based on plasma concentration *vs* time data were maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2}$), area under the plasma concentration *vs* time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$), volume of distribution at steady-state (V_{ss}) and plasma clearance (CL_p) (Rowland and Tozer, 1995). The fraction of drug excreted unchanged in urine (F_e) was calculated by dividing the cumulative amount of pemetrexed excreted unchanged in urine within 72 h (Ae_{0-72}) by the administered dose (Rowland and Tozer, 1995).

RESULTS

Patient disposition and characteristics

From October 2001 to September 2004, a total of 35 Japanese patients were enrolled and 31 were treated at four centres in Japan. Four patients were not treated owing to protocol criteria not met ($n=3$) and investigator decision ($n=1$). The majority of patients were male (65%), had an ECOG performance status of 1 (84%), were diagnosed with NSCLC (61%), and received prior chemotherapy (94%) (Table 1).

Table 1 Baseline patient characteristics

Parameter	N=31
Sex, n (%)	
Male	20 (65)
Female	11 (35)
Age, years	
Median (range)	59 (31–74)
Mean (s.d.)	57 (11)
ECOG performance status, n (%)	
0	4 (13)
1	26 (84)
2	1 (3)
Diagnosis, n (%)	
Non-small cell lung cancer	19 (61)
Malignant pleural mesothelioma	7 (23)
Thymoma	2 (7)
Alveolar soft part sarcoma	1 (3)
Rectal cancer	1 (3)
Unknown primary cancer	1 (3)
Prior therapy, n (%)	
Surgery	14 (45)
Radiation	9 (29)
Chemotherapy	29 (94)

ECOG = Eastern Cooperative Oncology Group; s.d. = standard deviation.

Table 2 Dose escalation and DLTs

Dose ($mg\,m^{-2}$)	Number of patients	DLTs (*n*)
300	3	None
500	3	None
600	3	None
700	6	G3 ALT elevation (1)
800	3	None
900	4[a]	None
1000	3	None
1200	6	G3 infection (1); G3 rash (1)

ALT = alanine transaminase; DLT = dose-limiting toxicity; G3 = grade 3. [a]One patient was excluded for DLT analysis because of grade 3 hyperglycemia at the beginning of the study.

Dose escalation and dose-limiting toxicities

Three or six patients were enrolled at each dose level from 300 to $1200\,mg\,m^{-2}$, except the $900\,mg\,m^{-2}$ dose level (Table 2). At this dose level, one additional patient was enrolled because a patient was excluded from the DLT analysis. Before the dose initiation, this patient had grade 3 fasting hyperglycemia that was aggravated after the start of dosing. Therefore, this patient was rated as inappropriate for evaluation.

The first DLT was observed at the $700\,mg\,m^{-2}$ dose level. This 66-year-old woman with NSCLC experienced grade 3 ALT elevation. After an additional three patients were enrolled, no other DLTs were observed.

The next DLTs were observed at the $1200\,mg\,m^{-2}$ dose level, which enrolled six patients at once. One patient, a 72-year-old woman with MPM, had grade 3 infection at day 6 of cycle 1. Neutropenia was not simultaneously observed in this cycle. After 12 days, the event was resolved with antibiotics. This patient continued in study with dose reduction to $1000\,mg\,m^{-2}$. The other patient, a 68-year-old man with NSCLC, had grade 2 rash at day 5 of cycle 1. The severity of the event reached grade 3 at day 7. After 9 days from the occurrence, rash was resolved with dexamethasone and H_1-antihistamine. This patient continued in study without dose reduction. As two DLTs were observed, the $1200\,mg\,m^{-2}$ dose level was considered as the MTD. The RD for subsequent phase II studies was then evaluated to be pemetrexed $1000\,mg\,m^{-2}$. Both events were considered as drug-related events by investigators.

Safety

The safety evaluation was completed from data obtained from cycle 1–6 for all dose levels except $1200\,mg\,m^{-2}$ (cycle 1–3). These data were collected and analysed to evaluate safety when the MTD and RD were determined. The major toxicities observed in >50% of patients during all cycles evaluated for this report included rash, nausea, anorexia, fatigue, ALT elevation, AST elevation, lactate dehydrogenase elevation, leucopenia, neutropenia, lymphopenia, hematocrit decreased, haemoglobin decreased and erythropenia (Table 3). The most commonly reported grade 3/4 toxicity was neutropenia: nine patients (29%) had grade 3 neutropenia, and one patient (3%) had grade 4 neutropenia. Other grade 3/4 hematologic toxicities were grade 3 leucopenia in four patients (13%), grade 4 leucopenia in one patient (3%), grade 3 lymphopenia in four patients (13%), and grade 3 haemoglobin decreased in two patients (6%). The most commonly reported grade 3 nonhematologic toxicity was ALT elevation (four patients (13%)). Other grade 3 toxicities included AST elevation in one patient (3%), anorexia in one patient (3%), infection in one patient (3%), malaise in one patient (3%), and rash in one patient (3%) were observed. No grade 4 nonhematologic toxicities were reported.

The only serious adverse event was observed at the $900\,mg\,m^{-2}$ level. This 71-year-old man with NSCLC experienced grade 1 pyrexia at day 18 of cycle 3 and was hospitalized; however, the event was resolved the next day. The investigator did not consider it as a drug-related event. One patient at $900\,mg\,m^{-2}$ level discontinued treatment owing to adverse events (neutropenia, anorexia, and pyrexia). No deaths were observed during the study period or for 31 days after the last dose.

At the $900\,mg\,m^{-2}$ and higher dose levels, all patients had either grade 1/2 or grade 3/4 rash. At cycle 1, 25 patients experienced rash. Of these, 20 patients received corticosteroid. At or after cycle 2, corticosteroid treatment was given only for nine rash events, whereas rash events were observed in 20 cycles in cumulative total among patients. In addition, the severity of rash quickly improved or disappeared after administration of corticosteroid. Although the protocol allowed corticosteroid use for prevention of rash from cycle 2, only seven patients actually received the preventive treatment. Among those who did not receive the prophylactic

Table 3 Incidence of clinically relevant toxicities

	Dose ($mg\,m^{-2}$) (*n*)															
	Grade															
	300 (3)		500 (3)		600 (3)		700 (6)		800 (3)		900 (4)		1000 (3)		1200 (6)	
Toxicity	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
Hematologic																
Erythropenia	1	0	1	0	3	0	4	0	2	0	2	0	2	0	5	0
Hematocrit decreased	1	0	1	0	3	0	4	0	3	0	2	0	2	0	5	0
Haemoglobin decreased	2	0	2	0	2	0	3	0	2	0	1	1	2	0	4	1
Leucopenia	1	0	3	0	2	1	3	1	1	1	1	1	1	0	5	1
Lymphopenia	0	0	2	1	0	1	3	0	1	0	1	1	3	0	4	1
Neutropenia	1	0	1	2	1	2	3	2	0	2	1	1	2	0	2	1
Thrombocytopenia	0	0	2	0	1	0	2	0	2	0	2	0	1	0	2	0
Nonhematologic																
ALT elevation	0	0	2	0	2	0	2	3	3	0	1	1	1	0	5	0
AST elevation	0	0	3	0	2	0	4	1	3	0	3	0	2	0	5	0
Blood bilirubin increased	0	0	1	0	0	0	2	0	0	0	0	0	0	0	1	0
LDH elevation	0	0	3	0	3	0	5	0	3	0	2	0	1	0	4	0
Alopecia	0	0	0	0	2	0	2	0	1	0	2	0	0	0	0	0
Anorexia	0	0	1	0	3	0	5	0	3	0	0	1	3	0	4	0
Constipation	1	0	1	0	0	0	1	0	0	0	0	0	2	0	1	0
Diarrhoea	0	0	2	0	1	0	1	0	1	0	1	0	1	0	2	0
Fatigue	1	0	2	0	2	0	2	0	3	0	1	0	2	0	3	0
Infection	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	1
Nausea	2	0	3	0	3	0	5	0	3	0	2	0	2	0	5	0
Malaise	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	2	0	2	0	1	0	0	0	1	0	2	0
Rash	3	0	2	0	3	0	5	0	2	0	4	0	3	0	5	1
Vomiting	2	0	3	0	2	0	3	0	1	0	1	0	1	0	0	0

ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase.

corticosteroid, the incidence of a rash observed at, or after, cycle 2 was about one-third of the incidence observed in cycle 1.

Pharmacokinetic analysis

Mean dose-normalised pemetrexed plasma concentration *vs* time profiles following single doses of 300–1200 $mg\,m^{-2}$ pemetrexed are provided in Figure 1. This body surface area (BSA)-normalized dose range represents absolute doses of 414–2018 mg in Japanese patients with a mean BSA of 1.64 m^2 (range, 1.36–1.97 m^2).

Pharmacokinetic parameters for each dose group are summarised in Table 4. Lack of a monotonic trend in CL_p and V_{ss} between cohorts indicated that pemetrexed pharmacokinetics are consistent across dose groups. Consistency of pemetrexed pharmacokinetics across dose groups is also illustrated by the lack of systematic pattern across dose groups in the dose-normalised plasma concentration *vs* time profiles (Figure 1). The overall mean $t_{1/2}$ is approximately 2.74 h and was essentially similar across all dose groups (range, 2.28–3.62 h).

In this study, pemetrexed was primarily excreted unchanged in urine, which is consistent with its known elimination pathway (i.e., renal excretion). The F_e averaged 0.752 (range, 0.645–0.827). Mean F_e values were consistent across dosing cohorts.

Tumour response

In this study, 23 of the 31 patients were evaluable for response by RECIST criteria (Table 5). Partial responses (PRs) were observed in four patients with NSCLC (one patient each at 500, 700, 800, and 1200 $mg\,m^{-2}$) and one patient with thymoma at 500 $mg\,m^{-2}$. In addition, one patient with NSCLC at 500 $mg\,m^{-2}$ had a PR by the World Health Organization criteria, but was not evaluable via RECIST.

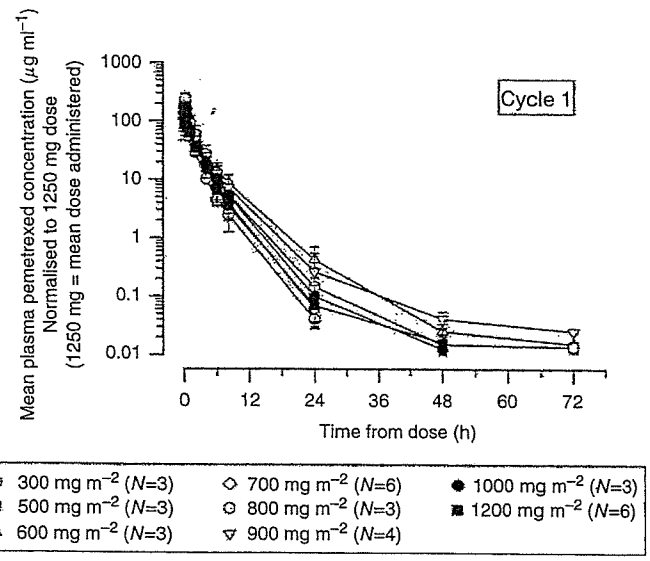

Figure 1 Mean dose-normalised pemetrexed plasma concentration–time profiles following single-dose administration in Japanese patients.

DISCUSSION

This is the first phase I study of pemetrexed in Japanese patients. The MTD for pemetrexed administered with FA/VB_{12} was 1200 $mg\,m^{-2}$ and determined the RD for subsequent phase II studies was 1000 $mg\,m^{-2}$.

In contrast with the previously determined MTD (600 $mg\,m^{-2}$) without vitamin supplementation (Rinaldi *et al*, 1999), our MTD

Table 4 Summary of pemetrexed pharmacokinetic parameters by dosing cohort arithmetic mean (CV%)

	Dose ($mg\,m^{-2}$) (n)							
Parameter	**300 (3)**	**500 (3)**	**600 (3)**	**700 (6)**	**800 (3)**	**900 (4)**	**1000 (3)**	**1200 (6)**
Dose (mg)	459 (12.4%)	783 (7.56%)	919 (8.28%)	1180 (8.06%)	1280 (16.5%)	1550 (5.47%)	1820 (7.04%)	1910 (6.71%)
C_{max}, ($\mu g\,ml^{-1}$)	58.2 (7.15%)	115 (19.1%)	178 (15.7%)	172 (9.30%)	240 (14.5%)	217 (7.05%)	269 (17.8%)	212 (13.2%)
$AUC_{0-\infty}$, ($\mu g\,h\,ml^{-1}$)	70.1 (7.04%)	158 (21.6%)	290 (12.5%)	250 (23.5%)	361 (17.0%)	388 (19.6%)	382 (6.55%)	337 (24.6%)
CL_p ($ml\,min^{-1}$)	109 (5.89%)	86.5 (32.5%)	53.0 (3.95%)	83.4 (27.7%)	61.4 (35.2%)	68.5 (20.0%)	79.3 (2.57%)	99.7 (24.7%)
V_{ss} (l)	13.5 (22.2%)	12.1 (20.1%)	11.5 (25.5%)	11.7 (20.0%)	10.6 (33.6%)	13.9 (31.7%)	14.4 (7.40%)	14.8 (9.41%)
$t_{1/2}$ (h)	2.28 (25.2%)	2.62 (3.29%)	3.62 (28.7%)	2.51 (3.91%)	2.93 (14.6%)	3.02 (17.8%)	2.67 (1.90%)	2.55 (10.9%)
F_e	0.659 (8.78%)	0.645 (8.34%)	0.788 (3.76%)	0.807 (10.1%)	0.705 (34.9%)	0.797[a] (5.11%)	0.648[a] (12.5%)	0.827[a] (7.58%)

CV% = coefficient of variation expressed as a percentage; C_{max} = maximum observed drug concentration; $AUC_{0-\infty}$ = area under the concentration versus time curve from zero to infinity; CL = total body clearance of drug after intravenous administration; V_{ss} = volume of distribution at steady state; $t_{1/2}$ = half-life associated with the terminal rate constant; F_e = fraction of dose eliminated unchanged in urine. [a]The numbers of patients in 900, 1000, and 1200 $mg\,m^{-2}$ were three, two, and five, respectively, owing to incompletion of urine collections for patients 209, 210, and 306.

Table 5 Antitumour activity by dose (RECIST)

		Evaluable ($n=23$)				
Dose ($mg\,m^{-2}$)	**Number of patients**	**CR**	**PR[a]**	**s.d.**	**PD**	**NE**
300	3	0	0	2	0	1
500	3	0	2	0	0	0
600	3	0	0	1	0	0
700	6	0	1	3	1	0
800	3	0	1	0	1	1
900	4	0	0	2	0	1
1000	3	0	0	1	1	0
1200	6	0	1	2	1	0
Total	31	0	5	11	4	3

NSCLC = non-small cell lung cancer; CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; s.d. = stable disease. [a]In addition, one NSCLC patient at 500 $mg\,m^{-2}$ had PR via WHO criteria.

increased by a factor of 2 whereas maintaining a tolerable safety profile. Niyikiza *et al* (2002a, b) conducted a multivariate analysis on 246 patients in phase II pemetrexed studies without vitamin supplementation, and the incidence of grade 4 neutropenia was 32% and grade 4 thrombocytopenia was 8% . Also 6% of patients had grade 3/4 diarrhoea, 5% had grade 3/4 mucositis, and a 5% incidence of drug-related death occurred. In contrast, our study had grade 4 neutropenia of only 3% (one patient) and no grade 4 thrombocytopenia. In addition, no grade 3/4 diarrhoea or mucositis, and no drug-related deaths were observed.

In the pivotal phase III study of NSCLC patients, those who received pemetrexed (500 $mg\,m^{-2}$) plus vitamin supplementation had a lower incidence of severe toxicities compared to those who received docetaxel (75 $mg\,m^{-2}$), including grade 3/4 neutropenia (5.3 *vs* 40.2%) and grade 3/4 diarrhoea (0.4 *vs* 2.5%) (Hanna *et al*, 2004).

Dose-dependency for toxicity of pemetrexed plus supplementation was further investigated to understand the effect of supplementation on safety. The patients in this study were divided into three groups by doses: low dose (300–600 $mg\,m^{-2}$ ($n=9$)), middle dose (700–900 $mg\,m^{-2}$ ($n=13$)), and high dose (1000 and 1200 $mg\,m^{-2}$ ($n=9$)). Grade 1/2 toxicity such as erythropenia, lymphopenia, hematocrit decreased, ALT and AST elevation, and anorexia increased dose dependently from approximately 20–50% to approximately 75%. However, there was no obvious correlation between grade 3/4 toxicity and dose group. Therefore, high dose levels of pemetrexed with FA/VB_{12} is expected to be tolerable enough for patients.

In this study, severe rash was rarely observed even without the prophylactic corticosteroid. Although this result suggests that the steroid premedication for prevention of severe rash is no longer necessary for patients with pemetrexed treatment if the FA/VB_{12} is concomitantly conducted, it would be too early to conclude it as the data of patients untreated with the premedication are limited at this moment.

The pharmacokinetic results in our study were consistent with a phase I study of pemetrexed without vitamin supplementation in western patients by Rinaldi *et al* (1999) In that study, pemetrexed $t_{1/2}$ was 3.1 h; and CL was 85 ml/min (Rinaldi *et al*, 1999 and unpublished results). In our study, the $t_{1/2}$ of pemetrexed was about 2.7 h; and CL was 81.9 ml/min. Additionally, the F_e of pemetrexed was similar for Japanese patients (75% in our study) and western patients (78% in the Rinaldi study (Rinaldi *et al*, 1999)). These results indicate that pharmacokinetics of pemetrexed in Japanese patients are similar to those in western patients.

Although our study is the first phase I study to evaluate pemetrexed with FA/VB_{12} in Japanese patients, a similar phase I study has been conducted in western patients. In the preliminary results of that study, heavily pretreated patients had a MTD of 925 $mg\,m^{-2}$, and lightly pretreated patients had a MTD of 1050 $mg\,m^{-2}$ (Hammond *et al*, 2003). The comparison of these two studies suggests that the improved tolerability experienced by Japanese patients when pemetrexed is administered with FA/VB_{12} is not attributable to ethnic differences; rather, it is attributable to the vitamin supplementation.

In our phase I study, four NSCLC patients and one thymoma patient had PRs. Except for one, all of the patients with PR had $\geqslant 3$ prior chemotherapy regimens. The NSCLC patients with PRs received doses of pemetrexed higher than 500 $mg\,m^{-2}$, which is the approved dose for NSCLC treatment in a number of countries. Therefore, subsequent phase II studies using our RD of 1000 $mg\,m^{-2}$ with vitamin supplementation could show more prominent antitumour activity for cancer patients. To examine this hypothesis, a Japanese phase II study is being conducted, examining pemetrexed 500 or 1000 $mg\,m^{-2}$ every 3 weeks with full supplementation for patients with locally advanced or metastatic NSCLC. Clinical trials for other tumours, including MPM, are also ongoing. For the prophylactic corticosteroid, as severe rash was not frequently observed in this study, the steroid is not to be administered prophylactically in both currently on-going studies.

In conclusion, pemetrexed with FA/VB_{12} resulted in a tolerable toxicity profile. The MTD was 1200 $mg\,m^{-2}$. The RD was 1000 $mg\,m^{-2}$.

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Influence of histological type, smoking history and chemotherapy on survival after first-line therapy in patients with advanced non-small cell lung cancer

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The usual primary endpoint in clinical trials for first-line chemotherapy in advanced non-small cell lung cancer is overall survival. Second-line chemotherapy can also prolong overall survival. Non-smoking history has been associated with a treatment effect for epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) versus placebo for overall survival. We performed a retrospective analysis to identify prognostic factors for progression-free survival and overall survival in patients with advanced non-small cell lung cancer treated with first-line carboplatin/paclitaxel, and to examine the effect of second-line therapy on progression-free survival and overall survival. Ninety-eight patients (median age 61 years, 35 female, 74 adenocarcinoma, 68 smokers, 56 performance status 0) fulfilled our criteria, of which 75 patients (78%) received more than second-line therapy (docetaxel [54%] gefitinib [48%] erlotinib [4%]). For overall survival, smoking history and histology were significant prognostic factors. The 2-year overall survival rates were as follows: smokers, 17%; non-smokers, 52%, $P < 0.0001$; adenocarcinoma, 40%; other 15%, $P = 0.0017$. Multivariate analysis in patients who received second-line therapy showed treatment with EGFR-TKI was an independent predictor of overall survival. Smoking history and adenocarcinoma histology were prognostic factors for an improved outcome with carboplatin/paclitaxel in patients with non-small cell lung cancer. Our study results suggest that the use of EGFR-TKI after first-line treatment may be associated with an improvement in overall survival. (*Cancer Sci* 2007; 98: 226–230)

Lung cancer is the malignant tumor with the highest mortality rates in the world.[1] Approximately 80% of all lung cancer cases are non-small cell lung cancer (NSCLC) and patients with postoperative recurrence or advanced NSCLC may be treated with systemic chemotherapy. Platinum-based chemotherapy is widely used as first-line treatment. Various combination regimens are available — the Four-Arm Cooperative Study (FACS) conducted in Japan between October 2000 and June 2002 did not demonstrate any superiority of three experimental platinum-based regimens (cisplatin/gemcitabine, cisplatin/vinorelbine and carboplatin/paclitaxel) compared with the reference arm of cisplatin/irinotecan.[2,3] However, due to its good tolerability, ease of use and experience in Western countries, carboplatin/paclitaxel is currently the standard first-line chemotherapy for NSCLC in Japan.

Docetaxel has been widely used as second-line therapy for NSCLC in Japan. However, since its approval in July 2002, the use of gefitinib (IRESSA), an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has been increasing each year. Erlotinib, another EGFR-TKI, which is approved in a number of Western markets has also been used in clinical registration trials in some Japanese medical institutions. Gefitinib was the first molecular targeted agent to be approved for the treatment of NSCLC in Japan. Two international cooperative Phase II studies (IRESSA Dose Evaluation in Advanced Lung Cancer Trial: IDEAL1 and 2) demonstrated efficacy (response rates, 12.0–18.9%) and favorable tolerability of gefitinib in the treatment of NSCLC after failure of platinum-based chemotherapy.[4,5] Furthermore, the results of subset analyses of IDEAL1 indicated that the patient characteristics of Japanese nationality, female gender and adenocarcinoma histology were associated with longer overall survival (OS).[4]

In a placebo-controlled Phase III study (BR21) erlotinib significantly prolonged OS compared with placebo in patients with previously treated NSCLC.[6] A similar Phase III study (IRESSA Survival Evaluation in Lung Cancer [ISEL]) of gefitinib in refractory, advanced NSCLC showed an improvement in survival compared with placebo in the overall study population, which did not reach statistical significance.[7] However, in a subset analysis, statistically significantly longer survival was demonstrated in patients of Asian origin and in patients who had never smoked.[7] With the availability of new second-line anti-cancer agents such as gefitinib and erlotinib, it is necessary to consider more fully the influence of second-line treatment on evaluation of OS following standard first-line treatment. Since the opening of our department in October 2002, carboplatin/paclitaxel has been used as the standard first-line therapy for NSCLC, while the use of gefitinib as second-line therapy is increasing each year. In this study we performed retrospective analyses of data from patients who had received carboplatin/paclitaxel, in order to identify prognostic variables affecting OS and progession-free survival (PFS), and also to determine the contribution of second-line and subsequent treatment to prolongation of OS.

Patients and Methods

Patients. This retrospective study recruited patients with NSCLC who had received chemotherapy at the Thoracic Oncology Division, Shizuoka Cancer Center, Japan, between October 2002 and September 2005. Patients met all of the following criteria:[1] clinical stage IIIB or IV;[2] patients were administered carboplatin area under the curve (AUC) 6 + paclitaxel 200 mg/m^2 as first-line chemotherapy; and[3] performance status (PS) 0 or 1.

Target patients were identified in our electronically controlled clinical database and the following information extracted from their data:[1] patient demographics at the start of first-line chemotherapy (age, gender, smoking history, histology, stage);[2] objective tumor response;[3] time to disease progression;[4] OS;

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and second-line and subsequent chemotherapy regimens.[5] The tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) using existing images and graded as complete response, partial response, stable disease, progressive disease or not evaluable.

Treatment. Patients received carboplatin and paclitaxel as first-line chemotherapy. Patients received paclitaxel 200 mg/m^2 as a 3-h intravenous infusion, followed by carboplatin AUC 6 (Calvert's setting) as a 1-h infusion on Day 1. Courses of treatment were repeated every 3 or 4 weeks for 4–6 cycles, until disease progression or severe toxicity. When a patient developed National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 non-hematological toxicity (except nausea and anorexia) after the start of treatment, the dose was reduced to carboplatin AUC 5 + paclitaxel 150 mg/m^2.

Statistical analysis. Kaplan-Meier plots were prepared for OS and PFS and median values were calculated. OS was measured from the first day of first-line treatment to the day of death or the day last seen alive (cut-off). PFS was measured from the first day of first-line treatment to the earliest observation of documented progressive disease, or the day of death if the patient died before observation of progressive disease. Univariate and multivariate analyses were performed for OS and PFS stratified by baseline factors. To identify factors influencing PFS and OS, multivariate analysis was performed with covariates including disease stage (IIIB versus IV), histology (adenocarcinoma versus other), smoking history (non-smoker versus smoker), gender (female versus male) and PS (0 versus 1). Multivariate analysis was performed by the stepwise regression method using a Cox proportional hazards model. To evaluate potential interaction between clinical variables such as smoking history or histology and EGFR-TKI treatment, patients who received second-line therapy were included in subsequent exploratory Cox analysis in which non-smokers and adnocarcinoma patients were divided by EGFR-TKI treatment, with smokers and nonadnocarcinoma patients set as references, respectively. Statistical analyses for this study were conducted using the Stat View software statistical tool.

Results

Patient characteristics. In total, 98 patients met the eligibility criteria and their demographic data are presented in Table 1. The majority of patients were male (64%), had a smoking history (69%), adenocarcinoma histology (76%), stage IV disease (70%) and PS 0 (57%). The median duration of first-line carboplatin/paclitaxel therapy was 3 cycles (range, 1–6 cycles). The median follow-up time was 24.8 months (range: 4.2–43.9). 57 patients died. 41 patients were still alive.

Table 1. Patient demographics ($n = 98$)

Gender *n* (%)	
Male	63 (64)
Female	35 (36)
Median (range) age, years	61 (34–78)
ECOG PS, *n* (%)	
0	56 (57)
1	42 (43)
Smoking history, *n* (%)	
Smoker	68 (69)
Non-smoker	30 (31)
Histology, *n* (%)	
Adenocarcinoma	74 (76)
Other	24 (24)
Stage, *n* (%)	
IIIB	29 (30)
IV	69 (70)

ECOG, European Cooperative Oncology Group; PS, performance status.

Table 2. Best overall objective response, *n* (%)

	Total population ($n = 98$)	By histology	
		Adenocarcinoma ($n = 74$)	Other ($n = 24$)
Partial response	20 (20)	15 (20)	5 (21)
Stable disease	53 (54)	42 (57)	11 (46)
Progressive disease	25 (26)	17 (23)	8 (33)

Efficacy. The overall response rate to first-line carboplatin/paclitaxel therapy was 20% (20/98), with outcomes similar in patients with adenocarcinoma and other histological subtypes (20% versus 21%, respectively) (Table 2). In the overall population, median PFS was 4.8 months and median OS 16.5 months, with a 1-year survival rate of 64%.

For PFS, only disease stage was a significant prognostic factor (Table 3). For OS, histology, smoking history and PS were significant prognostic factors (Table 3).

Multivariate analyses assessing the effects of histology and smoking history on PFS and OS were performed. No significant difference was observed for PFS between adenocarcinoma versus other histology ($P = 0.40$; Fig. 1) or non-smokers versus smokers ($P = 0.22$; Fig. 2). In contrast, OS differed significantly between adenocarcinoma versus other histology ($P = 0.0017$)

Table 3. Efficacy among patient subgroups: Cox regression analysis

Factor	Variable	PFS *P*-value HR (95% CI)	OS *P*-value HR (95% CI)
Histology	Adenocarcinoma versus other	0.2045 –	0.0020 0.410 (0.233–0.723)
Smoking	Non-smoker versus smoker	0.1351 –	<0.0001 0.222 (0.109–0.450)
Gender	Female versus male	0.2206 –	0.2691 –
PS	0 versus 1	0.9575 –	0.0109 0.499 (0.292–0.852)
Stage	IIIB versus IV	0.0074 0.536 (0.339–0.847)	0.2024 –

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NS, not significant; PS, performance status.

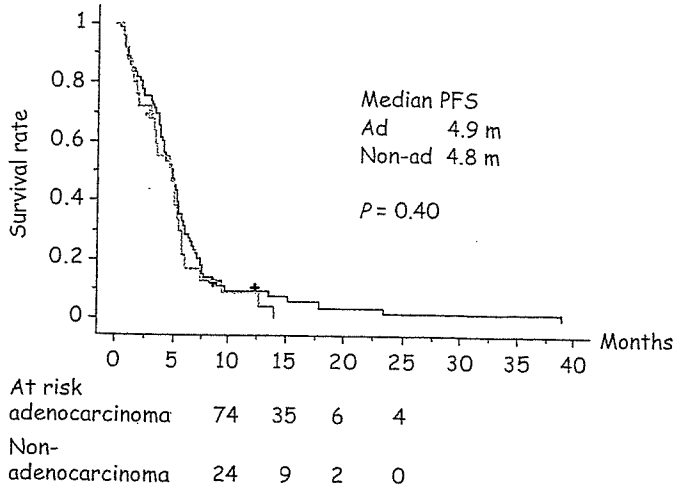

Fig. 1. Kaplan-Meier plot of progression-free survival (adenocarcinoma versus nonadenocarcinoma histology).

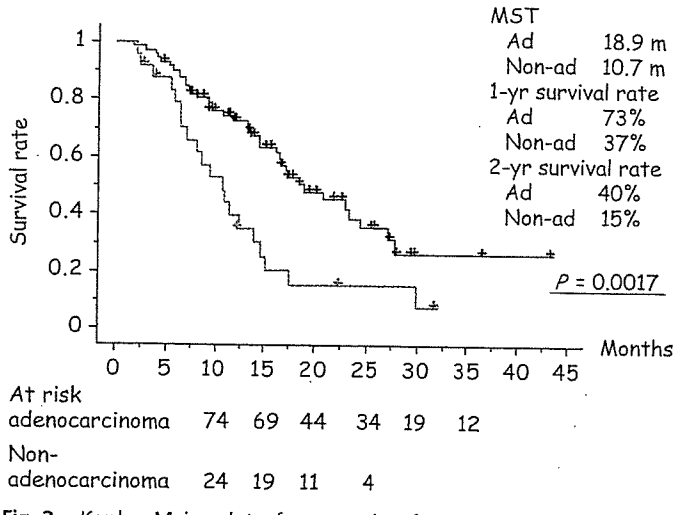

Fig. 2. Kaplan-Meier plot of progression-free survival (smoker versus non-smoker).

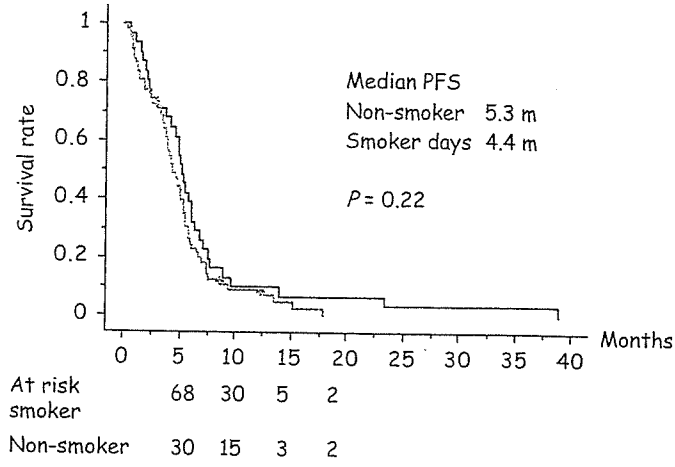

Fig. 3. Kaplan-Meier plot of overall survival (adenocarcinoma versus nonadenocarcinoma histology).

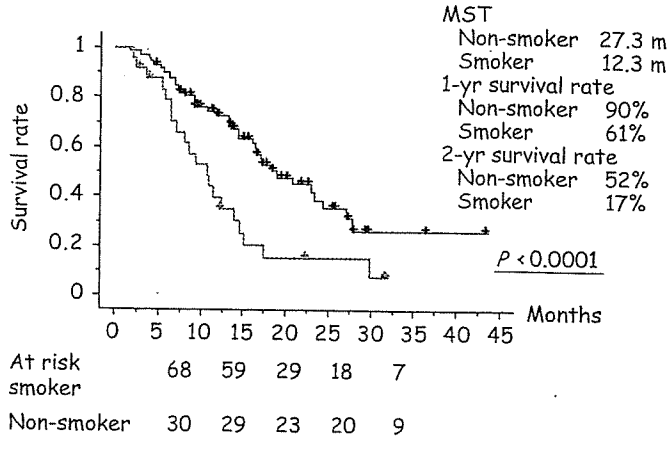

Fig. 4. Kaplan-Meier plot of overall survival (smoker versus non-smoker).

and between non-smokers versus smokers ($P < 0.0001$). Of particular note, median OS of smokers was 12.3 months, and non-smokers was 27.3 months. Two-year survival rates were 17% and 52% in smokers and non-smokers, respectively (Figs 3,4).

To identify factors influencing OS in patients who received second-line therapy ($n = 76$), multivariate analysis was performed with covariates including histology (adenocarcinoma versus other), smoking history (non-smoker versus smoker), PS (0 versus 1), docetaxel (use versus non-use) and EGFR-TKI (use versus non-use). The use of EGFR-TKI was identified as a significant prognostic factor associated with longer OS, together with non-smoking history and PS 0. The use of docetaxel was not associated with an increase in OS in this study (Table 4). When interaction terms between clinical variables and EGFR-TKI treatment were included in the model, no significant interaction was detected ($P = 0.354$ and 0.515 for smoking history × EGFR-TKI and histology × EGFR-TKI, respectively). In the exploratory Cox analysis, prognostic advantage for non-smoking history and adnocarcinoma histology was more prominent in patients who received EGFR-TKI treatment after adjustment for PS, suggesting a potential interaction between these favorable clinical variables and EGFR-TKI treatment. Compared with smokers, hazard ratio of non-smokers with or without EGFR-TKI was 0.961 (95% CI, 0.209–4.420) and 0.193 (0.083–0.449), respectively. Likewise, the hazard ratio of adenocarcinoma patients with or without EGFR-TKI was 0.429 (0.138–1.334) and 0.387 (0.187–0.800), respectively, compared with patients with other histologies.

Table 4. Cox regression analysis of prognostic factors for overall survival after second-line treatment: a stepwise forward procedure

Factor	Variable	*P*-value HR (95% CI)
Histology	Adenocarcinoma versus other	0.0639 –
Smoking	Non-smoker versus smoker	0.0052 0.325 (0.148–0.715)
PS	0 versus 1	0.0258 (0.258–0.917)
Docetaxel	– versus +	0.6720 –
EGFR-TKI	– versus +	0.0084 2.844 (1.306–1.823)

PS, performance status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval.

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Table 5. Historical comparison of outcomes in our study and the FACS study[2]

	FACS[1] (n = 145)	This study (n = 98)
Response rate (%)	32	20
Median PFS (months)	4.5	4.8
Median OS (months)	12.3	16.5
1-year survival rate (%)	51	64
Second-line therapy, n (%)	87 (60)	76 (78)
Docetaxel	25 (17)	42 (43)
EGFR-TKI	9 (6)	29† (30)
Other	58 (40)	5 (5)

†25 patients were treated with Gefitinib. FACS, Four-Arm Cooperative Study; PFS, progression-free survival; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

Discussion

Since the results of a large meta-analysis revealed that platinum-based chemotherapy prolonged OS of patients with advanced NSCLC compared with best supportive care (BSC)[8] this therapy has been considered standard first-line treatment for advanced NSCLC worldwide. Median OS with carboplatin/paclitaxel – the most commonly used standard therapy outside Japan – has been reported to be 8–14 months[9–13] similar to the median OS (12.3 months) observed in the FACS trial conducted in Japan.[2,3]

Comparison of outcomes following carboplatin/paclitaxel treatment in our study with the results obtained with the same regimen in the FACS study, showed there was little difference in median PFS (4.8 versus 4.5 months), but median OS was approximately 4 months longer at our hospital (16.5 versus 12.3 months). With the recent approval of EGFR-TKIs, the use of these agents as second-line chemotherapy has increased since the FACS study was performed (30% of patients in this study versus 6% of patients in the FACS study) (Table 5). This observation suggests that the better treatment outcomes obtained in our study compared with those of FACS may be attributable to the effect of anticancer agents used in second-line and subsequent treatment, especially EFGR-TKI (gefitinib was used in most cases). In fact, the result of subgroup analysis by patient demographics in our study demonstrated a marked prolongation of OS for non-smokers and patients with adenocarcinoma, both of which are known to be factors associated with high responsiveness to EGFR-TKI. Furthermore, the multivariate analysis in patients receiving second-line treatment, revealed that EGFR-TKI use was an independent prognostic factor.

Generally, the prolongation of OS is the ultimate goal of anticancer therapy and an important clinical outcome in the evaluation of the effect of first-line treatment for NSCLC. With the emergence of potent anticancer agents in the second-line setting, therapy administered after the occurrence of progressive disease becomes a confounding factor in the interpretation of OS. To overcome this issue of confounding, there may be value in using prolongation of PFS as the primary outcome of first-line trials. Currently, the Food and Drug Administration (FDA) requires an applicant to demonstrate prolonged survival as an approval condition for new anticancer agents.[14] However, the European Agency for Evaluation of Medical Products (EMEA) has accepted PFS as the primary endpoint in some instances, and our present study result supports this view.[15]

The results of the BR21 trial showed that erlotinib significantly prolonged OS compared with placebo (6.7 versus 4.7 months, hazard ratio [HR] = 0.70). In the multivariate analysis, Asian origin (P = 0.01), adenocarcinoma histology (P = 0.004) and non-smoking status (P = 0.048) correlated with prolonged OS.[6] In the preplanned subgroup analysis in the ISEL trial, significantly longer survival was seen with gefitinib compared with placebo in patients of Asian origin (9.5 versus 5.5 months, HR = 0.66) and never-smokers (8.9 versus 6.1 months, HR = 0.67).[7] Although these two studies did not include Japanese patients, the findings might be extrapolated into Japanese populations. Since the reports of Paez *et al.*[16] and Lynch *et al.*[17] in April and May 2004, respectively, numerous studies of EGFR mutations have been conducted in a short period and studies conducted in Japan have reported a good correlation between OS and EGFR mutations in patients treated with gefitinib.[18–20] Moreover, the incidence of EGFR mutations is more frequent in women, patients with adenocarcinoma, never-smokers and Japanese patients[16,17] suggesting that there is a correlation between clinical and molecular factors and clinical benefit from EGFR-TKIs.

Although EGFR mutations are of interest as a biomarker that can be predictive of the effect of gefitinib, especially in patients of Asian or Japanese origin, their immediate clinical application for patient selection is not always possible, due to issues including method determination, cost and convenience. Correlation between response to gefitinib and EGFR copy number determined by fluorescence *in situ* hybridization (FISH) has attracted attention in the West as an alternative potential biomarker[21,22] and this needs to be further investigated in Japan. Acknowledging the need to pay close attention to future research trends, we believe further discussion into how to select those patient populations most likely to benefit from gefitinib in routine clinical practice is required. It is important to establish whether patients could be selected on the basis of biomarker data such as EGFR mutations, or EGFR over-expression, or clinical characteristics such as histological subtype and smoking history. Nevertheless, selection of appropriate patients for EGFR-TKI therapy is undoubtedly necessary, and we hope that future research will be able to identify possible methods as soon as possible. Once identified these will require validation in large-scale prospective clinical studies.

In conclusion, this retrospective study demonstrated a marked prolongation of overall survival in patients with adenocarcinoma and non-smoking history who received carboplatin/paclitaxel as first-line treatment. Our study results suggest that the use of EGFR-TKI (especially gefitinib) after first-line treatment may be associated with an improvement in overall survival.

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