systemic arterial supply to an occluded lung, related to the location of thrombi, is hyperplasia of the pulmonary artery vasa vasorum, which is of bronchial arterial origin[6,17] In addition, the extent of central disease per se may lead to nonhemodynamic factors, including pro- and anti-angiogenic factors. Our previous study showed that monocyte chemoattractant protein-1 is produced in endothelial cells, mononuclear cells, and smooth muscle cells in the fibrinous portion adjacent to the vascular lumen in endarterectomized tissue[18] Herve and Fadel speculated that macrophages infiltrating the wall of an occluded pulmonary artery stimulate proliferation of the vasa vasorum and lead to delivery of bone marrow-derived endothelial progenitor cells for local vasculogenesis within the nonresolving clots[6] Other nonhemodynamic factors that are elevated in patients with CTEPH, such as endothelin-1[19] might play a role in development of dilated BAs.

We also showed that the total area of the BAs was significantly reduced after PTE. However, the total area of the BAs after PTE was greater compared with that in the post-APTE group. A certain number of thrombi remained after PTE, which would keep the BAs dilated. Fadel et al showed that in piglets revascularization after a period of left pulmonary artery occlusion normalized the systemic blood flow to the left lung[20] Our finding is consistent with their experimental model and we believe that reduction in the total area of the BAs after PTE can prevent hemoptysis, a life-threatening complication of CTEPH.

When we divided the CTEPH group into main type, lobar type and segmental type based on the most proximal location of thrombi, we did not find any significant difference between the total area of the BAs in the segmental type of CTEPH and that in PAH. Some previous studies have indicated that the finding of dilated BAs can help distinguish CTEPH from idiopathic PAH[3] or APTE;[4] however, those studies made no mention of the central extent of thrombi in the CTEPH patients. Although dilatation of the BAs is a common finding in CTEPH, it seems to be relatively limited to the central type of CTEPH.

Although it did not reach statistical significance (p=0.06), the change in PaO_2 after PTE moderately correlated with the total area of the BAs. In patients without lung disease, the bronchial circulation supplying the systemic arterial flow is estimated to be 1% of cardiac output[21] In CTEPH patients, this bronchopulmonary shunt volume can increase up to approximately 30% of cardiac output[1,2] Some animal models have confirmed that bronchial circulation supports ischemic parenchymal lung tissue[5] Besides that support, prolonged lung ischemia damages the pulmonary endothelium and leads to increasing permeability in the lung[22] In that condition, ischemic–reperfusion injury after PTE could happen to varying degrees. Development of bronchial circulation was shown to attenuate ischemic–reperfusion lung injury in some experimental models[23–25] and our data also suggest a supportive role of the BAs in the ischemic lung and their importance for gas exchange after PTE.

We did not find any other relationships between surgical outcomes, including % reduction in PVR, and the total area of the BAs. Kauczor et al found a lower postoperative mortality rate in patients with dilated BAs after PTE[8] In our study, only 2 patients died during the early postoperative period, so we did not evaluate the mortality rate. Heinrich et al reported that the postoperative PVR was significantly lower in patients with dilated BAs than in those without;[9] they classified patients into 2 groups, with (≥1.5 mm) and without (<1.5 mm) dilated BAs. In our study, as 23 of 24 patients undergoing PTE had BAs ≥1.5 mm, it is likely that we performed surgery only for the relatively central type of CTEPH and assessed only the patients with dilated BAs, and thus we could not apply their criterion for determining any correlation between postoperative PVR and bronchial arterial dilatation.

The major difference between the current study and earlier studies is that we used the total cross-sectional area of the BAs to evaluate the development of the systemic collateral supply instead of their diameters. Evaluation of bronchial arterial dilatation in CTEPH is intended for assessment of the role of systemic circulation to the lung, so a method of quantifying the systemic collateral supply would be desirable. In our study we could determine a relationship between the total cross-sectional area of the BAs and the central extent of thrombi or the increase in PaO_2 after PTE, and we believe that it is reasonable to use the total area of the BAs to assess the role of systemic circulation to the lung in patients with CTEPH.

Study Limitations

First, none of our patients underwent conventional angiography of the BAs or measurement of the bronchopulmonary shunt volume, so we could not confirm the accuracy of our findings with a "gold standard". Second, the CT protocol was optimal for pulmonary artery visualization because all CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH. However, we could depict the BAs sufficiently for evaluation, except for 14 cases. Third, the number of patients in each group was small. Larger studies are needed to confirm the relationship between dilated BAs and the central extent of thrombi or surgical outcomes after PTE.

In conclusion, the total cross-sectional area of the BAs correlated with the extent of central disease in patients with CTEPH and it might be useful for predicting gas exchange improvement after PTE.

Acknowledgment

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Efficacy and Safety of Erlotinib Monotherapy for Japanese Patients with Advanced Non-small Cell Lung Cancer

A Phase II Study

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Introduction: The aim of this study was to evaluate the efficacy and safety of Erlotinib in Japanese patients with previously treated non-small cell lung cancer (NSCLC). Available tumor biopsy samples were analyzed to examine relationships between biomarkers and clinical outcome.

Methods: This open-label phase II trial enrolled stage III/IV NSCLC patients who had progressive disease after at least one prior platinum-based chemotherapy regimen. Erlotinib was administered at a dose of 150 mg/d orally until disease progression or intolerable toxicity. Analysis of epidermal growth factor receptor gene mutations in exon 18–21 by direct sequencing was performed in tumor tissue specimens obtained at the first diagnosis.

Results: Sixty-two patients were enrolled and 60 patients were evaluable for efficacy. Objective response rate and disease control rate were 28.3% and 50.0%; median time to progression and overall survival were 77 days and 14.7 months, respectively. In logistic regression analysis, only smoking history was proved to be a statistically significant predictive factor for response (odds ratio: 0.06, $p < 0.001$). Only 7 patients had samples available for mutation analysis. Three patients who had deletion mutations on exon 19 (del E746-A750 or del S752-I759) exhibited objective response. Common toxicities were rash (98%), dry skin (81%), and diarrhea (74%). Discontinuation due to adverse events occurred in 11 patients (18%). Four patients (6%) experienced interstitial lung disease-like events, one of whom died.

Conclusion: Erlotinib is efficacious in Japanese patients with previously treated NSCLC. The toxicity profile was similar to that in Western patients, except for a somewhat higher incidence of skin disorders and interstitial lung disease. Further studies are needed to determine the relationship between epidermal growth factor receptor mutations and outcomes with Erlotinib in Japanese patients.

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Lung cancer affects approximately 1.2 million people annually, and is the leading cause of cancer death in the world.[1] More than 80% of affected patients are diagnosed with non-small cell lung cancer (NSCLC). The standard first-line treatment for metastatic NSCLC is a combination of platinum chemotherapy with a third-generation agent such as docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan.[2,3] Although patients with stage II, IIIA, or IIIB NSCLC receive platinum-based chemotherapy as part of combined modality treatment with thoracic radiotherapy or surgery, many will be candidates for second or third-line chemotherapy. Docetaxel is the only cytotoxic agent with a proven survival advantage over supportive care in patients with disease progression after cisplatin-based chemotherapy for NSCLC.[4] The other agent for which a survival benefit has been demonstrated in this setting is erlotinib,[5] which was approved in Japan for the treatment of relapsed NSCLC in October 2007. Erlotinib is a selective, orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). In contrast to the experience with the cytotoxic chemotherapeutic agents, response to treatment with EGFR-TKIs has been reported to be influenced by gender, histological type, race or ethnic origin, and smoking status.[5–8]

Tumor molecular markers, including *EGFR* gene mutations and protein expression, have been widely studied in patients with NSCLC, and there is strong evidence that the presence of *EGFR* gene mutations is a predictor of tumor response and resistance.[9–12] However, few prospective studies have evaluated molecular markers as predictors of outcome, and their clinical usefulness is unproven.

This report presents the results of the first phase II study of erlotinib conducted in Japanese patients with NSCLC. The purpose was to evaluate the efficacy and safety of erlotinib in this population. Where available, tumor biopsy samples were analyzed for EFGR-related markers.

PATIENTS AND METHODS

This phase II, multicenter, open-label study recruited patients at 11 hospitals in Japan. The primary end point was the objective response rate (ORR) to erlotinib treatment (150 mg/d). Secondary endpoints were disease control rate (DCR), response duration, time to progression, overall survival (OS), quality of life (QoL), and safety. The protocol was approved by the ethics review boards of all participating institutions, and conducted in accordance with Japanese Good Clinical Practice guidelines.

Patient Selection

Patients with histologically or cytologically documented stage IIIB or IV NSCLC at study entry (not curable with surgery or radiotherapy) that was recurrent or refractory to treatment with one or more chemotherapy regimens (including at least one platinum-containing regimen), were enrolled into this study. Additional eligibility criteria included: the presence of measurable lesions by Response Evaluation Criteria in Solid Tumors (RECIST); age ≥20, <75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and adequate bone marrow, hepatic, and renal function, i.e., aspartate aminotransferase and alanine aminotransferase (ALT) levels ≤2.5 times the upper limit of normal and total bilirubin of ≤1.5 times the upper limit of normal. Patients with existing or previous interstitial lung disease (ILD) were excluded, although a history of radiation pneumonitis (limited to the field of radiation treatment) was permitted. Concomitant anticancer treatment and prophylactic medication for adverse events (AEs) were not permitted, nor was prior use of anti-EGFR or anti human epidermal growth factor receptor (HER2) agents (small molecules and monoclonal antibodies). Written informed consent was obtained from all patients.

Treatment Procedure

After completion of the baseline assessments (see below), all patients received erlotinib (150 mg orally) each morning, 1 hour before breakfast, until the occurrence of progressive disease (PD) or unacceptable toxicity (all AEs were graded using the National Cancer Institute Common Toxicity Criteria Version 2.0). In the event of treatment-related toxicity, 2 dose reductions of 50 mg were permitted per patient, and dosing could also be interrupted for up to 14 days. For grade 3 or intolerable grade 2 rash, treatment was withheld until the rash improved to grade 2 or less, when a lower dose of erlotinib was initiated. For grade 3 diarrhea, treatment was withheld until the diarrhea was grade 1 or less, when a lower dose was started. For ILD of any grade, or any grade 4 toxicity, treatment was immediately and permanently discontinued.

Evaluation of Efficacy

Objective tumor response was assessed in accordance with RECIST.[13] Tumor assessments were performed at baseline, then every 4 weeks until week 16, and then every 8 weeks thereafter. Confirmation of complete or partial responses (PR) was required, by means of a second assessment conducted 28 days or more after the initial assessment. Stable disease (SD) was defined as disease control (absence of progression) maintained for at least 6 weeks. An independent response evaluation committee consisting of 2 oncologists and a radiologist reviewed images of patients with complete response, PR, and SD. Individual survival times were determined from the survival status of each patient during the study period and at the post study follow-up survey conducted in June-July 2005 and May-July 2006. OS was defined as the time from first administrated to death.

Quality of Life Evaluation

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire (Version 4-A)[14] was used to assess QoL. The full FACT-L questionnaire was administered at baseline and then every 28 days. In addition, the Lung Cancer Subscale (LCS), an independently validated component of FACT-L, was administered weekly during the treatment period. Best responses on the LCS were analyzed for all patients with a baseline LCS score of 24 or less (out of a possible 28 points) and symptomatic improvement was defined as an increase from the baseline score of 2 or more points, sustained for at least 4 weeks.

Evaluation of Safety

Baseline assessment included a full patient history, physical examination, standard laboratory tests, electrocardiography, chest radiography, pregnancy test, and ophthalmologic tests (vision test and slit-lamp examination). Every week until week 8 and every 2 weeks thereafter, vital signs and ECOG PS were monitored and blood samples were taken for hematology and blood chemistry tests. A radiograph examination to assess pulmonary toxicity was conducted weekly until week 4 and every 2 weeks thereafter. Ophthalmologic examinations were repeated at week 8 and at the end of the study. Observation and evaluation of AEs was conducted as appropriate throughout the study period. All AEs were graded using National Cancer Institute Common Toxicity Criteria Version 2.0. For all ILD-like events, the data safety monitoring board (which consisted of oncologists and pneumonologists) reviewed the clinical data and images; the images were also examined by a review committee of radiologists with expertise in drug-induced pulmonary disorders.

Biomarker Analysis

EGFR mutations and EGFR and HER2 protein expression were assessed in patients with suitable tumor tissue specimens at first diagnosis or surgery; these assessments were done only with separate written consent. Tumor samples were obtained from each center as formalin-fixed and paraffin-embedded blocks, or as thinly sliced tissue sections mounted on glass microscope slides. For the mutation analysis, the tissue was microdissected by Targos Molecular Pathology (Kassel, Germany) and direct sequencing was conducted at the Roche Centre of Medical Genomics (Basel, Switzerland), using a nested polymerase chain reaction of exon 18–21. EGFR protein expression was analyzed by Lab Corp (Mechelen, Belgium). EGFR expression analysis was conducted by immunohistochemistry using Dako EGFR PharmDx™ kits (Dako, Carpinteria, CA). A positive test was

defined as membranous staining in ≥10% of the tumor cells. HER2 protein expression was measured using HercepTest™ (Dako, Carpinteria, CA), and a score of 1+ or above (possible scores were: 0, 1+, 2+, 3+) was regarded as positive.

Statistical Analysis

Given an expected ORR of 20%, a Fisher's exact test was performed (one-sided $\alpha = 2.5\%$). Based on 50 patients, the power to test the null hypothesis (ORR = 5%) was 89.66%. The target sample size of 60 patients was chosen on the expectation that a proportion of patients would prove to be ineligible for the study. The main analysis of efficacy was conducted on the full analysis set (FAS), which was produced by omitting ineligible patients. The 95% confidence interval (CI) for ORR, DCR, and symptom improvement rate was calculated by the Clopper-Pearson method. The time-to-event variables were estimated by the Kaplan-Meier method. Logistic regression and Cox proportional hazards regression analysis was conducted on best response and survival time, respectively. In both cases, univariate and multivariate analyses were used to evaluate the effects of 11 factors relating to patient and disease characteristics, and previous treatment.

RESULTS

Patient Characteristics

A total of 62 patients were enrolled between December 2003 and January 2005. All were evaluable for safety and 60 were evaluable for efficacy (FAS). Two patients did not have a measurable lesion according to RECIST. The baseline characteristics of the patients, including their treatment history, are shown in Table 1. The median age was 60.5 years (range: 28–74 years), and 71% of patients were male. Fifty-seven patients (92%) had adenocarcinoma, and 20 (32%) were never-smokers. Twenty-seven patients (44%) had received only one previous chemotherapy regimen.

Efficacy

Tumor response rates in the FAS (as assessed by extrainstitutional review) are shown in Table 2. Seventeen patients were assessed as having a PR and 13 as having SD. The ORR was 28.3% (95% CI: 17.5–41.4%) and the DCR was 50% (95% CI: 36.8–63.2%). In three patients, objective response could not be adequately confirmed, because each discontinued treatment early in the study due to AEs. The median duration of response was 278 days (95% CI: 203–422 days), and time to progression was 77 days (95% CI: 55–166 days). OS was determined based on information collected until the follow-up survey conducted in May–July 2006. The median survival time was 14.72 months (95% CI: 11.07–20.57 months; 19 censored cases) and the 1-year survival rate was 56.5% (95% CI: 43.9–69.1%) (Figure 1). The median OS of patients with PD was 9.95 months. The symptom improvement rate measured using the LCS was 42.1% (24/57; 95% CI: 29.1–55.9%).

The overall response rate was higher in women (58.8%; 10/17) than in men (16.3%; 7/43, χ^2 test: $p = 0.0029$), and in never-smokers (63.2%; 12/19) than in current or former smokers (12.2%; 5/41, $p = 0.0002$). There was no statistically significant difference between the response rate in patients with adenocarcinoma (28.6%; 16/56) and nonadenocarcinoma histology (25.0%; 1/4, $p = 1.0000$). The response

TABLE 1. Summary of Baseline Patient Characteristics and Demographics

Patient and Disease characteristics	No. of Patients ($n = 62$)	%
Age (yr)		
Median	60.5	
Range	28–74	
Sex		
Female	18	29
Male	44	71
Performance status		
0	20	32
1	41	66
2	1	2
Histology		
Adenocarcinoma	57	92
Squamous cell	4	6
Unclassified	1	2
Stage		
IIIB	8	13
IV	54	87
Smoking history		
Never smoked	20	32
Current- or former smoker	42	68
Time since initial diagnosis (d)		
Median	304.0	
Range	2–2353	
Prior chemotherapy regimens		
1	27	44
2	23	37
≥3	12	19
Prior taxanes		
No	10	16
Yes	52	84
Time since last regimen (d)		
Median	80.0	
Range	29–528	

TABLE 2. Response Assessment

Parameter	n	(%)
Partial response	17	28.3
Stable disease	13	21.7
Progressive disease	27	45.0
Not assessable	3	5.0
Response rate (%) (95% CI)	28.3 (17.5–41.4)	
Disease control rate (%) (95% CI)	50.0 (36.8–63.2)	
Duration of response (median: days)[a] (95% CI)	278 (203.0–422.0)	
Time to progression (median: days)[a] (95% CI)	77 (55–166)	

[a] Kaplan–Meier method.
CI, confidence intervals.

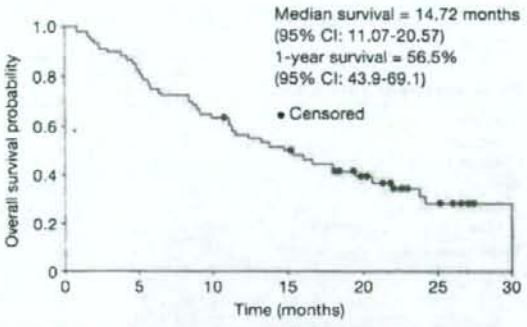

FIGURE 1. Kaplan-Meier plot showing overall survival.

rate was not affected by the number of previous chemotherapy regimens, however, being 27% for patients with one previous regimen (7/26) and 29% for those with 2 or more regimens (10/34). No statistically significant differences were found between other patient subgroups. In a multivariate logistic regression analysis, only smoking history was found to be a statistically significant predictor of response. A multivariate Cox regression analysis showed that both smoking history and ECOG PS were significant predictors for OS (Table 3).

Safety

All 62 patients who received erlotinib were assessed for safety. Treatment-related AEs were observed in all patients, and there were 24 serious AEs in 18 patients (29%). AEs led to discontinuation of erlotinib in 11 patients (18%), including 3 due to ILD-like events, 2 due to ALT elevation, and one each due to rash, paronychia, punctate keratitis, dyspnea/hypoxia, pneumonia and fever/inflammatory neck swelling, and to dose interruptions in 30 patients (48.4%). While the main reasons for the dose interruptions were rash (n = 15; 24.2%) and diarrhea (n = 4; 6.5%), only one patient with rash

TABLE 3. Logistic and Cox Regression Analysis

	Odds Ratio[b]	(95% CI)	p
Logistic regression analysis of response			
Univariate analysis			
Sex (female vs male)	0.14	0.04–0.48	0.002
Age (<65 vs ≥65)	1.26	0.38–4.13	0.704
Histology (non-AD vs AD)	1.20	0.12–12.41	0.878
Smoking history (never vs current or former)	0.08	0.02–0.30	<0.001
Performance status (0 vs ≥1)	0.62	0.19–1.98	0.420
Prior regimens (1 vs ≥2)	1.13	0.36–3.53	0.832
Stage (IIIB vs IV)	0.99	0.17–5.65	0.988
KL-6 (baseline) (<median [496.5 U/ml[a]] vs ≥median)	1.64	0.53–5.12	0.392
Best response to previous chemotherapy (non-PR vs PR)	0.90	0.24–3.33	0.869
Prior taxanes (no vs yes)	0.43	0.10–1.84	0.253
Time since initial diagnosis (≤12 mo vs >12 mo)	1.02	0.31–3.30	0.976
Multivariate analysis			
Smoking history (never vs current or former)	0.06	0.02–0.28	<0.001
Time since initial diagnosis (<12 mo vs ≥12 mo)	2.22	0.49–10.20	0.304
Cox regression analysis of survival			
Univariate analysis			
Sex (female vs male)	1.76	0.85–3.61	0.126
Age (<65 vs ≥65)	0.86	0.44–1.71	0.675
Histology (non-AD vs AD)	0.55	0.19–1.55	0.255
Smoking history (never vs current or former)	1.90	0.93–3.90	0.079
Performance status (0 vs ≥1)	2.31	1.12–4.73	0.023
Prior regimens (1 vs ≥2)	0.93	0.50–1.75	0.833
Stage (IIIB vs IV)	1.38	0.49–3.89	0.542
KL-6 (baseline) (<median [496.5 U/ml[a]] vs ≥median)	1.64	0.87–3.06	0.125
Best response to previous chemotherapy (non-PR vs PR)	0.66	0.31–1.44	0.300
Prior taxanes (no vs yes)	2.09	0.74–5.90	0.163
Time since initial diagnosis (≤12 mo vs >12 mo)	0.76	0.40–1.47	0.418
Multivariate analysis			
Smoking history (never vs current or former)	2.20	1.06–4.56	0.035
Performance status (0 vs ≥1)	2.59	1.25–5.37	0.011

[a] Or 629 ng/ml.
[b] Left site of 'vs' indicates reference group.
PR, partial response; AD, adenocarcinoma; CI, confidence interval.

TABLE 4. Major Treatment-Related Adverse Events and Interstitial Lung Disease-Like Events

Event[a]	*n*	%	NCI-CTC Grade (*n*)			
			1	2	3	>4
Rash	61	98.4	18	41	2	0
Dry skin	50	80.6	44	6		
Diarrhea	46	74.2	33	10	3	0
Pruritus	45	72.6	38	7	0	
Stomatitis	24	38.7	19	4	1	0
Fatigue	21	33.9	15	6	0	0
Anorexia	19	30.6	11	6	2	0
Paronychia	18	29.0	12	5	1	0
C-reactive protein increased	15	24.2	8	7	0	0
Alanine aminotransferase increased	15	24.2	11	2	2	0
Total bilirubin increased	15	24.2	8	7	0	0
Weight loss	13	21.0	13	0	0	
ILD-like events	4	6.5	1	0	2	1[b]

Case	Sex	Age	Smoking History	Brinkman Index	Performance Status	Histology	Onset (day)	Outcome	Relation to Erlotinib[c]
1	Male	75	Former	640	1	Adenocarcinoma	52	Recovery	Probable
2	Male	67	Never	—	1	Adenocarcinoma	103	Death (145)	Possible
3	Female	39	Never	—	0	Adenocarcinoma	85	Recovery	Probable
4	Male	69	Former	1000	1	Adenocarcinoma	13	Recovery	Unlikely

[a] Categorized by MedDra Ver.7.1 (except for event).
[b] Grade 5.
[c] Judged by ILD review committee.
NCI-CTC, National Cancer Institute Common Toxicity Criteria; ILD, interstitial lung disease.

had to discontinue treatment, and no patients had to discontinue because of diarrhea or any other digestive toxicity. Fourteen patients (23%) had dose reductions due to AEs, mostly due to rash ($n = 9$; 15%). Treatment-related AEs with an incidence of 20% or more are shown in Table 4; the main events were rash (98%), dry skin (81%), and diarrhea (74%). Elevated laboratory test values related to liver function were found in some patients (total bilirubin: 24%, ALT: 24%), and grade 3 ALT elevation led to treatment discontinuation in 2 patients. Four patients had ILD-like events, including worsening of radiation pneumonitis in one patient, and one died (Table 4). All four (three men; one woman) had an ECOG PS of 0–1 and 2 were former smokers. The patient who died was a 67-year-old man with adenocarcinoma and no history of smoking who discontinued treatment on day 84 due to PD. He developed interstitial pneumonia on day 103 and received 3 days of palliative thoracic irradiation from day 99, after completing the study (3 Gy × 3 days). A computed tomography scan showed characteristic features of ILD (cryptogenic organizing pneumonia-like pattern), and the ILD review committee decided that use of erlotinib could not be excluded as the cause. For the patient with worsening of radiation pneumonitis (case 4), the committee concluded that there was a possible influence of previous radiation therapy, and that this could be seen in the computed tomography scan on day 1. There was, therefore, little reason to suspect that the use of erlotinib had been the cause. Rather, it appeared that the radiation pneumonitis had worsened according to the normal course of illness.

Biomarker Analysis

Tissue samples for measurement of *EGFR* mutations were available for 16 of the 60 patients evaluated for efficacy. For 7 patients, all base sequences were successfully identified in the 4 segments of exons 18–21. All seven (three men, four women) had adenocarcinoma; three were never-smokers, three former smokers and one a current smoker. Three had PR, two SD and two PD. Five of the seven patients had *EGFR* gene mutations and, in all, seven different mutations were detected. The 3 patients with PR all had deletion mutations in exon 19 (del E746-A750 or del S752-I759). One of the 2 patients with PD had no mutations and the other had 2 substitution mutations: L858R in exon 21 and the resistance mutation T790M in exon 20 (Table 5).

Paraffin-embedded tissue samples for immunohistochemistry were available from 12 patients, among whom, 11 had successful determinations of immunohistochemical staining (including 3 patients with PR). Six of the 11 were found to be EGFR-positive and 4 were HER2-positive. However, there were no notable relationships between the EGFR and HER2 expression status and either tumor response or patient characteristics such as sex, histological type or smoking history (data not shown).

DISCUSSION

The present study was conducted on the basis of results from a phase I study of erlotinib in Japanese patients with solid tumors,[15] which showed erlotinib to be well tolerated at

TABLE 5. *EGFR* Mutation Analysis

Response	TTP (d)	Survival (d)	Sex	Histology	Smoking history	Mutation status	Exon	Type of Mutation
PR	222	546	Female	Adenocarcinoma	Never	+	19	del E746 A750
PR	230	811+	Male	Adenocarcinoma	Current	+	19	del S752 -I759 and T751N
PR	278+	911	Female	Adenocarcinoma	Never	+	19	V786M, del E746 A750
SD	224	649+	Male	Adenocarcinoma	Former	+	21	del V834-
SD	77	737	Female	Adenocarcinoma	Former	−	—	
PD	60	604+	Female	Adenocarcinoma	Never	+	20, 21	L858R, T790M
PD	19	347	Male	Adenocarcinoma	Former	−	—	

TTP, time to progression; PR, partial response; SD, stable disease; PD, progressive disease.

a dose of 150 mg/d, as well as a phase II study of erlotinib in NSCLC conducted in the United States.[16] In this study, erlotinib achieved an ORR of 28.3%, which was higher than expected, and a DCR of 50%. The response rate was higher than that determined in the above-mentioned phase II study[16] and in keeping with the rate seen in the Japanese subgroup in the phase II study of gefitinib (IDEAL1; 27.5%).[6] Assessment of QoL using the LCS demonstrated a clinically meaningful rate of symptom improvement of 42.1%.

The characteristics of the patients in this study were generally similar to those of NSCLC patients as a whole, in terms of their demographics and disease and treatment history, with the exception of a particularly high proportion of patients with adenocarcinoma (92%). The possibility of enrollment bias on the basis of histological type cannot be ruled out, in part because enrollment coincided with the emergence of reports that the efficacy of EGFR-TKI therapy was greater in patients with adenocarcinoma.[17] However, we also observed one PR and two SDs among three patients with squamous cell carcinoma (FAS population), and our results do not rule out the efficacy of erlotinib in any patient subtype. A multivariate logistic regression analysis showed that smoking status was significantly associated with tumor response, in agreement with previous studies of predictive factors for response to EGFR-TKIs.[5,18,19]

The median survival time with erlotinib was an encouraging 14.7 months. One of the reasons for this long survival may be the high proportion of never-smokers and patients with adenocarcinoma compared with those of other studies, particularly the multinational phase III erlotinib study (BR.21).[5] On the other hand, the presence of *EGFR* gene mutations is currently regarded as an important determinant of treatment response to EGFR-TKIs[20,21] and may be the most important factor in relation to the favorable results seen in the present study. However, it is important to recognize that the potential prognostic effect of mutation status cannot be excluded. The sample size of this and previous trials limits the interpretation of this effect, which will be adequately assessed only by means of appropriately powered trials specifically designed to examine these factors.

Assessment of the presence or absence of *EGFR* gene mutation was possible in only seven patients in the present study. Despite this, the results were consistent with the results of some previous studies. All three of the patients who had a PR (including a male current smoker) had an in-frame deletion in exon 19, which is considered to be the most frequent mutation site in the EGFR-TK domain.[22] One of the 2 patients with PD had a point substitution mutation (L858R) in exon 21, the second most frequent mutation site,[22] and a point mutation (T790M) in exon 20, which is suggested to be involved in tolerance to EGFR-TKI.[12,23,24] It would be valuable to conduct further prospective randomized studies on the association between these markers and survival during treatment with erlotinib in Japanese patients.

Rash and diarrhea were the main AEs reported by patients on erlotinib treatment, as reported in previous studies.[5,15,16] Rash was observed in almost all patients, and was the main reason for treatment interruptions or dose reductions. Although the protocol allowed treatment to be interrupted for grade 3 rash (or intolerable grade 2 rash), grade 3 rash only occurred in 2 patients, leading to discontinuation of treatment in one. Most cases of rash responded to symptomatic treatment and either interruption or dose reduction of erlotinib. Despite suggestions in some reports that the presence of erlotinib-related rash is associated with treatment efficacy and can be used to predict response,[25] no supportive evidence was found in the present study.

The incidence of ILD, which is the most clinically problematic AE associated with erlotinib, tended to be higher than that reported in other clinical studies of erlotinib.[5,26] This is in keeping with this class of agent, and is not unexpected in the Japanese population.

We would recommend that careful screening of patients for ILD risk factors, particularly signs of interstitial pneumonia and pulmonary fibrosis, is done before erlotinib therapy is initiated. Individuals with any previous history of ILD were excluded from this study.

In conclusion, erlotinib (150 mg/d) was shown to have promising antitumor efficacy in Japanese patients with previously treated NSCLC, leading to clinically meaningful improvements in symptoms and an encouraging median survival time. Despite, as expected, a high rate of rash and diarrhea, erlotinib was well tolerated at a dose of 150 mg/d by the majority of patients.

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Efficacy and Safety of Pemetrexed in Combination with Cisplatin for Malignant Pleural Mesothelioma: A Phase I/II Study in Japanese Patients

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Background: Pemetrexed in combination with cisplatin (Pem/Cis) is used globally for the treatment of malignant pleural mesothelioma (MPM). This Phase I/II study was conducted to determine the recommended dose (RD) (Phase I) of Pem/Cis, and evaluate the efficacy and safety (Phase II) in Japanese MPM patients.
Methods: Key eligibility criteria were histologic diagnosis of MPM incurable by surgery, no prior chemotherapy, and a performance status 0–1. Under full vitamin supplementation, pemetrexed was intravenously administered on Day 1 of a 21-day cycle, followed by cisplatin. A cohort of six patients, starting from pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (Level 1), were studied in the dose-escalation Phase I (Step 1). The RD determined in Step 1 was carried forward into Phase II (Step 2). Planned number of patients treated with Pem/Cis was 18–38.
Results: In Step 1, 13 patients were enrolled: seven in Level 1 and six in Level −1 (pemetrexed 500 mg/m^2, cisplatin 60 mg/m^2). Two of six evaluable patients had dose-limiting toxicities (pneumonitis and neutropenia) in Level 1, establishing Level 1 as the RD. In Step 2, 12 patients were enrolled, for a total of 19 patients treated at the RD. Seven patients achieved a partial response among these patients, for a response rate of 36.8% (95% confidence interval: 16.3–61.6); overall survival was 7.3 months. One drug-related death occurred due to worsening of a pre-existing pneumonia. Common grade 3/4 toxicities were neutropenia and decreased-hemoglobin.
Conclusion: The Pem/Cis combination provides promising activity and an acceptable safety profile for chemonaive Japanese MPM patients with the same recommend dosage and schedule used in rest of the world.

Key words: cisplatin – mesothelioma – pemetrexed – phase I/II

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a tumor derived from the mesothelium covering the surface of pleural membranes or from undifferentiated mesenchymal cells in connective tissue under the membranes. MPM is a locally invasive and aggressive tumor with a poor prognosis and a median survival time (MST) of ≈9–16 months (1).

MPM is known to be linked to asbestos exposure, and the incidence of this tumor is expected to increase in the next 10–20 years according to an estimation of asbestos consumption in

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the world (9). Recently, the prevalence of MPM in Japan was widely recognized after uncovering the high incidence of MPM and MPM-related deaths in ex-workers of asbestos factories and in residents of the surrounding areas who may have been subject to non-occupational exposure to asbestos fibers.

Surgical resection offers local control of the tumor but its effect on survival remains unclear. In addition, application of radiation therapy is limited because of the diffuse extension of tumor spread. Regimens applied to lung cancer such as platinum-containing chemotherapy have been used for MPM in Japan; however, the efficacy outcomes of these therapies are not satisfactory. Therefore, effective systemic chemotherapy for MPM is clearly needed.

Pemetrexed is a novel antifolate (12) that inhibits three enzymes in folate metabolism: thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase (11). Because of the multi-targeted profile of this compound, broad and preferable anti-tumor activity is expected. Pemetrexed has shown clinical activity in various tumors including mesotheliomas (6). A pivotal multicenter, randomized Phase III study of pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) versus cisplatin alone (cisplatin 75 mg/m^2) in patients with MPM who had no prior chemotherapy was conducted in 20 countries (not including Japan) (16). A total of 448 patients were randomized and treated in this study (226 treated by pemetrexed/cisplatin (Pem/Cis) and 222 treated by cisplatin). MST in the Pem/Cis arm was 12.1 months compared with 9.3 months in the cisplatin arm ($P = 0.020$, two-sided log rank test). This was the first confirmation of significant prolongation of survival for patients with MPM. On the basis of this evidence, the combination of pemetrexed and cisplatin was approved for the treatment of MPM in the USA in 2004. Since then, the combination therapy has been approved in more than 80 countries and regions for the treatment of MPM, and recognized as a standard care for MPM (8).

In 2005, we initiated a Phase I/II study of Pem/Cis therapy in Japanese patients with MPM who had no prior chemotherapy. The primary objectives of this study were to determine the clinically recommended dose (RD) of Pem/Cis therapy in the Phase I portion of the study (Step 1), and to examine tumor response of the combination therapy in the Phase II portion (Step 2). The secondary objectives included time-to-event efficacy outcomes [the duration of response, progression free survival (PFS), and overall survival time], 1-year survival rate, quality of life (QOL) assessments, pulmonary function tests and safety.

PATIENTS AND METHODS

Patient selection

Chemonaive patients with histological diagnosis of MPM, regardless of clinical stage and who were not candidates for curative surgery, were assessed for eligibility. Eligible patients needed to be 20–74 years old with a life expectancy $\geq$12 weeks and an Eastern Cooperative Oncology Group performance status (PS) 0 or 1. Patients were also required to have adequate organ functions: bone marrow reserve [platelets $\geq 100 \times 10^3/mm^3$, hemoglobin $\geq$9.0 g/dl, and absolute neutrophil count (ANC) $\geq 2.0 \times 10^3/mm^3$], hepatic function [bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), aspartate/alanine transaminase (AST/ALT) $\leq 2.5 \times$ ULN, and serum albumin $\geq$2.5 g/dl], renal function (serum creatinine $\leq$ULN, and calculated creatinine clearance $\geq$45 ml/min using the Cockcroft and Gault formula), lung function (functional oxygen saturation [SpO_2] $\geq$92%) and normal electrocardiogram.

Patients were excluded from this study for active infection, symptomatic brain metastasis, a wide-spread diffuse shadow in the lung caused by interstitial pneumonitis diagnosed by chest X-ray, pregnancy, serious concomitant systemic disorders incompatible with the study, clinically significant effusions, Common Terminology Criteria for Adverse Events (CTCAEs) v3 grade $\geq$2 peripheral neuropathy, the inability to discontinue aspirin and other non-steroidal anti-inflammatory agents or the inability or unwillingness to take folate and vitamin B_{12} during the study.

This study was conducted in compliance with the guidelines of good clinical practice and the Declaration of Helsinki, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry. The Efficacy and Safety Evaluation Committee (ESEC), an independent body, was consulted if any efficacy and safety issues arose in the study.

Study Design

This was a Phase I/II, multicenter, single-arm, open-label study, performed in two steps. The RD level established in Step 1 was carried forward in Step 2. Patients enrolled in Step 1 at the RD level could continue in Step 2 unless otherwise indicated. The planned number of patients in total of Steps 1 and 2 treated with Pem/Cis was 18–38 for examination of efficacy and safety profile. In Step 1, six patients were to be enrolled in each dose level. The lower number of the planned number of patients, 18, was set as the minimum number of patients needed to confirm that the response rate of the study drugs was significantly larger than the threshold rate of 10% at one-sided significant level 0.05 with $\geq$80% power.

Study Treatment

Pemetrexed was intravenously administered as a 10-min infusion on Day 1 of a 21-day cycle, followed by cisplatin administration intravenously as a 2-h infusion 30 min after pemetrexed administration. Patients were instructed to take a daily 1 g multivitamin containing 500 μg of folate beginning 1 week prior to Day 1 of Cycle 1 until study discontinuation. Vitamin B_{12} (1000 μg) was intramuscularly injected, starting 1 week prior to Day 1 of Cycle 1 and repeated every 9 weeks until study discontinuation. Patients remained on study unless they were discontinued, for instance, due to disease progression and unacceptable adverse events.

Determination of RD for Step 2

In Step 1 (Phase I), four escalating dose levels were planned: pemetrexed at 500 (Level 1), 700 (Level 2), 900 (Level 3) and 1000 mg/m^2 (Level 4) with cisplatin held at 75 mg/m^2. In addition, a lower dose level (Level −1) was planned at pemetrexed 500 mg/m^2 and a lower dose of cisplatin 60 mg/m^2 for a failure case of dose-escalation in Level 1. In the dose-escalation procedure, the starting dose of pemetrexed was set to be 500 mg/m^2 which is ca. 40% of the maximum tolerated dose (MTD) of pemetrexed monotherapy with folic acid and vitamin B_{12} supplementation determined in a Japanese Phase I study; the MTD and RD of pemetrexed were determined to be 1200 and 1000 mg/m^2, respectively (7). The percentage of the starting dose to the MTD was based on a guideline for Phase I/II study on anticancer drugs (10). For escalation of pemetrexed dose, a modified Fibonacci dose-escalation method was used (2). Dose level reduction or escalation depended on the incidence of dose-limiting toxicity (DLT) at a given dose level (Fig. 1). If two of six patients at Levels 1, 2 or 3 developed DLT, that dose level was considered the RD for Step 2 (Phase II) of the study, and then Step 2 was initiated. This was also the case for Level −1 or 4 if 0–2 patients developed DLT. If three or more patients developed DLT at a given dose level (except dose Level −1), the next lower dose level was considered the RD level for Step 2. If three or more patients had DLT at Level −1, a decision was made as to whether the study should be continued.

A DLT was defined as a toxicity occurring in Cycle 1 meeting one of the following criteria: any grade ≥3 non-hematologic toxicity (except nausea, vomiting, anorexia and fatigue), grade ≥2 peripheral neuropathy or hearing loss/impairment, grade ≥3 febrile neutropenia (<1000/mm^3 with ≥38.5°C), grade 4 leukopenia (<1000/mm^3) or neutropenia (<500/mm^3) lasting ≥3 days, thrombocytopenia (<25000/mm^3), or thrombocytopenia requiring platelet transfusion. A failure to start the second cycle by Day 29 due to toxicity was also considered a DLT. All toxicities were assessed according to CTCAE.

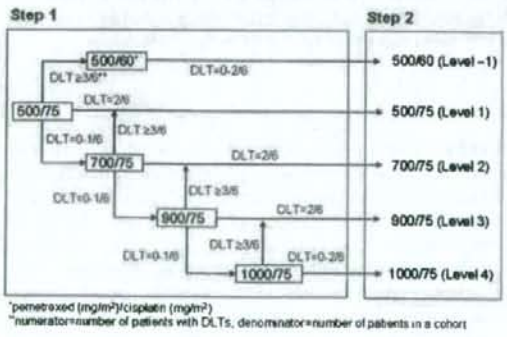

Figure 1. Scheme of dose-escalation Steps 1 and 2. DLT, dose-limiting toxicity.

Treatment Assessments

Anti-tumor Activity

Disease staging was assessed according to International Mesothelioma Interesting Group Tumor Node Metastasis (IMIG TNM) staging criteria (13). Within 28 days before the first treatment and approximately every 4 weeks after the first treatment, computer tomography or X-ray imaging of each lesion was performed. Tumor response was assessed using the modified Southwest Oncology Group (SWOG) criteria. Unidimensionally measurable lesions were defined as *Measurable disease*, and assessed objectively by the sum of the greatest diameters of them. Bidimensionally measurable lesions defined in the standard SWOG criteria (5) were assessed in the similar way. Best overall response selected from total overall response assessments was determined according to assessment of the Extramural Case Judgment Committee (E-CJC). Duration of response was measured as from the date of the first objective assessment of complete response (CR) or partial response (PR) until the date of the first assessment of progression of disease (PD). PFS was measured as from the registration date of Cycle 1 treatment until the first date of PD or death from any cause. Overall survival time was measured as from the registration date of Cycle 1 treatment until the date of death from any cause or until the last follow-up date in survival surveillance period.

QOL Assessments and Pulmonary Function Tests

QOL surveillance was employed using the following questionnaires: QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD), and functional assessment of cancer therapy for lung cancer (FACT-L). These questionnaires were used on Day 1 of Cycles 1 and 2, and on 3 months after Day 1 of Cycle 1. QOL-ACD consists of four subscales (activity, physical condition, psychological condition and social relationships) and a total QOL scale (face scale) (4). The lung cancer subscale (LCS) score of FACT-L was used (3). As pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) were measured using a spirometer in the sitting position. All tests followed the Japanese Respiratory Function Test guidelines (14).

Safety

Adverse events were recorded throughout the study and after the last drug administration until signs of recovery were evident. Adverse events were evaluated according to treatment-emergent adverse events (TEAEs) definitions, and coded using the Medical Dictionary for Regulatory Activities (MedDRA v9.0). The severity (grade) of an adverse event was assessed according to CTCAE v3.

Statistical Analysis

The evaluation period of efficacy and safety in this study was defined as from the beginning of the study treatment to 5 months after the last patient began study treatment. For the

evaluations of overall survival time and 1-year survival rate, survival surveillance period was defined as from the beginning of the study treatment to 1 year after the last patient began study treatment. Patients who received the study drugs and complied with all inclusion/exclusion criteria were included in full analysis set (FAS). Patients who were treated with the RD level in Step 1 or 2 among FAS were included in efficacy analysis set for efficacy evaluation. Patients who received the study drugs at least once were included in safety analysis set for safety evaluation.

Assessment results of the best overall response by the E-CJC were used for efficacy analysis. Statistical tests based on binominal distribution were done to confirm that the response rate of the study drugs was significantly larger than the threshold rate of 10% at one-sided significant level 0.05. The threshold rate 10% was set on the basis of historical data on the response rate of cisplatin alone arm reported in other studies (15,16).

RESULTS

Patient Characteristics

From 2005 to 2006, a total of 25 Japanese patients with MPM were enrolled in Steps 1 and 2 at seven centers in Japan. All patients met the eligibility criteria and received study treatment; all were included in FAS. One patient was still receiving the study drug at the time of the efficacy and safety evaluations in this report.

Patient characteristics are summarized in Table 1. The majority of patients were male (22 patients, 88.0%). The median age was 61 years (range: 50–74 years). Most patients had a PS of 1 (18 patients, 72.0%) and clinical stage IV (21 patients, 84.0%). The predominant histologic subtype was epithelial in 64% of patients. Two demographic characteristics showed differences among dose levels. There were more patients with PS 0 in Level −1 (50.0%) than in Level 1 (21.1%). All six (100%) patients in Level −1 had the epithelial subtype versus 10 (52.6%) patients in Level 1.

Table 1. Patient characteristics

	Step 1 Level −1 ($n = 6$)	Level 1 ($n = 19$)	All treated ($n = 25$)
Gender			
Male	5	17	22
Female	1	2	3
Age			
Mean	61	61	61
SD	3.9	6.3	5.8
Med	61	59	61
Weight(kg)			
Mean	62.8	58.1	59.2
SD	8.51	11.19	10.65
Performance status prior to Cycle 1			
0	3	4	7
1	3	15	18
Histological subtype			
Epithelioid mesothelioma	6	10	16
Sarcomatoid mesothelioma	0	5	5
Biphasic mesothelioma	0	4	4
Other	0	0	0
Asbestos exposure			
Had no exposure	2	3	5
Had exposure	4	16	20
Stage of disease			
Ia	0	0	0
Ib	0	1	1
II	0	1	1
III	1	1	2
IV	5	16	21

Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2
Level −1: pemetrexed 500 mg/m^2 + cisplatin 60 mg/m^2
SD, standard deviation.

Dose-Escalation, Dose-Limiting Toxicity and RD

One patient in Level 1 of Step 1 died on Day 14 of Cycle 1 due to exacerbation of pneumonia, respiratory failure (hypoxia) and disseminated intravascular coagulation (DIC). The ESEC evaluated the case of the early death. Since the patient had had the shadow of the lung detected by radiographic image prior to receiving study treatment, it was unlikely that the administration of pemetrexed was the primary cause of the pneumonia. The autopsy of this patient showed that interstitial changes in the lung were mild and the pathological diagnosis was an organizing pneumonia. The result of the autopsy was compatible with the clinical course and suggested that the direct cause of the death was not the drug-induced interstitial pneumonia but the exacerbation of infectious pneumonia, worsened by the study treatment. The case, therefore, was considered not appropriate for the DLT evaluation.

One patient was added in this dose level to assess the safety profile additionally. Among the six patients in Level 1 excluding the case inappropriate for the DLT evaluation, two patients showed DLTs: drug-induced pneumonitis in one patient and dose delay of Cycle 2 initiation due to decreased neutrophil count in the other. According to the protocol definition, Level 1 was determined to be an RD for the next phase (Fig. 1).

The ESEC, however, recommended examining the treatment at Level −1 (pemetrexed 500 mg/m^2 and cisplatin 60 mg/m^2) exploratively to accumulate more safety information. Accordingly, six patients were enrolled and treated at Level −1, and no DLTs were observed in this dose level.

Evaluating the data of these two levels together, the ESEC agreed to continue Step 2 carefully with the dose of Level 1. The sponsor decided to carry forward into Step 2 with

an RD of Level 1 (pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2). In Step 2, 12 patients were treated at Level 1.

Efficacy

Nineteen patients (7 in Step 1 and 12 in Step 2) in Level 1 were included in the efficacy analysis set and of 19 patients, seven patients had PR, five patients had stable disease (SD), six patients had PD and one patient was classified as not evaluated. An overall response rate (ORR) was 36.8% [95% confidence interval (CI): 16.3%–61.6%]. The 95% one-sided confidence lower limit was 18.8%, exceeding the threshold level of 10%. The six patients in Level −1 had PR; thus, the ORR for all 25 patients treated with the study drug reached 52.0% (13 total PR, 95% CI: 31.3%–72.2%).

The secondary efficacy variables were time-to-event outcomes (the duration of response, PFS and overall survival time), 1-year survival rate, QOL and pulmonary function test. The median duration of response was 5.2 months (95% CI: 4.3–7.3 months) for the seven responders in the efficacy analysis set (Table 2). The median duration of response for the six responders at Level −1 was again 5.2 months. For the efficacy analysis set, median PFS was 4.7 months (95% CI: 1.3–6.5 months) and MST was 7.3 months (95% CI: 4.6–14.2 months, Fig. 2) with 1-year survival rate of 36.8% (95% CI: 15.2%–58.5%). Median PFS for the six patients at Level −1 was 10.1 months. MST at Level −1 could not be calculated by Kaplan–Meier method. The 1-year survival rate of Level −1 (66.7%) was beyond 50%.

The QOL-ACD and FACT-L measures were used for QOL evaluation. There were no major changes from prior to Cycle 1 to 3 months after Cycle 1 treatment in the mean scores for the activity and physical condition subscales of QOL-ACD (Table 3); however, mean scores from prior to Cycle 1 to 3 months after Cycle 1 treatment for the psychological condition and social relationships subscales numerically increased. The mean LCS score of FACT-L did not change substantially from prior to Cycle 1 to 3 months after Cycle 1 treatment (data not shown). These score changes indicate that QOL of the patients was maintained without worsening from baseline. Pulmonary function was also maintained with no worsening from baseline observed in the pulmonary function tests (FEV_1, FVC and VC) in the efficacy analysis set (data not shown).

Safety

Of 25 patients of the safety analysis set, three died during the study period: one (Level 1, Step 1) from exacerbation of pneumonia as a pre-existing complication, respiratory failure, and DIC, as described earlier, and the other two (Step 2) due to study disease. Two patients experienced non-fatal serious adverse events (fever and aspiration pneumonia, respectively). A causal relationship between fever and the study drugs could not be ruled out, but the aspiration pneumonia was not considered related to study drugs. Adverse events leading to discontinuation from study treatment were observed in six patients: one patient at Level 1 and three patients at Level −1 in Step 1 and in two patients in Step 2. Adverse event leading to discontinuation in two or more patients was increased blood creatinine (two patients).

Table 2. Summary of time-to-event outcomes and 1-year survival rates

	Step 1 Level −1 ($n = 6$)	Level 1 ($n = 19$)	All treated ($n = 25$)
Duration of response (months)			
Responders	6	7	13
Med	5.2	5.2	5.2
(95% CI)	3.1 − *	4.3–7.3	4.3–7.3
Range	2.7–9.6	2.0–7.3	2.0–9.6
Censored (%)	50	14.3	30.8
Progression free survival (months)			
Med	10.1	4.7	4.8
(95% CI)	4.3 − *	1.3–6.5	2.5–7.1
Range	3.3–12.1	0.5–9.6	0.5–12.1
Censored (%)	50	10.5	20
Overall survival (months)			
Med	NA	7.3	9.2
(95% CI)	11.1 − *	4.6–14.2	5.8–14.4
Range	8.6–19.3	0.5–21.5	0.5–21.5
Censored (%)	66.7	21.1	32
1-year survival rate (%)			
	66.7	36.8	44.0
(95% CI)	28.9–100.0	15.2–58.5	24.5–63.5

*Not calculated. NA, not assessed.
Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2.
Level −1: pemetrexed 500 mg/m^2 + cisplatin 60 mg/m^2.
CI, confidence interval.

Grade 3 or more laboratory TEAEs were observed in 16 patients: four patients at Level 1 and five patients at Level −1 in Step 1 and in seven patients in Step 2. Laboratory TEAEs observed in at least half of the 25 patients were decreased-hemoglobin, decreased red blood cell count, decreased neutrophil count, decreased white blood cell count, decreased lymphocyte count, increased blood urea and decreased body weight (Table 4). Grade 3 or more non-laboratory TEAEs were observed in eight patients: three patients at Level 1 and one patient at Level −1 in Step 1 and in four patients in Step 2. Non-laboratory TEAEs observed in at least half of the 25 patients were nausea, anorexia, vomiting and malaise. No major differences between Levels 1 and −1 (Step 1) in the incidence of TEAEs were noted.

For the 19 patients at Level 1, laboratory TEAEs of grade 3 or higher, possibly related to drug, and observed in at least two patients were decreased neutrophil count (seven patients, 36.8%), decreased hemoglobin (six patients, 31.6%), decreased white blood cell count (five patients, 26.3%), decreased lymphocyte count (five patients, 26.3%),

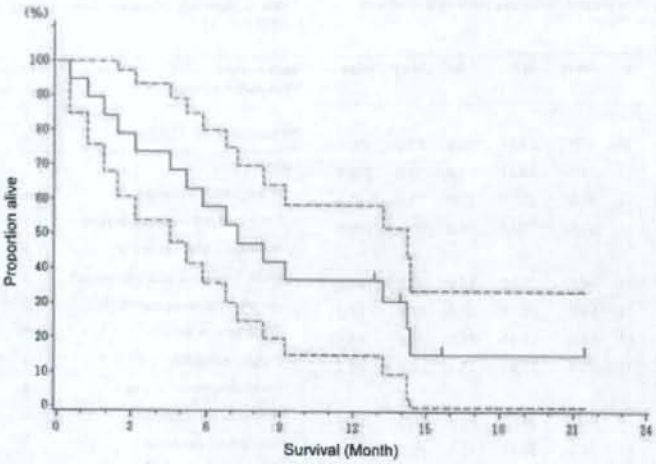

Figure 2. Kaplan–Meier plot of overall survival in the efficacy analysis set. Solid lines, overall survival; dotted lines, high and low limits of 95% confidence interval.

decreased platelet count (two patients, 10.5%) and decreased blood potassium (two patients, 10.5%). Non-laboratory adverse drug reactions of grade 3 or higher observed in at least two patients were vomiting (three patients, 15.8%), anorexia (three patients, 15.8%), nausea (two patients, 10.5%) and malaise (two patients, 10.5%). Adverse drug reactions of grade 3 or higher for the six patients in Level −1 were decreased neutrophil count (three patients), decreased-hemoglobin (two patients), decreased lymphocyte count (two patients) and decreased red blood cell count (one patient).

DISCUSSION

This Phase I/II study reports the first experience of the combination of pemetrexed and cisplatin therapy in Japanese patients. The RD of Pem/Cis combination therapy was established at pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, with pemetrexed administration on Day 1 of each 21-day cycle followed by cisplatin, which is the same regimen used in worldwide for patients with MPM (16).

Of the 19 patients evaluable for efficacy at the RD level, there were PRs in seven patients, for an ORR of 36.8% (95% CI: 16.3%–61.6%). A pivotal Phase III study of the same regimen as that applied of the present study, yielded a response rate of 41.3% (95% CI: 34.8%–48.1%) in 225 patients (16). The response rates from both studies are comparable despite of the large difference in sample size.

The response rate of all the 25 treated patients was higher than the response rate for the 19 patients treated at the RD (52.0% versus 36.8%). This is due to the fact that all the six patients in Level −1 had PR. The excellent outcome observed in Level −1 may be attributed to differences between those patients who received the RD and those patients in Level −1 in the histological subtype of mesothelioma. All six patients in Level −1 had an epithelial subtype, which is known as a favorable prognostic factor, while only about half of the 19 patients at the RD had this subtype. In addition, the PS of the patients in Level −1 was better than the patients at RD.

A secondary efficacy endpoint MST showed 7.3 months in this study, shorter than that of the Pem/Cis arm in the Phase III study (12.1 months) (16). Although it would be difficult to compare MST of this study derived from a small sample size with the large Phase III study ($n = 226$), the discrepancy of survival between the two studies could be ascribed for the demographic characteristics of patients in both. There are less patients who had good prognostic factors in this study than in the Pem/Cis arm of the Phase III study: epithelial subtype: 52.6% versus 68.1%, a good PS: 21.1% (PS = 0) versus 51.8% (Karnofsky PS = 90/100) and clinical stage I/II: 8.0% versus 22.6% (16).

In this study, the most common adverse events (>50% of patients) were decreased-hemoglobin, erythropenia, neutropenia, leukopenia and lymphopenia for laboratory parameters, and nausea, anorexia, and vomiting for non-laboratory parameters. These hematologic and gastrointestinal events were similarly observed in the Pem/Cis arm of the pivotal Phase III study (16). No grade 3/4 febrile neutropenia toxicity which is a potentially life-threatening event was reported in our study. One death by pneumonitis was observed in this study; however, the patient was considered to have a pre-existing condition before initial treatment with study therapy. Adverse events observed in this study were predictable from safety profile observed in overseas trials and market experiences of pemetrexed and cisplatin combination therapy.

Table 3. Summary of QOL questionnaire for cancer patients treated with anticancer drugs (Level 1, $n = 19$)

Subscale	Measurement Point	n	Mean	SD	Min	Med	Max
Activity							
	Prior to Cycle1	19	62.9	25.35	20.0	60.0	100.0
	Prior to Cycle2	15	61.8	32.27	5.0	70.0	100.0
	Prior to Cycle3	14	69.6	21.79	20.0	75.0	95.0
	Cycle1 + 3M	11	60.5	32.13	5.0	70.0	100.0
Physical							
	Prior to Cycle1	19	64.7	22.33	15.0	70.0	100.0
	Prior to Cycle2	15	64.3	18.11	20.0	65.0	95.0
	Prior to Cycle3	14	66.2	18.33	30.0	70.0	85.0
	Cycle1 + 3M	11	61.4	21.46	35.0	60.0	95.0
Psychological							
	Prior to Cycle1	19	53.2	20.62	12.5	56.3	81.3
	Prior to Cycle2	15	59.6	24.87	12.5	62.5	100.0
	Prior to Cycle3	14	58.0	17.41	31.3	56.3	87.5
	Cycle1 + 3M	11	61.4	18.07	37.5	68.8	87.5
Social							
	Prior to Cycle1	19	32.9	21.56	5.0	25.0	75.0
	Prior to Cycle2	15	33.7	19.13	0.0	25.0	70.0
	Prior to Cycle3	14	43.6	19.94	10.0	42.5	85.0
	Cycle1 + 3M	11	36.4	22.59	10.0	30.0	85.0
Face scale							
	Prior to Cycle1	19	50.0	23.57	0.0	50.0	100.0
	Prior to Cycle2	14	55.4	24.37	0.0	50.0	100.0
	Prior to Cycle3	14	64.3	23.44	25.0	50.0	100.0
	Cycle1 + 3M	11	63.6	20.50	25.0	75.0	100.0

Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 M, months.
QOL, quality of life.

CONCLUSION

The RDs for the Pem/Cis combination are pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, which is the same regimen used in worldwide for patients with MPM. The combination shows promising efficacy with an acceptable safety profile in Japanese patients with MPM.

On January 2007, Pem/Cis combination therapy was approved and launched for the treatment of patients with MPM in Japan. Intensive post-marketing surveillance in patients with MPM is ongoing.

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Conflict of interest statement

S.A. and Y.N. are employed by the sponsor, Eli Lilly Japan K.K.; N.S. and M.F. are paid consultants to the sponsor.

Table 4. Summary of treatment-emergent adverse events (TEAEs) reported >25% patients

System organ class preferred term	Step 1 Level −1 ($n = 6$)	Level 1 ($n = 19$)	All treated ($n = 25$)
Patients with ≥1 TEAEs	6	19	25
Laboratory			
Hemoglobin decreased	6	18	24
Red blood cell count decreased	6	16	22
Neutrophil count decreased	5	16	21
White blood cell count decreased	5	15	20
Lymphocyte count decreased	5	12	17
Blood urea increased	5	11	16
Weight decreased	3	12	15
Blood albumin decreased	2	10	12
Platelet count decreased	4	8	12
Protein total decreased	3	9	12
Blood creatinine increased	4	7	11
Neutrophil count increased	2	8	10
White blood cell count increased	2	8	10
Blood sodium decreased	2	7	9
Alanine aminotransferase increased	1	7	8
Protein urine present	1	7	8
Aspartate aminotransferase increased	1	6	7
Blood magnesium decreased	2	5	7
Blood potassium decreased	0	7	7
Non-laboratory			
Nausea	6	18	24
Anorexia	6	16	22
Vomiting	3	15	18
Malaise	5	10	15
Constipation	3	9	12
Hiccups	3	5	8
Rash	2	6	8
Diarrhoea	1	6	7
Oedema	2	5	7
Pyrexia	2	5	7
Dysgeusia	3	4	7
Headache	1	6	7

Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2
Level −1: pemetrexed 500 mg/m^2 + cisplatin 60 mg/m^2
MedDRA Ver 9.0.

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ORIGINAL ARTICLE

Efficacy and safety of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer

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Abstract
Purpose We retrospectively evaluated the efficacy and safety of combination therapy of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer (MBC).
Methods Patients with HER2-positive MBC who had been administered the combination therapy between July 2003 and July 2006 at the Cancer Institute Hospital, Tokyo, were retrospectively reviewed. Capecitabine (828 mg/m^2) was given twice daily for 3 weeks followed by a 1-week rest period; this was repeated every 4 weeks. Trastuzumab was given at 4 mg/kg as an initial loading dose intravenously, followed by 2 mg/kg weekly. We investigated objective response rate (ORR), clinical benefit rate (CBR), and time-to-treatment failure (TTF) according to the Response Evaluation Criteria in Solid Tumors guidelines. Adverse events were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0.
Results A total of 49 patients were assessed and median follow-up time of patients was 16.2 months (1.4–43.5 months). ORR was 16% (95% confidence interval: 7–30%) and CBR was 47% (95% confidence interval: 32–62%). Median TTF was 5.4 months. Common adverse effects were hand–foot syndrome, liver dysfunction, and bone marrow suppression. Grade 3 adverse events were observed in nine patients (18%). One patient (2%) suffered from symptomatic chronic heart failure, which improved after discontinuation of trastuzumab.
Conclusions The combination therapy of trastuzumab plus capecitabine is effective and tolerable for heavily pretreated patients with HER2-positive MBC.

Keywords Capecitabine · Trastuzumab · HER2-positive · Metastatic breast cancer

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Introduction

HER2/neu is a surface membrane protein, member of the type I epidermal growth factor receptor family, encoded by the c-erb-b2 gene. In human breast cancer, c-erb-b2 gene amplification occurs in 25–30% of patients [1, 2]. The gene amplification induces HER2/neu protein overexpression. The overexpression results in a constitutive activation of the HER2/neu signaling pathways and an increase of cell proliferations [3]. Clinically, HER2/neu alteration is associated with an adverse prognostic profile, including shortened time to progression and overall survival in patients whose primary breast tumors contain the HER2/neu abnormality [1, 2, 4].

Trastuzumab is a humanized monoclonal antibody that binds with a specific epitope of the HER2 protein [1, 2, 4]. Trastuzumab as a single agent induced responses in 15–20% of patients with HER2-overexpressing breast cancer [5–7]. Furthermore, there is clear synergism between trastuzumab and several chemotherapeutic agents including cisplatin [8], docetaxel [9], paclitaxel [10], and vinorelbine [11, 12]. So, many clinicians continue trastuzumab therapy and change one chemotherapeutic agent for another sequentially in patients with HER2-positive metastatic

breast cancer (MBC), when the disease has progressed during treatment, in the hope of taking advantage of this possible synergy.

Capecitabine is an oral fluoropyrimidine carbonate, which is converted to 5FU selectively in tumors through a cascade of three enzymes [13]. Based on the differential distribution of these three enzymes in different tissues, this drug is designed to yield more 5FU in cancer cells than in bone marrow cells or gastrointestinal epithelial cells [13]. Capecitabine is effective and well tolerated for MBC patients who have failed anthracycline- and taxane-containing regimen [14–19]. Therefore, capecitabine is one of key drugs for patients with MBC.

However, for patients with HER2-positive MBC, there are not enough data about the efficacy and safety of the combination therapy of trastuzumab plus capecitabine. Therefore, the purpose of the present single-institute retrospective study is to evaluate efficacy and safety of combination therapy of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive MBC.

Materials and methods

Patients

Patients with HER2-positive MBC who had been administered combination therapy of trastuzumab plus capecitabine between July 2003 and July 2006 at the Cancer Institute Hospital, Tokyo, were retrospectively reviewed. The eligibility criteria were as follows: (1) trastuzumab plus capecitabine, (2) metastatic breast cancer, (3) HER2-positive cancer (HER2 protein scored as 3+ in immunohistochemistry or HER2 gene-amplified twofold or greater in fluorescence in situ hybridization), (4) lesion(s) measurable according to the Response Evaluation Criteria in Solid Tumors guidelines, (5) performance status of three or less according to the Eastern Cooperative Oncology Group's scale.

Treatment plan

Capecitabine was given orally at a dosage of 828 mg/m^2, twice daily for 3 weeks followed by a 1-week rest period. This was repeated every 4 weeks. The dose was calculated on the basis of body surface area at baseline (Table 1). The schedule of trastuzumab is 4 mg/kg as an initial loading dose intravenously, followed by 2 mg/kg weekly. This regimen was registered with the hospital.

Patients with an objective response or stable disease (SD) could continue to receive the combination treatment until progressive disease (PD) or unacceptable toxicity developed.

Table 1 Determination of capecitabine dose according to body surface area

Body surface area (m^2)	Dose (mg, twice daily)
<1.31	900
1.31–1.64	1,200
≥1.64	1,500

Treatment interruption and/or individual dose adjustment of capecitabine was considered when patients experienced any adverse events assessed at grade 2 or more as defined by the National Cancer Institute, Common Toxicity Criteria, version 3.0.

Evaluation of efficacy and safety

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines by the investigators and the independent reviewers, with computed tomography scans at baseline and every 2 or 3 months. Complete response (CR) was defined as the disappearance of all known lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of the sum of all measurable lesions by at least 30%. PD was defined as an increase of the sum of all measurable lesions by than greater 20% or as the appearance of a new lesion and stable disease (SD) was defined as neither CR, PR, nor PD. Long SD was defined as SD lasting for more than 24 weeks.

Objective response rate (ORR) was defined as the sum of CR and PR rates. Clinical benefit rate (CBR) was defined as the sum of CR, PR, and long SD rates. Time-to-treatment failure (TTF) was defined as the period from the commencement of capecitabine to discontinuation of capecitabine and/or trastuzumab due to PD or unacceptable toxicity.

All adverse events and laboratory parameters were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0. Objective and subjective adverse events were assessed every week and laboratory parameters were assessed every 4 weeks.

Statistical analysis

Calculation of TTF was done by the Kaplan–Meier method, in order to analyze censored data. Confidence intervals (CI) were set at the 95% level.

Results

Patient characteristics

In the present study, 49 patients were assessed. Median follow-up time of patients was 16.2 months and the range was