	SD	>170[b]
12	150	70	M	1	Smoker[a]	NSCLC	Adenocarcinoma	PR	>170[b]
13	150	53	F	0	Smoker[a]	Colorectal	Adenocarcinoma	PD	
14	150	58	M	1	Smoker[a]	Head and Neck	Adenocarcinoma	PD	
15	150	58	M	1	Smoker[a]	NSCLC	Adenocarcinoma	PR	>170[b]

M male, *F* female, *PS* performance status, *NSCLC* non-small-cell lung cancer, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

[a] Former smoker

[b] shifted to the continuous administration study from phase I portion of trial ($n = 4$)

Pharmacokinetics

Plasma sampling for PK analyses was performed in all 15 patients on days 1 and 4. However, plasma sampling on days 10, 17 and 23 was not undertaken in one patient due to withdrawal following pulmonary toxicity.

The PK profile of erlotinib is summarized in Table 5, and the mean plasma concentration-time profiles of erlotinib and its principal metabolite OSI-420, after treatment with erlotinib 150 mg/day are illustrated in Fig. 2. Following oral ingestion of erlotinib on day 1, mean T_{max} was 6.00 h (range, 1–24 h), with a long plasma half-life ($t_{1/2}$; mean 25.92 h, range 14.84–40.02). The Cl/*F* of erlotinib showed moderate inter-individual variability and the mean ± standard deviation (SD) [CV%] of Cl/*F* on day 1 for erlotinib doses of 50, 100 and 150 mg/day were 12.23 ± 9.03 [73.8%], 8.84 ± 4.48 [50.7%] and 5.42 ± 1.58 [29.2%] l/h, respectively. Steady-state plasma concentrations of erlotinib were achieved by day 10 at all doses. Both C_{max} and $AUC_{0–inf}$ on day 1 generally increased with erlotinib dose, suggesting linear PK in the range 50–150 mg/day (Fig. 3). The estimated and observed accumulation indexes, which were termed "R_{est}" and "$R_{obs}(AUC_{0–24})$", were 1.70 ± 0.61 and 2.01 ± 1.27 (mean ± SD) at the dose of 100 mg/day, respectively, and 2.12 ± 0.55 and 3.71 ± 2.40 at the dose of 150 mg/day, respectively.

OSI-420 could be reliably measured even when erlotinib was administered at a dose of 50 mg/day. When erlotinib was given at 150 mg/day on day 1, mean T_{max} was 9.7 h (range, 1–24 h), and the mean ± SD values of C_{max} and $AUC_{0–24}$ were 62.7 ± 41.4 ng/ml and 789.6 ± 300.8 ng hr/ml, respectively. Exposure to OSI-420 relative to that of erlotinib was low, and the mean ± SD values for the ratio of OSI-420 $AUC_{0–24}$ to erlotinib $AUC_{0–24}$ on days 1 and 23 were 0.055 ± 0.006 and 0.074 ± 0.025, respectively. Although there was a small number of patients in this phase I study, rash seemed to be correlated with C_{max} and $AUC_{0–inf}$ of erlotinib (Fig. 4).

Discussion

Here we report a phase I dose-finding study of the oral EGFR tyrosine-kinase inhibitor erlotinib, administered daily to Japanese patients with solid tumors. In a previous, US-based phase I study, the MTD of erlotinib was determined as 150 mg/day, and this was established as the recommended dose [10]. Based on the results of this earlier study, dose escalation in the present study was limited to the assessment of erlotinib doses up to 150 mg/day (50, 100 and 150 mg/day). Only one DLT (grade 5 pulmonary toxicity) was observed in this study and the major toxicities were rash, diarrhea and elevated hepatic transaminases. At doses of erlotinib up to 150 mg/day, these toxicities were generally mild in severity, and treatment interruption was not required. Furthermore, severe haematological toxicity associated with conventional chemotherapy (such as febrile neutropenia or anemia requiring blood transfusions) was

Table 5 Pharmacokinetic parameters of erlotinib

Dose level (mg/day)	Day	No. of patients	C_{max} (ng/ml)	T_{max} (h)	Cl/*F* (l/h)	$t_{1/2}$ (h)	Css, min (ng/ml)	AUC_{0-24} (ng hr/ml)	AUC_{0-inf} (ng hr/ml)	R_{est}	R_{obs} (AUC_{0-24})
50	1	3	193.67 ± 84.39	5.00 ± 3.61	12.23 ± 9.03	14.76 ± 10.51		3265.82 ± 1777.92	6320.86 ± 5015.47		
	23	3	820.33 ± 347.25	4.33 ± 4.93	3.92 ± 2.36	23.60 ± 15.83	538.67 ± 286.49	15843.67 ± 7991.56	37798.87 ± 29387.24	1.51 ± 0.54	4.89 ± 0.58
100	1	6	570.67 ± 266.97	6.00 ± 9.01	8.84 ± 4.48	17.98 ± 11.06		7704.90 ± 3550.83	14095.46 ± 7194.74		
	23	5	1023.40 ± 320.15	3.00 ± 2.00	10.03 ± 8.95	15.56 ± 8.66	453.00 ± 380.27	14622.61 ± 7007.19	25616.14 ± 15011.00	1.70 ± 0.61	2.01 ± 1.27
150	1	6	958.00 ± 457.19	6.00 ± 8.92	5.42 ± 1.58	25.92 ± 9.31		12845.48 ± 3774.53	29473.52 ± 7569.01		
	23	6	2384.33 ± 932.43	1.83 ± 0.41	5.08 ± 4.51	27.19 ± 9.07	1642.00 ± 1085.15	42678.50 ± 20434.75	107751.87 ± 73129.00	2.12 ± 0.55	3.71 ± 2.40

Data represent mean ± SD

Cl/*F* (day 1), Dose/AUC_{0-inf} (day 23), Dose/AUC_{0-24}, *F* bioavailability, *Inf* infinity, R_{est} estimated accumulation index, R_{obs}(AUC_{0-24}) observed accumulation index of AUC_{0-24} on day 23

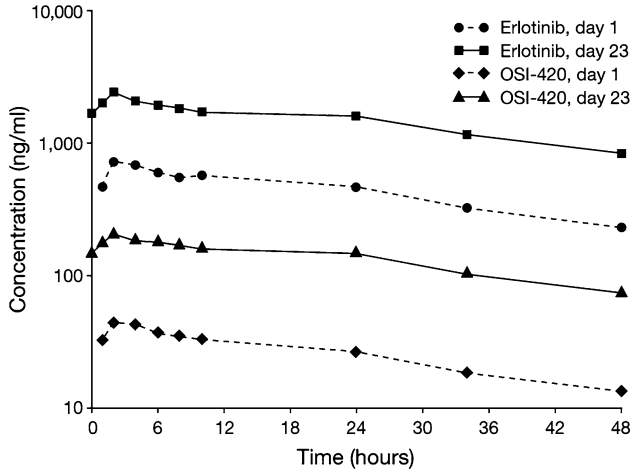

Fig. 2 Mean plasma concentration–time profiles of erlotinib and OSI-420 following administration of erlotinib 150 mg

not observed. Therefore a dose of erlotinib 150 mg/day was determined as the recommended dose for further study in Japanese patients. The major toxicities observed in this study have also been reported for other EGFR inhibitors [2, 3, 15]. Exposure to erlotinib appears to be an important factor for the onset of certain toxicities. In the US phase I study of erlotinib, the incidence and severity of rash and diarrhea were related to the dose of erlotinib [10]. Although there was a limited number of patients and dose escalation was not planned above the dose of 150 mg/day, PK analyses in the present study also suggested a correlation between rash and drug exposure (e.g. C_{max} and AUC). Other PK analyses performed in this study showed that although there was moderate inter-individual variability, linear PK profiles were observed in the range of erlotinib 50–150 mg/day, and there was no significant drug accumulation. In addition, several PK findings concerning the influence of smoking have been reported [6, 8]. Smoking could cause induction of the CYP1A2 enzyme which plays an important role in erlotinib metabolism. Although this effect could reduce the AUC of erlotinib, the effect of enzyme induction could be expected to last for only 1–2 weeks after stopping smoking. As none of the patients were current smokers, the study can provide no useful information on the impact of smoking status on erlotinib PK.

For the 150 mg/day dose, values for the main PK parameters measured in this study were very similar to those reported in the US phase I study. This suggests that at the recommended dose, exposure to erlotinib is similar between Japanese and Western patients.

Suspected drug-induced lung injury, manifesting as interstitial pneumonitis was observed clinically in one patient who received erlotinib 100 mg/day. Although this toxicity is serious, the reported incidence of ILD was very low in studies of erlotinib in the USA and Europe; in a

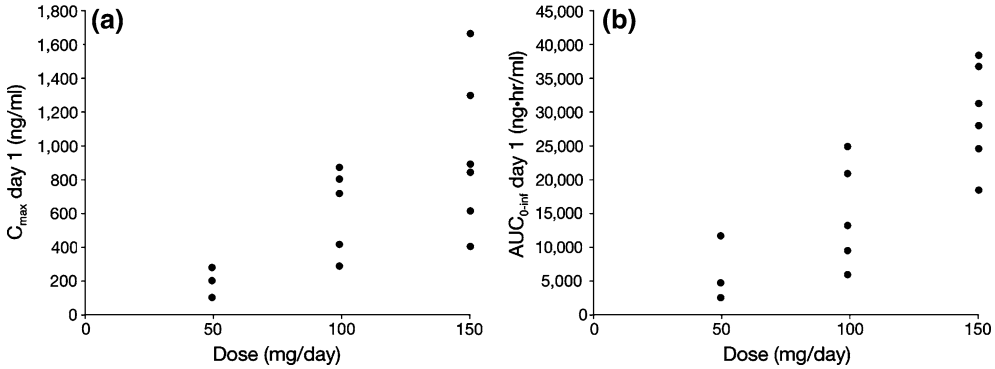

Fig. 3 C_{max} (**a**) and $AUC_{0–inf}$ (**b**) according to erlotinib dose on day 1 following oral administration

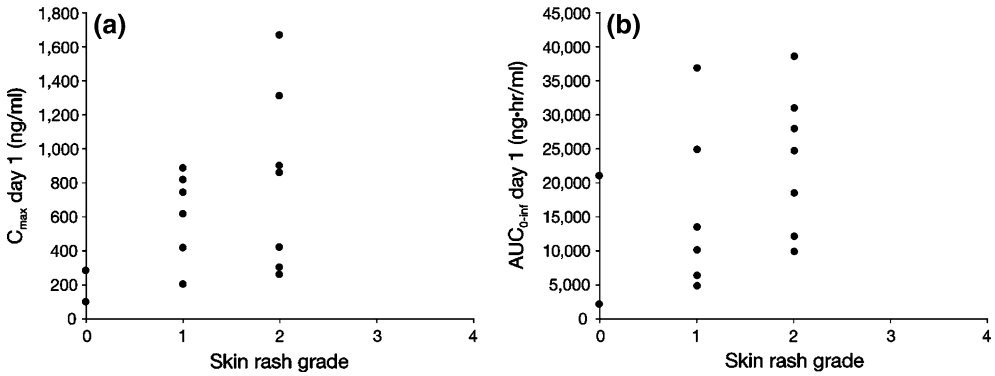

Fig. 4 Relationships between **a** rash and C_{max} on day 1, and **b** rash and $AUC_{0–inf}$ on day 1

phase III study (BR.21) of erlotinib monotherapy in relapsed NSCLC, ILD occurred at the same incidence in the erlotinib and placebo arms (0.8%) [19]. ILD has also been reported with gefitinib, another EGFR tyrosine-kinase inhibitor [11, 22]. In patients treated with gefitinib, the onset of ILD is generally acute (i.e. within 4 weeks of treatment) and the incidence has been reported as 5.8% in Japanese patients [27]. The reported incidence of ILD with gefitinib is higher in Japan than elsewhere, although the reason for this is unknown. This may represent a greater prevalence of the toxicity, greater awareness and reporting, or an increased genetic susceptibility in the Japanese population. However, the biological mechanisms, such as environmental, clinical and genetic factors that may contribute to this toxicity have not yet been elucidated. Thus, further investigation to identify the mechanism of drug-induced interstitial pneumonitis associated with EGFR tyrosine-kinase inhibitors is warranted.

In the current trial, four of 11 evaluable patients (3 males and 1 female) achieved a partial response, all of whom had NSCLC of adenocarcinoma subtype. The three males were former smokers with more than 50 pack years. These results are particularly interesting as clinical characteristics that have been reported as favorable factors for clinical benefit with gefitinib and erlotinib in NSCLC patients include female gender, adenocarcinoma subtype, and never-smoking status [18, 22]. Our results are, however, not unexpected, as data from the placebo-controlled BR.21 study of erlotinib in relapsed NSCLC demonstrated that the survival benefit with erlotinib was not restricted to particular sub-populations [19]. Recently, it has been reported that certain mutations in the tyrosine-kinase domain of EGFR are present in a subset of NSCLCs, most commonly in patients who have never smoked, and these mutations appear to be associated with a greater likelihood of response to gefitinib and erlotinib [13, 16, 17]. Importantly, however, not all patients with mutations obtain a response, and some patients without mutations do obtain a response. The incidence of EGFR mutations in Japanese patients with NSCLC is about 40%, which is higher than that in Caucasian patients (10–15%) [13, 20]. However, any possible association between EGFR mutations and survival with EGFR tyrosine-kinase inhibitors is presently unclear. In a retrospective analysis of samples from the BR.21 study, the presence of EGFR mutations was significantly associated with response to erlotinib but not with survival [24, 25]. Other markers that are under investigation as potential predictors of clinical benefit with EGFR tyrosine-kinase inhibitors are EGFR expression and EGFR gene copy number [7]. None of these markers of EGFR status were assessed in

the current study, although such assessments would be important in future studies, including those restricted to Japanese patient populations.

In conclusion, the results of this study confirm that in Japanese patients, the recommended dose of erlotinib is 150 mg/day. At this dose level, erlotinib has acceptable toxicity with a PK profile similar to that seen in a US phase I study. Several partial responses were observed, all in patients with NSCLC, including male smokers. Analysis of the clinical benefits of erlotinib in Japanese patients with NSCLC entered into phase II/III trials are ongoing.

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