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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Full Paper

A phase I study of pemetrexed (LY231514) supplemented with folate and vitamin B_{12} in Japanese patients with solid tumours

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The purpose of this study was to determine the maximum tolerated dose (MTD) and recommended dose (RD) of pemetrexed with folate and vitamin B12 supplementation (FA/VB_{12}) in Japanese patients with solid tumours and to investigate the safety, efficacy, and pharmacokinetics of pemetrexed. Eligible patients had incurable solid tumours by standard treatments, a performance status 0–2, and adequate organ function. Pemetrexed from 300 to 1200 mg m^{-2} was administered as a 10-min infusion on day 1 of a 21-day cycle with FA/VB_{12}. Totally, 31 patients were treated. Dose-limiting toxicities were alanine aminotransferase (ALT) elevation at 700 mg m^{-2}, and infection and skin rash at 1200 mg m^{-2}. The MTD/RD were determined to be 1200/1000 mg m^{-2}, respectively. The most common grade 3/4 toxicities were neutropenia (grade (G) 3:29, G4:3%), leucopenia (G3:13, G4:3%), lympopenia (G3:13%) and ALT elevation (G3:13%). Pemetrexed pharmacokinetics in Japanese were not overtly different from those in western patients. Partial response was achieved for 5/23 evaluable patients (four with non-small cell lung cancer (NSCLC) and one with thymoma). The MTD/RD of pemetrexed were determined to be 1200/1000 mg m^{-2}, respectively, that is, a higher RD than without FA/VB_{12} (500 mg m^{-2}). Pemetrexed with FA/VB_{12} showed a tolerable toxicity profile and potent antitumour activity against NSCLC in this study.

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Pemetrexed (LY231514, Alimta®, Eli Lilly and Company, IN, USA) is a novel antifolate (Taylor and Patel, 1992) that is approved in the United States and a number of European Union countries , for treatment of patients with malignant pleural mesothelioma (MPM) in combination with cisplatin, and non-small cell lung cancer (NSCLC) after prior chemotherapy as a single agent. *In vitro* experiments show that pemetrexed inhibits three enzymes in folate metabolism: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (Shih *et al*, 1998). Given the schedule dependency observed preclinically, three regimens were explored in phase I studies: (1) 0.2–5.2 mg m^{-2} daily for 5 days every 3 weeks (McDonald *et al*, 1998); (2) 10–40 mg m^{-2} weekly for 4 weeks repeated every 6 weeks (Rinaldi *et al*, 1995); and (3) 50–700 mg m^{-2} every 3 weeks (Rinaldi *et al*, 1999).

The third regimen (one dose every 3 weeks) was chosen for subsequent phase II studies because of its convenient administration, ability to give repeated doses, and occurrence of objective responses. The original maximum tolerated dose (MTD) and the recommended dose (RD) was 600 mg m^{-2}, but was decreased to 500 mg m^{-2} owing to toxicities experienced early in phase II studies. The initial phase I and II studies showed that myelosuppression was the principle drug-related toxicity, with a frequency of grade 3/4 neutropenia of 50% and grade 3/4 thrombocytopenia of 15% (Hanauske *et al*, 2001). Less than 10% of patients experienced gastrointestinal toxicities such as diarrhoea or mucositis. Although the prevalence of gastrointestinal toxicities and severe hematologic toxicities was low, these toxicities were associated with a high risk of mortality.

Infrequent severe myelosuppression with gastrointestinal toxicity has been observed not only for pemetrexed, but for the class of antifolates, including the DHFR inhibitor methotrexate (Morgan *et al*, 1990), the TS inhibitor raltitrexed (Maughan *et al*, 1999), and the GARFT inhibitor lometrexol (Alati *et al*, 1996; Mendelsohn *et al*, 1996). Clinical experience and nonclinical studies with methotrexate and lometrexol indicated that severe toxicity may be associated with nutritional folate status (Morgan *et al*, 1990; Alati *et al*, 1996; Mendelsohn *et al*, 1996). In fact, in the study of lometrexol, a significant effect of folate supplementation on toxicity was observed (Laohavinij *et al*, 1996). Based on these experiences, Niyikiza *et al* (2002a) investigated relationships between toxicity and baseline patient characteristics for early pemetrexed studies. They found total plasma homocysteine and methylmalonic acid levels to predict severe neutropenia and

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thrombocytopenia, with or without grade 3/4 diarrhoea, mucositis, or infection. Homocysteine and methylmalonic acid are known as indicators of folate and vitamin B_{12} deficiencies (Rosenberg and Fenton, 1989; Savage *et al*, 1994). Thus, it was hypothesized that a patient's risk for severe toxicity could be reduced by decreasing the levels of homocysteine and methylmalonic acid with folate and vitamin B_{12} supplementation (FA/VB_{12}) (Niyikiza *et al*, 2002a).

FA/VB_{12} is now required for all patients participating in pemetrexed studies. Using this strategy, the pivotal phase III studies for MPM and NSCLC were successfully conducted with amelioration of severe drug-related toxicity (Niyikiza *et al*, 2002b; Vogelzang *et al*, 2003; Hanna *et al*, 2004).

One may expect that pemetrexed administration with supplementation would be more tolerable for patients and permit significant dose escalation above the current RD of 500 mg m^{-2}. Therefore, we conducted a phase I study to determine the MTD of pemetrexed with FA/VB_{12} for Japanese patients with solid tumours and to identify the RD for subsequent Japanese phase II studies. Our secondary objectives were to investigate the safety, antitumour effect, and pharmacokinetics of pemetrexed with supplementation in Japanese patients. A similar phase I study has been conducted outside Japan, but only preliminary data are available at this time (Hammond *et al*, 2003).

PATIENTS AND METHODS

Patient selection

Eligible patients had histologic or cytologic diagnosis of solid cancer that was incurable by standard treatments. Patients also must have been between 20 and 75 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and have an estimated life expectancy of at least 3 months. Adequate organ function was required, which included bone marrow reserve (white blood cell count $4.0-12.0 \times 10^3\,mm^{-3}$, platelets $\geqslant 100 \times 10^3\,mm^{-3}$, haemoglobin $\geqslant 9.0\,g\,dl^{-1}$, and absolute granulocyte count $\geqslant 2.0 \times 10^3\,mm^{-3}$), hepatic function (bilirubin $\leqslant 1.5 \times$ upper limit of normal, aspartate/alanine transaminase (AST/ALT) $\leqslant 2.5 \times$ upper limit of normal, and serum albumin $\geqslant 2.5\,g\,dl^{-1}$), renal function (serum creatinine $\leqslant$ upper limit of normal and Cockcroft and Gault creatinine clearance $\geqslant 60\,ml\,min^{-1}$), and lung function (PaO2 $\geqslant 60$ torr).

Prior chemotherapy or hormone therapy was allowed if it was carried out $\geqslant 14$ days before study entry ($\geqslant 35$ days for nitrosourea or mitomycin-C). Previous radiotherapy was also allowed, but only if $\leqslant 25\%$ of marrow was irradiated and if it was completed $\geqslant 21$ days before study entry. Pretreated patients must have recovered from all toxicities before study entry. Prior surgery was allowed if patients recovered from the effect of the operation. Patients were excluded from this study for active infection, symptomatic brain metastasis, interstitial pneumonitis, or pulmonary fibrosis diagnosed by chest X-ray, serious concomitant systemic disorders incompatible with the study, clinically significant effusions, or the inability to discontinue aspirin and other nonsteroidal anti-inflammatory agents during the study.

This study was conducted in compliance with the guidelines of good clinical practice and the Declaration of Helsinki Principles, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry.

Treatment

Pemetrexed was administered as a 10-min infusion on day 1 of a 21-day cycle. Patients remained on study unless they were discontinued because of disease progression, unacceptable adverse events, inadvertent enrollment, use of excluded concomitant therapy, cycle delay >42 days, or patient refusal.

Patients were instructed to take a daily 1 g multivitamin with 500 μg of folate beginning 1 week before day 1 of cycle 1 until study discontinuation. Vitamin B_{12} (1000 μg) was intramuscularly injected, starting 1 week before day 1 of cycle 1 and repeated every 9 weeks until study discontinuation.

Patients enrolled in pemetrexed clinical studies have received dexamethasone prophylactically to avoid pemetrexed-induced rash. As this was the first study of pemetrexed in Japanese patients and the incidence of the drug-induced rash in Japanese patients was unknown, the steroid was not to be administered prophylactically.

Dose escalation

In this study, 10 dose levels of pemetrexed, 300, 500, 600, 700, 800, 900, 1000, 1200, 1450, and 1750 mg m^{-2}, were to be examined with a starting dose of 300 mg m^{-2}. At dose levels from 300 to 1000 mg m^{-2}, three patients were to be treated initially. If no dose-limiting toxicities (DLTs) occurred during cycle 1, escalation proceeded to the next dose level. If 1 DLT occurred, three patients were added. If no additional DLTs were observed, escalation proceeded to the next dose level. At dose levels from 1200 to 1750 mg m^{-2}, six patients were to be treated at once. If two or more patients had DLTs at any dose level, dose escalation stopped, and this dose level was considered the MTD. The RD was then established by discussion with principal investigators, and the Efficacy and Safety Evaluation Committee.

A DLT was defined as the occurrence of one of the following toxicities during cycle 1: any grade 3/4 nonhematologic toxicity (except grade 3 nausea/vomiting and AST, ALT, or alkaline phosphatase elevation $<10 \times$ upper limit of normal that returns to grade 0–1 by the beginning of cycle 2), grade 3/4 febrile neutropenia ($<1000\,mm^{-3}$ with $\geqslant 38.0°C$), grade 4 leucopenia ($<1000\,mm^{-3}$) or neutropenia ($<500\,mm^{-3}$) lasting $\geqslant 4$ days, thrombocytopenia ($<20\,000\,mm^{-3}$), or thrombocytopenia ($\geqslant 20\,000\,mm^{-3}$) requiring platelet transfusion. A failure to start the second cycle by day 42 owing to toxicity was also considered a DLT. All toxicities were assessed according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.

Treatment assessments

Tumour response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Evaluable patients were subjected to CT or MRI measurement to determine the size of tumours at anytime at the discretion of investigators.

Pharmacokinetic analysis

Blood and urine were collected from each patient over a period of 72 h following administration in cycle 1. Blood samples were taken just before administration, at the end of infusion, and approximately 5, 15, 30 min and 1, 2, 4, 6, 8, 24, 48 and 72 h after the start of infusion. Urine was collected over the following time intervals: 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–60, and 60–72 h. Plasma and urine samples were analysed for pemetrexed at Taylor Technology Inc., Princeton, NJ, USA. Plasma samples were analysed using a validated liquid chromatography/electrospray ionisation-tandem mass spectrometry method that generated a linear response over the concentration ranges of 10–2000 ng/ml and 1000–200 000 ng/ml (Latz *et al*, 2006). Urine samples were analysed using a similar analytical technique (Chaudhary *et al*, 1999).

Pharmacokinetics were evaluated using noncompartmental methods (WinNonlin Professional Version 3.1; Pharsight Corporation, Cary NC, USA). Pharmacokinetic parameters determined

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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

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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.

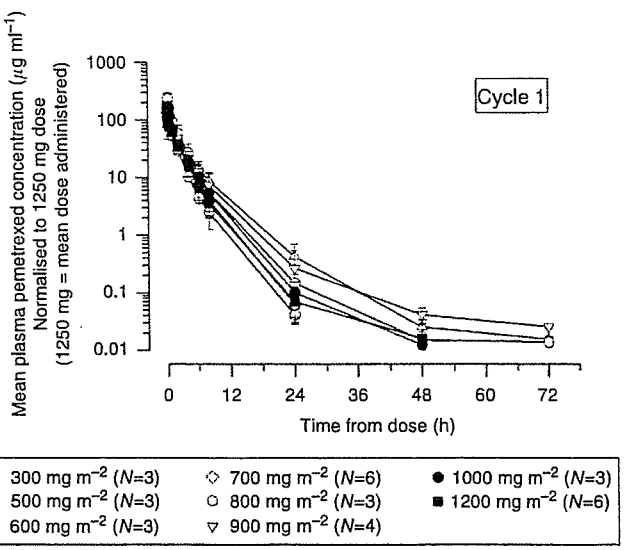

Figure 1 Mean dose-normalised pemetrexed plasma concentration–time profiles following single-dose administration in Japanese patients.

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

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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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Phase II Study of 3-Week Scheduling of Irinotecan in Combination With Cisplatin in Patients With Advanced Nonsmall-Cell Lung Cancer

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Objectives: The combination of irinotecan and cisplatin given every 4 weeks is one of the standard treatments for advanced nonsmall-cell lung cancer (NSCLC) in Japan. The purpose of this study is to evaluate the efficacy, safety and dose-intensity as a measure of the feasibility of 3-week scheduling of irinotecan and cisplatin in patients with advanced NSCLC in phase II study.

Methods: Previously untreated patients with stage IIIB and IV NSCLC were treated intravenously with irinotecan (60 mg/m^2) on days 1 and 8 and cisplatin (60 mg/m^2) on day 1 of a 3-week cycle.

Results: Of the 28 patients enrolled, 27 were evaluable for response and toxicity. The response rate was 30% (95% confidence interval, 14–50%). The median duration of response was 16 weeks (range, 10–26 weeks). The median survival time for all patients was 52 weeks and the 1-year and 2-year survival rates were 48% and 29%, respectively. The dose-intensity of irinotecan was 34 mg/m^2/wk (range, 19–40). The major toxicities observed were neutropenia (grade 3, 30%; 4, 30%), leukopenia (grade 3, 30%), and diarrhea (grade 3, 22%). Other toxicities were generally mild.

Conclusions: Three-week scheduling of irinotecan and cisplatin is effective and feasible in advanced NSCLC.

Key Words: irinotecan, cisplatin, nonsmall-cell lung cancer

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Lung cancer is the leading cause of cancer mortality. Nonsmall-cell lung cancer (NSCLC) accounts for 80% to 85% of patients with lung cancer and approximately two-thirds of them are inoperable at the time of diagnosis. Therefore, chemotherapy is a mainstay of the treatment of advanced nonsmall-cell lung cancer (NSCLC).[1] Recent meta-analyses have shown that cisplatin-based chemotherapy produces improved survival in advanced NSCLC.[2,3] Several new agents including irinotecan, taxanes, vinorelbine, and gemcitabine are active as single agents against NSCLC with the response rate ranging from 20% to 27%.[4] Among these, irinotecan hydrochloride, a camptothecin derivative, is active against NSCLC with a response rate of 32% as a single agent when given on a weekly basis.[5] The combination of irinotecan and cisplatin is considered to be synergistic and is active against advanced NSCLC.[6,7] A phase III study performed in Japan has revealed that a combination therapy with irinotecan and cisplatin given every 4 weeks produced comparable survival to a combination of cisplatin and vindesine in patients with advanced NSCLC.[8] In the subgroup analysis, the combination of irinotecan and cisplatin was also superior to the combination of cisplatin and vindesine in terms of survival prolongation in patients with stage IV disease.[8] Based on these results, the combination of irinotecan and cisplatin given every 4 weeks is one of the standard treatments for advanced NSCLC in Japan. In that study, there were considerable delays in treatment with or dose omissions of irinotecan, mostly on day 15, because of leukopenia and/or diarrhea, and the dose intensity of irinotecan was only 30 mg/m^2/wk (range, 12–46) in contrast to the planned dose intensity of 45 mg/m^2/wk.[8] Therefore, we conducted this phase II study of irinotecan and cisplatin scheduled every 3 weeks to evaluate response rate, safety and dose intensity as a measure of feasibility in patients with advanced NSCLC.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically proven diagnosis of NSCLC were eligible for this study. Other eligibility criteria included the following: stage IIIB with malignant pleural or pericardial effusion or contralateral hilar node metastasis that precluded curative radiotherapy or stage IV; measurable disease; no prior therapy including chemotherapy, radiotherapy or surgery to the primary tumor; age ranging from 20 to 74 years; a life expectancy ≥12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; an adequate baseline organ function defined

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as leukocyte count from 4000 to 12,000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥9.5 g/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, total bilirubin ≤1.5 mg/dL, serum creatinine ≤ the institutional upper limit of normal or 24-hour creatinine clearance ≥60 mL/min, and PaO_2 at rest ≥60 mm Hg. Patients were ineligible if they had the following criteria: superior vena caval syndrome; history of serious drug allergy; massive pleural or pericardial effusion or ascites that required drainage; active infection; persistent diarrhea (watery stool); paralytic ileus; interstitial pneumonia or pulmonary fibrosis; symptomatic brain metastasis; other concurrent active malignancy; uncontrolled diabetes mellitus; pregnancy or lactation, other concomitant serious medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave written informed consent before enrollment.

Study Evaluations

Pretreatment baseline evaluation included a complete medical history and physical examination, complete blood cell count (CBC), blood chemistry studies, chest radiography, computed tomography (CT) of the chest, CT or ultrasound study of the abdomen, CT or magnetic resonance imaging of the brain, bone scintigraphy and electrocardiography. Complete blood cell count and blood chemistry studies were repeated weekly.

Treatment Schedule

Patients were treated intravenously with irinotecan 60 mg/m^2 on days 1 and 8 and cisplatin 60 mg/m^2 on day 1. Irinotecan was reconstituted in 250 mL of normal saline or 5% dextrose in water and infused over 60 minutes. Cisplatin was administered over 60 minutes with adequate hydration, usually ≥2500 mL infusion. Diuretics and antiemetics were given at the discretion of each treating physician. Therapy was repeated every 3 weeks for at least 4 cycles unless there was evidence of disease progression, unacceptable toxicity or withdrawal of consent.

Dose Modification

Dose modifications were made in response to any myelosuppression and nonhematologic toxicity that occurred. If a leukocyte count of less than 3000/mm^3 or a platelet count of less than 100,000/mm^3 was determined or if the patient had fever (≥38.0°C) or grade ≥1 diarrhea, or other grade ≥3 toxicity on days 8 through 15, irinotecan was withheld. Irinotecan was decreased by 10 mg/m^2 in the subsequent cycle if a leukocyte nadir count of less than 1000/mm^3 or a platelet nadir count less than 50,000/mm^3 or grade ≥2 diarrhea, or other grade ≥3 nonhematologic toxicity (excluding electrolytes imbalance, nausea, appetite loss, fatigue, and hair loss) was observed during the previous course of treatment. Cisplatin was decreased by 10 mg/m^2 in the subsequent cycle if grade ≥2 creatinine or other grade ≥3 nonhematologic toxicity (excluding electrolyte imbalance, nausea, appetite loss, fatigue, and hair loss) was observed during the previous course of treatment.

Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for response assessment.[9] Toxicity was evaluated according to National Cancer Institute-Common Toxicity Criteria (version 2.0). An independent review was conducted to validate the eligibility of the patients, staging, response, and toxicity.

Statistical Analysis

The primary end point of this study was the estimate of the response rate. We assumed that the response rate was 45% from a prior trial reported by Negoro et al[8] and the distance from the point estimate to the 95% confidence interval (CI) was 20%. Thus, 24 evaluable patients were required. If 11 out of 24 evaluable patients have response, the response rate is 46% with the exact 95% CI of 26% to 67%. Durations of response and survival were measured from the first day of the treatment, and the overall survival curve and progression-free survival curve were calculated by the method of Kaplan and Meier.[10]

RESULTS

Patient Characteristics

Between January and June 2003, 28 patients were entered in this study. Baseline characteristics of the evaluable patients were listed in Table 1. Twenty patients (74%) had stage IV disease and 11 patients (41%) had ECOG performance status of 0. Adenocarcinoma was the dominant histology (74%).

Treatment Administration

Patients received a median of 4 treatment cycles (range, 1–6 cycles). Seven patients received only 1 cycle of treatment because of adverse events (4 patients) and progressive disease (3 patients). A total of 92 cycles were given. Irinotecan administration on day 8 was withheld in 9 cycles (10%)

TABLE 1. Patients Characteristics

No. patients	27
Age (years)	
Median	63
Range	38–72
Gender (% of patients)	
Male	19 (70)
Female	8 (30)
Performance status (ECOG) (% of patients)	
0	11 (41)
1	16 (59)
Stage (% of patients)	
IIIB	7 (26)
IV	20 (74)
Histology (% of patients)	
Adenocarcinoma	20 (74)
Squamous cell carcinoma	7 (26)

ECOG, Eastern Cooperative Oncology Group.

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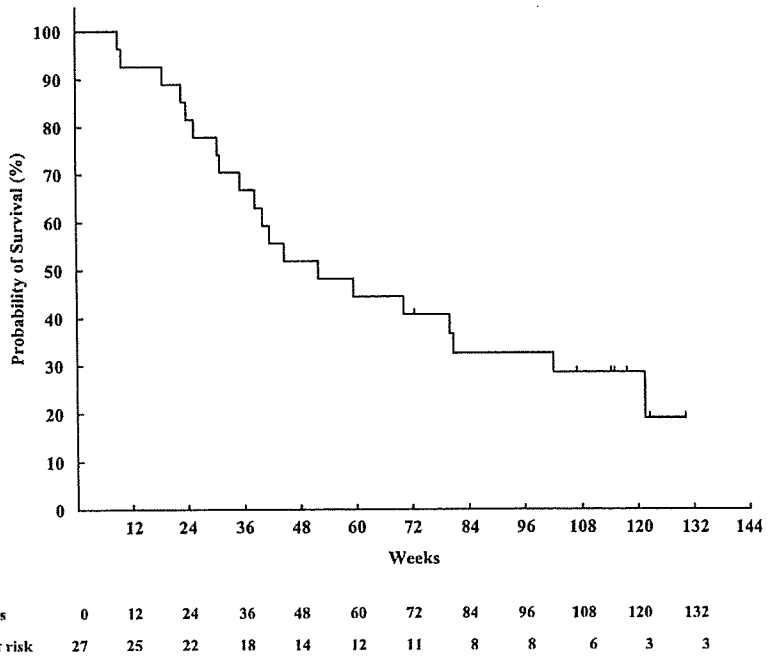

FIGURE 1. Kaplan-Meier survival curve of 27 evaluable patients with advanced nonsmall cell lung cancer.

and dose reduction was made in 41 cycles (45%). The dose of cisplatin was reduced in 18 cycles (20%). The dose-intensity of irinotecan was 34 mg/m^2/wk (85% of the planned dose) and cisplatin 19 mg/m^2/wk (95% of the planned dose).

Response and Survival

Three of 7 patients (43%) with stage IIIB disease achieved partial response while 5 of 20 patients (25%) with stage IV disease showed partial response, with an overall response rate of 30% (95% CI, 14–50%). The response rate for adenocarcinoma and squamous cell carcinoma were 20% and 57%, respectively. Thirteen patients showed stable disease and 6 had progressive disease. No complete response was seen. The median duration of response was 16 weeks (range, 10–26 weeks). The median survival time for all patients was 52 weeks and a 1-year and 2-year survival rate was 48% (95% CI, 29–67%) and 29% (95% CI, 11–46%), respectively (Fig. 1).

Toxicity

The major adverse events were shown in Table 2. Hematologic toxicity was the principal toxicity of this regimen. Grade 4 neutropenia and anemia was observed in 8 patients (30%) and 1 patient (4%), respectively. There was no grade 4 leukopenia. Thrombocytopenia was predominantly mild (grade 1–2) and only 1 patient had grade 3 toxicity. Nonhematologic toxicities mainly consisted of diarrhea, nausea and vomiting, and anorexia. Grade 3 diarrhea was observed in 6 patients (22%) but no patient had grade 4 diarrhea. Grade 3 infection was observed in 4 patients (15%) and 1 patient had febrile neutropenia. There were no treatment-related deaths.

TABLE 2. Major Toxicities by Patient and Cycle

	Grade 3/4	
	Patients (%), n = 27	Cycles (%), n = 92
Neutropenia	8/8 (59)	27/8 (38)
Leukopenia	8/0 (30)	10/0 (11)
Anemia	5/1 (22)	7/1 (9)
Thrombocytopenia	1/0 (4)	1/0 (1)
Diarrhea	6/0 (22)	9/0 (10)
Nausea	8/0 (30)	9/0 (10)
Vomiting	2/0 (7)	2/0 (2)
Infection	4/0 (15)	4/0 (4)
Anorexia	9/0 (33)	13/0 (14)

DISCUSSION

In this phase II study, we have explored the potential advantages of 3-week schedule of irinotecan and cisplatin in patients with advanced NSCLC and have achieved a 30% response rate. In the chemotherapy of advanced lung cancer, irinotecan is usually given weekly on days 1, 8, and 15 in a combination with cisplatin and the treatment cycle is repeated every 4 weeks. Masuda et al reported a 48% response rate in 4-week scheduled therapy for irinotecan and cisplatin in a phase II study.[7] Based on this result, 2 randomized phase III studies have been conducted in Japan. Negoro et al[8] compared a combination of irinotecan and cisplatin with a combination of cisplatin and vindesine and irinotecan alone while Niho et al[11] compared a combination of irinotecan and cisplatin with a combination of cisplatin and vindesine. The response rates of irinotecan and cisplatin were 44% and 29%,

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respectively. Despite the difference of the response rates between the 2 phase III studies, the median survival times (50 versus 45 weeks) and the 1-year survival rates (47 versus 43%) were comparable between the 2 studies. These 2 studies have revealed that a combination therapy with irinotecan and cisplatin given every 4 weeks produced comparable survival to a combination of cisplatin and vindesine in patients with advanced NSCLC.[8,11] Furthermore, Negoro et al reported that in the subgroup analysis, the combination of irinotecan and cisplatin was superior to the combination of cisplatin and vindesine in survival prolongation in patients with stage IV disease.[8] The response rate of 30% in our study is between those of the 2 phase III studies evaluating 4-week scheduled therapy for irinotecan and cisplatin. This, plus the median survival time of 52 weeks and the 1-year survival of 48% in our study are encouraging.

Two groups evaluated 3-week scheduled therapy for irinotecan and cisplatin in patients with advanced NSCLC in the phase II studies.[12,13] Takeda et al administered irinotecan (75 mg/m^2) and cisplatin with antilate-diarrheal program and reported the response rate of 63%.[12] Han et al evaluated 2 sequences of 3-week scheduled therapy for irinotecan (80 mg/m^2) and cisplatin without any antidiarrheal measures and reported the overall response rate of 47%.[13] These studies including our own suggest that 3-week cycle of irinotecan and cisplatin is effective in patients with advanced NSCLC. Recently, another randomized phase III study conducted in Japan has compared the 4-week scheduled therapy for irinotecan and cisplatin as the control arm with 3 platinum-based doublets with new agents (carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine).[14] This study has shown that 4-week scheduled therapy for irinotecan and cisplatin was comparable to other platinum doublet therapy with new agents in terms of response rate and survival with different toxic profiles. Further evaluation will be necessary to clarify whether 3-week scheduled therapy for irinotecan and cisplatin is superior in terms of survival and toxicity to 4-week scheduled therapy as well as other platinum doublet therapy with new agents in the treatment of advanced NSCLC.

Neutropenia was the most prominent toxicity in this study and grade 4 neutropenia was observed in 8 patients (30%). This incidence was lower than in other studies evaluating the 4-week scheduled therapy for irinotecan and cisplatin, in which the incidence of grade 4 neutropenia was 37% to 38%.[7,8] The incidence of grade 4 neutropenia in the 4-week scheduled therapy for irinotecan and cisplatin was lower than in the platinum-based doublet in a combination with a new agent such as paclitaxel, gemcitabine, vinorelbine, and docetaxel.[15–18] In 3-week scheduled therapy, the incidence of grade 4 neutropenia is further reduced. Leukopenia was usually less severe than neutropenia. In our study, grade 3 leukopenia was observed in 30% of the patients and there was no grade 4 leukopenia observed. Anemia and thrombocytopenia were relatively mild with this regimen. Diarrhea was the most troublesome nonhematologic toxicity in irinotecan-containing regimens.[5,19] We observed grade 3 diarrhea in 22% of our patients and no patient experienced grade 4 diarrhea. Antilate-diarrheal program may be beneficial to further reduce moderate to severe diarrhea.[12]

Another aim of this study was to evaluate dose-intensity as a measure of the feasibility of a 3-week schedule of irinotecan and cisplatin. In the previous phase III study, the dose intensity of irinotecan was only 30 mg/m^2/wk (67% of the planned dose).[8] We planned to administer irinotecan at a dose of 60 mg/m^2 on days 1 and 8, giving the planned dose-intensity of irinotecan of 40 mg/m^2/wk. The actual dose-intensity of irinotecan administered was 34 mg/m^2/wk (85% of the planned dose). In contrast, the actual dose intensities of irinotecan in the studies of Takeda et al and Han et al were 48.5 mg/m^2/wk and 44 mg/m^2/wk, respectively.[12,13] One explanation for this difference is that we reduced the dose of irinotecan based on the toxicity in the previous cycle while they did not reduce the dose of irinotecan based on the toxicity in the previous cycle. Despite this difference, these data suggest that 3-week cycle of irinotecan and cisplatin is better tolerated than the 4-week scheduling of irinotecan and cisplatin with greater irinotecan dose-intensity.

In summary, this study suggests that therapy with a 3-week cycle of irinotecan and cisplatin is effective and feasible in the treatment of advanced NSCLC. Further evaluation of the combination of irinotecan and cisplatin, at the doses and schedule used in this study, is warranted in advanced NSCLC.

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Phase II Study of Weekly Paclitaxel for Relapsed and Refractory Small Cell Lung Cancer

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Abstract. *The purpose of this study was to evaluate the efficacy and toxicity of single-agent paclitaxel given weekly to patients with relapsed and refractory small cell lung cancer (SCLC). Patients were treated with 80 mg/m^2 paclitaxel administered weekly for 1 h for 6 weeks in an 8-week cycle. Twenty-two patients were enrolled, 21 of whom were eligible. The patient characteristics included: 20 males, 1 female; median age 66 years (range 48 - 75); performance status 0/1 in 19 and 2 in 5 patients. Grade 3/4 leukopenia and neutropenia occurred in 47.5% and 64%, respectively. Other grade 3/4 toxicities included infection, skin rash, neuropathy and pulmonary toxicity. There were 5 partial responses in 3 out of the 11 sensitive cases and 2 out of the 10 refractory cases, respectively. Paclitaxel, administered as a weekly infusion at a dose of 80 mg/m^2, was effective in treating relapsed and refractory SCLC.*

More than 95% of patients with small cell lung cancer (SCLC), who are initially treated with paclitaxel 80 mg/m^2, present a relapse and their response to a second-line therapy is poor. The responses obtained are usually brief, and the median survival is generally less than 4 months (1). Nevertheless, second-line chemotherapy may provide a significant palliation of symptoms and does result in a prolongation of survival in many patients.

The activity of paclitaxel as a single agent has been investigated in both previously-untreated and -treated SCLC patients. Two phase II trials were conducted to investigate its efficacy as a first-line treatment for SCLC. In a trial conducted by the Eastern Cooperative Oncology Group (ECOG), Ettinger *et al.* administered 250 mg/m^2 paclitaxel as a 24-h infusion to 36 patients (2), among whom 11 partial responses were observed. Kirschling *et al.* obtained a similar response rate, 41%, in a group of 37 patients on an identical paclitaxel dose-schedule (3). The results of a phase II study in previously treated patients were reported by Smit *et al.* (4). All 24 patients in that trial developed progressive disease within 3 months of receiving at least one previous chemotherapy regimen. Seven patients (29%) had a partial response to 175 mg/m^2 paclitaxel as a 3-h infusion. These data show that paclitaxel exhibits single-agent efficacy in SCLC comparable to that of the best agents. The results of Smit *et al.'s* study in patients with refractory SCLC are particularly impressive, since most response rates reported with single-agent or combination regimens in this population have been less than 15%. However, life-threatening toxicity occurred in 4 of these patients, 2 of whom experienced hematological toxicity.

Recent reports of the activity and tolerability of weekly doses of paclitaxel have generated a great deal of clinical interest. Weekly paclitaxel therapy has generally been quite well tolerated, causing minimal toxicity and no apparent cumulative myelosuppression. Substantial evidence from clinical trials indicates that weekly paclitaxel is effective and generally well tolerated as both a first- and second-line treatment for advanced NSCLC. A phase I/II trial by Koumakis *et al.* in a second-line setting tested weekly paclitaxel infused for the first 6 weeks of each 8-week cycle, and demonstrated that a paclitaxel dose escalation from 60 mg/m^2 to 90 mg/m^2 was tolerated (5).

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Fennelly *et al.* reported a recommended dose of 80 mg/m^2 administered weekly for 6 weeks of an 8-week cycle in patients with recurrent ovarian cancer (6).

Based on this evidence, a phase II trial of 80 mg/m^2 weekly paclitaxel as a 1-h infusion for 6 consecutive weeks followed by 2 weeks without treatment (8-week cycle) was conducted in patients with relapsed SCLC. The objective of this study was to evaluate the efficacy and safety of weekly paclitaxel in patients with relapsed and refractory SCLC. The primary end-point was the response rate, while the secondary end-points were the toxicity profile and survival rate.

Patients and Methods

Patient selection. Patients who met all of the following criteria were considered eligible: a) histological or cytological proof of SCLC with no response to prior chemotherapy or progression after chemotherapy, b) measurable disease, c) most recent cytotoxic treatment less than 4 weeks before entry, d) ECOG performance status 0-2, e) age ≤75 years, f) adequate bone marrow function (leukocyte count ≥4,000/μl, hemoglobin level ≥9.0 g/dl and platelet count ≥100,000/μl), hepatic function (transaminases ≤2.5 times the upper limit of normal, bilirubin level ≤1.5 mg/dl), and renal function (creatinine ≤1.5 times upper limit of normal) and g) arterial oxygen partial pressure ≥60 torr. Excluded patients were those with any active concomitant malignancy, symptomatic brain metastases, a past history of drug allergy reactions, complication by interstitial pneumonia, treatment with non-steroidal anti-inflammatory drugs or steroids or other serious complications such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites or serious active infection. All patients gave written informed consent and our institutional review board for human experimentation approved the protocol.

Treatment schedule. Paclitaxel was infused intravenously (*i.v.*). over a 1-h period at a dose of 80 mg/m^2 each week for 6 consecutive weeks followed by a 2-week break. This 8-week period comprised one treatment cycle. Premedication consisted of 20 mg dexamethasone, 50 mg ranitidine and 50 mg diphenhydramine given *i.v.* 30 min prior to paclitaxel.

If the leukocyte count fell below 2,000/μl or the neutrophil count fell below 1,000/μl, recombinant granulocyte colony-stimulating factor (rhG-CSF) at a daily dose of 2 μg/kg was administered until the leukocyte count recovered to ≥10,000/μl, except on the days of paclitaxel administration. The toxicity assessment was based on the National Cancer Institute – Common Toxicity Criteria version 2.0. If grade 3 leukopenia, grade 4 neutropenia, grade 2 neuropathy or other grade 3 non-hematological toxicities occurred, the dose of paclitaxel in subsequent cycles was reduced by 10 mg/m^2 from the planned dose. Paclitaxel was not administered if the leukocyte count was <2,000/μl, the platelet count was <5,000/μl, or if there was grade 3 nausea/vomiting, infection with a fever of more than 38°C, or other grade 2 non-hematological toxicities except alopecia. The treatment was discontinued if there was disease progression, grade 3 neuropathy, other grade 4 non-hematological toxicities or a 2 consecutive weeks without paclitaxel administration.

Evaluation of response and survival. The tumor response was classified according to the WHO criteria (7). A complete response (CR) was defined as the total disappearance of all measurable and assessable disease for at least 4 weeks. Partial response (PR) was defined as a ≥50% decrease in the sum of the products of the 2 largest perpendicular diameters of all measurable tumors lasting for at least 4 weeks without the appearance of any new lesions. No change (NC) was defined as a decrease of <50% or an increase of <25% in tumor lesions for at least 4 weeks with no new lesions. Progressive disease (PD) was defined as the development of new lesions or an increase of 25% in the sum of the products of the 2 largest perpendicular diameters of all measurable tumors. The overall survival was measured from the time of study entry until death.

Statistical methods. The median probability of survival was estimated by the method of Kaplan and Meier (8). This study was designed as a phase II study, with the response rate as the main end-point. According to the Simons minimax design, with a sample size of 20 our study had a 90% power to accept the hypothesis that the true response rate was greater than 25%, while a 10% significance sufficed for rejection of the hypothesis that the true response rate was less than 5% (9).

Results

Patient characteristics. Between December 1999 and February 2002, a total of 22 patients were enrolled in the study, 1 of whom was deemed ineligible due to age (>75 years), leaving a total of 21 patients assessable for toxicity, response and survival. The main demographic characteristics of the cohort are summarized in Table I. The patient cohort consisted of 1 female and 20 males with a median age of 66 years (range, 48 to 75). Four patients exhibited limited disease and 19 exhibited extensive disease at the start of treatment. The majority of the patients had received no prior surgical treatment, while 67% had received prior radiation therapy. All patients had been treated with some form of cisplatin- or carboplatin-based combination chemotherapy regimen. Eighteen patients had received prior etoposide-containing chemotherapy and 10 prior irinotecan-containing chemotherapy. The median number of previous chemotherapy regimens administered was 1 (range, 1 to 2). Among the 10 patients who proved refractory to chemotherapy, 5 had NC or PD on first- or second-line treatment, 2 had PR but experienced disease progression during treatment and 3 had a relapse within a 90-day treatment-free interval after completing their treatments.

Toxicity. The toxicity of the regimen is summarized in Table II. Neutropenia was the main toxicity, with 6 out of the 21 patients experiencing grade 4 neutropenia during the entire study. Grade 3 anemia was observed in 2 patients. One patient experienced grade 4 anemia, secondary to digestive tract bleeding. Thrombocytopenia remained infrequent throughout the study. No cases of grade 3 or 4 thrombocytopenia were observed and there was no evidence of cumulative hematological toxicity.

Table I. *Baseline characteristics of all patients.*

Baseline characteristics		No. of patients
Sex	Male / Female	20 / 1
Age (years)	Median (Range)	66 (48-75)
ECOG PS	0/1/2	5 /12 /4
Disease extent	LD/ ED	4 / 17
Previous treatment	Chemotherapy only	4
	Chemotherapy + radiotherapy	14
	Chemotherapy + others	3
Previous chemotherapy	Platinum + etopoisde +/- others	18
	Including irinotecan HCl	10
	Others	1
No. of previous chemotherapy regimens	1 / 2 / 3	16 / 4 / 1
Response to prior chemotherapy	CR / PR / NC / PD / NE	2 / 13 / 5 / 0 / 1

No.: number
PS: performance status, LD: limited disease, ED: extensive disease.

Table II. *Toxicity of treatment for all cycles.*

Toxicity	No. of patients with event by grade				
	G0	G1	G2	G3	G4
Nausea	12	7	2	0	0
Vomiting	19	1	1	0	0
Diarrhea	17	3	1	0	0
Constipation	10	5	6	0	0
Mucositis	21	0	0	0	0
Gastric ulcer	20	0	1	0	0
Fever	16	3	2	0	0
Fatigue	13	0	8	0	0
Skin rash	20	0	0	1	0
Infection	18	0	0	3	0
Neuropathy	9	9	1	2	0
Myalgia	16	4	1	0	0
Dyspnea	17	0	1	2	1
Hemoglobin	1	9	9	1	1
WBC count	2	1	8	8	2
Neutrophil count	0	5	2	8	6
Platelet count	16	5	0	0	0
GOT	12	7	2	0	0
GPT	16	4	1	0	0
Total bilirubin	19	1	1	0	0

Other grade 3 and 4 toxicities included infection, skin rash, neuropathy and pulmonary toxicity. Grade 1 or 2 neuropathy was seen in 10 patients, and greater than grade 2 was observed in 2 individuals. No hypersensitivity reactions were encountered. Grade 3 or 4 pulmonary toxicity was reported in 3 patients and was characterized by dyspnea. Life-threatening complications of grade 4 infection and grade 4 dyspnea were encountered in 1 patient, who experienced febrile neutropenia and respiratory failure secondary to pneumonia after the third weekly dose. He was treated with antibiotics and supportive measures, but the respiratory distress worsened and he died on day 41. One of 2 grade 3 pulmonary toxicities was pneumonitis, probably induced by paclitaxel, but was resolved by steroid therapy.

Response to treatment and survival. The responses to therapy are shown in Table III according to whether the patient had primary refractory disease or primary sensitive cancer that subsequently relapsed. Although 1 out of the 21 patients was not assessable for response, having died during the first cycle, a ≥50% decrease in the sum of the products of the 2 largest perpendicular diameters of the tumor was achieved in this patient. Five of the 22 patients had a PR, but no CRs were observed and the overall response rate was 23.8% (95% confidence interval, 5.59 to 42.03). When only evaluable patients were included in the analysis, however, the response rate improved to 25% (95% confidence interval, 6.02 to 43.98). Two PRs (20%) occurred in refractory cases and 3 PRs (27%) were achieved in sensitive cases. Four patients showed no change, and 1 exhibited disease progression. The survival analysis was performed in January 2003, by which point 10 patients had died and 2 were still alive. The median survival time (MST) was 5.8 months and the 1-year survival rate was 13.4% (Figure 1).

Table III. *Response data.*

		No. of patients					Response rate (%)
		CR	PR	NC	PD	NE	
Total	21	0	5	4	11	1	23.8
Sensitive	11	0	3	3	5	0	27.3
Refractory	10	0	2	1	6	1	20.0

CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; NC = no change.

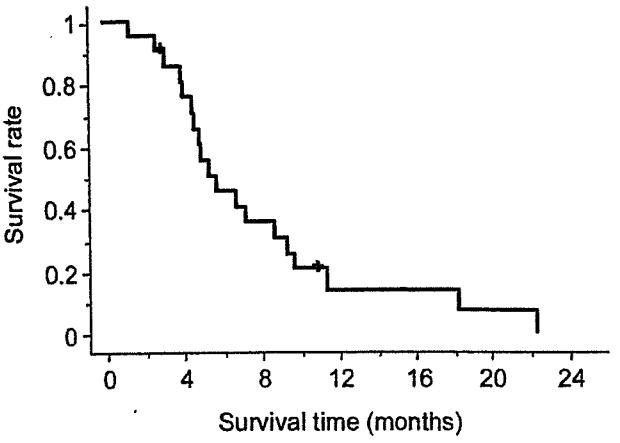

Figure 1. *Overall survival.*

Discussion

Since the outlook for SCLC patients who receive second-line therapy is poor, several new drugs, such as paclitaxel, docetaxel, gemcitabine, vinorelbine, topotecan and irinotecan, are currently under investigation. The new chemotherapy agents that have been most extensively evaluated in SCLC are the topoisomerase I inhibitors, including topotecan and irinotecan. Von Pawel *et al.* conducted a phase III study comparing single-agent topotecan with cyclophosphamide, doxorubicin and vincristine (CAV) in patients with progression at least 60 days after initial therapy and reported response rates of 24.3% for topotecan and 18.3% for CAV with a median survival time (MST) of 25.0 and 24.7 weeks, respectively, and found that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC (10). Two studies of irinotecan in patients with refractory SCLC have been reported in Japan and the response rates in both studies were high, *i.e.*, 50% in 16 patients, and 47% in 15 patients, respectively (11, 12). We therefore consider that topoisomerase I inhibitors, such as topotecan and irinotecan, are key drugs in the second-line treatment of SCLC. However, the number of SCLC patients treated with an irinotecan-containing regimen as first-line chemotherapy has increased in Japan since, in a randomized phase III trial in Japan (13), a combination of irinotecan and cisplatin was shown to yield better survival than the standard etoposide and cisplatin regimen in patients with untreated extensive SCLC. Therefore, the search for effective drugs, other than topoisomerase I inhibitors, for previously treated SCLC, especially refractory SCLC, must be continued.

Single-agent paclitaxel, at a dose of 175 mg/m^2 as a 3-h infusion every 3 weeks in patients with previously treated SCLC, produced a response rate of 29% and an MST of 100 days (4). The results of our phase II study demonstrated that weekly paclitaxel at a dose of 80 mg/m^2 yielded a similar response rate of 23.8% and a much better MST of 5.8 months than that of paclitaxel given every 3 weeks. Because the antiproliferative activity of paclitaxel is cell-specific, prolonging patient exposure to a low dose of the drug beyond a threshold concentration is ultimately more efficacious than a short-term exposure to higher drug concentrations, a hypothesis supported by *in vitro* experiments with a variety of cell lines and suggested by the results of clinical studies. As clinical experience with paclitaxel treatment of various types of tumors has progressed, so has the use of weekly regimens at lower doses administered as 1-h infusions, as opposed to standard higher doses delivered once every 3 weeks as 3-h infusions.

A response rate of more than 10% is considered evidence of drug efficacy in previously-treated SCLC patients (14). Before newer drugs, such as topoisomerase I inhibitors, taxane, gemcitabine and vinorelbine were introduced, salvage chemotherapy did not usually prolong survival in SCLC and MSTs after relapse were 2.5 – 3.9 months (1). Single-agent phase II trials of gemcitabine, docetaxel and vinorelbine in patients with relapsed or refractory SCLC have been reported. Smyth *et al.* (15), using a 100 mg/m^2 dose of docetaxel, obtained a response rate of 25% in 28 assessable patients who had received prior chemotherapy. A trial of gemcitabine in 46 previously-treated patients yielded an 11.9% response rate (16) and vinorelbine provided response rates of 12% and 16% in second-line patients with sensitive disease (17,18). Thus, the MST of 5.8 months and response rate of 23.8% in this study compare favorably with those of published single-agent trials in relapsed or refractory SCLC.

The toxicity profile noted in this trial was predictable based on the toxicity profile previously described in weekly paclitaxel trials, neutropenia being the major toxic effect. All side-effects, except fatal neutropenic pneumonia in 1 case, were manageble. Grade 3 or 4 neutropenia occurred in 14 of the patients in our study but was immediately alleviated by treatment with G-CSF. Grade 3 or 4 anemia occurred in 1 patient, but there was no grade 3 or 4 thrombocytopenia in our study. The incidence of grade 3/4 myelosuppression was considered tolerable. There were 3 cases of grade 3 or 4 pulmonary toxicity, 2 of which occurred due to bacterial infection. This regimen required a dose of 20 mg of dexamethasone weekly as premedication. We believe that this occurrence of bacterial pneumonia might be related to the use of steroids.

Testing new drugs in previously-treated patients has the clear advantages of determining the degree of non-cross resistance with other drugs. Its greatest disadvantage is the risk of a considerable dose reduction (especially of myelotoxic drugs) to avoid extensive hematological side-

effects, perhaps resulting in doses that are too low to fairly evaluate the drug. Since a weekly administration of paclitaxel causes only mild myelosuppression and as there may be no cross resistance with platinum, etoposide, irinotecan, or topotecan, which are usually used to treat SCLC, we find this regimen suitable for previously-treated SCLC.

In summary, the weekly paclitaxel regimen is moderately effective in SCLC patients who have received prior chemotherapy. Based on the statistical design of this study, the 5 PR observed suggest that weekly paclitaxel warrants further evaluation in this patient population. Additional investigations will serve to clarify the role of this agent, either alone or in combination with other agents. Combining paclitaxel with other agents with proven non-cross resistance such as irinotecan, topotecan, or gemcitabine or new target-based agents is the next step needed to evaluate second-line situations, especially in patients with resistant disease.

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Clinical development of EGFR-tyrosine kinase inhibitors in Japan

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Abstract Although the initial impact of the epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) gefitinib may have been less than spectacular in the field of non-small cell lung cancer (NSCLC), this EGFR-TKI does offer a therapy that, at least in the short term, markedly reduces tumors without bone marrow suppression including neutropenia and without causing severe nausea and vomiting even in NSCLC patients with the worst prognosis. This raises the possibility of putting the disease under control if only temporarily. Now we must be aware that overcoming gene mutation in lung cancer is the next significant milestone for new therapeutics. This report discusses clinical trials of EGFR-TKIs focusing on Japanese contributions to current knowledge, *EGFR* mutation, and future directions. A Japanese phase I clinical trial saw the first super-responders to gefitinib. Two randomized phase II trials identified Japanese, females, and those with adenocarcinoma of the lung as specific populations sensitive to gefitinib. Unexpectedly, in the context of first-line chemotherapy four phase III trials gave completely negative results for additional clinical benefit by EGFR-TKIs combined with standard chemotherapy. However, subset analysis suggested efficacy of this treatment strategy in nonsmokers and patients harboring activated-type *EGFR* mutations. In the settings of second-line and later therapy, two independent randomized placebo-controlled trials, BR.21 with erlotinib and ISEL with gefitinib, revealed better duration of overall survival, time to progression, and response rate in the EGFR-TKI versus control groups, although the result was nonsignificant in the latter study. Data suggesting that adenocarcinoma, Asian race, female, and nonsmoker are associated with better response to EGFR-TKI may be closely related with phenotype of *EGFR* mutations, making this parameter a "response predictive marker." On the other hand, some reports have stated that gene amplification of *EGFR* by FISH analysis shows better correlation with clinical benefit of EGFR-TKIs than that assessed by other means in large-scale phase III trials (BR21 and ISEL). Further validation of response predictive markers is needed. Recent studies of EGFR-TKIs in NSCLC provide novel biological insights and have given birth to the concept of patient selection for this disease. Further investigation of the biological significance of *EGFR* mutation and its validation as response predictive marker will lead to better treatments to come for NSCLC.

Keywords EGFR-TKI · Gefitinib · Erlotinib · *EGFR* mutation

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Introduction

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been clinically available for the treatment of nonsmall cell lung cancer

(NSCLC) for the past 4 years. In the course of clinical development of EGFR-TKIs, in comparison with conventional anticancer agents many unexpected findings were observed such as relating to tumor shrinkage, specific responder subsets, adenocarcinomatous disease, and gene mutation. Hence although knowledge concerning EGFR-TKIs and *EGFR* gene mutation is advancing in the laboratory setting, clinically it is unclear how we should use EGFR-TKIs in NSCLC and which patients might benefit most from these agents. In this review, clinical trials of EGFR-TKIs are recounted and a key factor for drug sensitivity, *EGFR* mutation, is discussed.

Clinical trials of EGFR-TKIs

Four phase I trials of EGFR-TKI including one Japanese study were performed in a total of 254 patients [4, 8]. These trials defined diarrhea and liver function test abnormality as dose-limiting factors. Five of 23 patients demonstrated partial responses (PRs) without dose–response tendency (Table 1). Toxicity profiles were quite different to those commonly observed with conventional anticancer agents. Ten percent of patients failed treatment at doses >600 mg/day and these early studies could not identify an optimal dosing schedule. Based on the results of phase I, the phase II IDEAL1 study was conducted in 210 previously treated advanced NSCLC patients in Japan, Australia, and Europe [1]. In this large-scale international study, a similar objective tumor response rate (20%) to those of previous studies was observed. There was no difference of clinical response between patients receiving 250 mg/day and those on 500 mg/day, whereas toxicity was more severe in the higher-dose group. Subset analysis revealed startling clinico-pathological subpopulations with especially high drug sensitivity to EGFR-TKI namely Japanese patients, females, nonsmokers, and those with adenocarcinoma (Table 2). In particular, Japanese females exhibited an overall response rate >50% in this analysis. For the first time, unlike conventional anticancer agents these results suggested that EGFR-TKIs are efficacious in specific subpopulations. While that phase II trial was ongoing, two large phase III trials in untreated NSCLC were begun in the USA and Europe [2, 3]. The rationale of these two clinical trials, INTACT1 and INTACT2, was based on preclinical studies that suggested synergistic effects of taxane plus gefitinib against cancer cells in vitro and in vivo. Hence, gefitinib or placebo was added onto standard chemotherapy regimens cisplatin/gemcitabine (INTACT1) and carboplatin/paclitaxel (INTACT2) [2, 3]. Both trials showed that there was no evidence for prolonged survival time with add-on gefitinib for either standard chemotherapy schedule. The same negative result was observed in another phase III trial using the same design with erlotinib as well as gefitinib [5]. However, in this trial subset analysis suggested enhanced efficacy of EGFR-TKI therapy among nonsmokers and those harboring activated-type *EGFR* mutations. Two subsequent studies of second-line and later treatment, BR.21 and ISEL, gave conflicting results for overall survival time, time to progression, and response rate: the former suggested additional benefit of add-on EGFR-TKI and the latter gave negative results [10, 11].

Table 1 Antitumor activity of gefitinib in Japanese phase I study

	Total	PR (%)
All cases	31	5 (16)
NSCLC	23	5 (22)
Histology		
Adenocarcinoma	19	5 (26)
Squamous cell carcinoma	4	0 (0)
Gender		
Male	15	1 (7)
Female	8	4 (50)

PR partial response

To clarify the clinical benefit of EGFR-TKIs in *EGFR* mutation-positive NSCLC, prospective phase II (WJTOG0403) and phase III (WJTOG3405) studies are now underway (Fig. 1). The results of these investigations aim to give us data that will enable us better to understand *EGFR* mutational status and whether mutant EGFR phenotype confers clinical benefit in patients.

EGFR mutation and drug sensitivity

To use gefitinib effectively in clinical settings we must first identify patient populations who respond well to this agent. As mentioned above, data from IDEAL1 revealed that gefitinib is highly effective in Japanese, females, adenocarcinomatous histology, good performance status (PS), and nonsmokers (Table 2). Since the target molecule of EGFR-TKIs is EGFR, some correlation between expression patterns of EGFR protein and clinical outcome was widely speculated. However, IDEAL1 and 2 found no correlation between these parameters clinically, questioning the concept of molecular-targeting drugs. However, the answer to this question was provided by the striking findings regarding *EGFR* gene mutations [7, 9]. These *EGFR* mutations, located on the ATP binding site (exon 19–21) of

Table 2 Overall survival by patient characteristics: IDEAL1

Characteristic	Evaluable (*n*)	MST, days (95%CI)	*P*-value[a]	ORR, % (*n*)
All patients	209	241 (205–276)		18.7 (39/208)
Dose				
250 mg/day	103	232 (161–318)	0.716	18.4 (19/103)
500 mg/day	106	243 (203–309)		19.0 (20/105)
Age				
<65 years	145	238 (198–284)	0.5598	19.4 (28/144)
>65 years	64	241 (188–371)		17.2 (11/64)
Gender				
Female	61	397 (261–439)	0.0025	34.4 (21/61)
Male	148	212 (161–243)		12.2 (18/147)
WHO PS				
0–1	182	268 (234–318)	<0.0001	21.0 (38/181)
2	27	83 (57–121)		3.7 (1/27)
Histology				
Adenocarcinoma	131	300 (236–371)	<0.0001	26.0 (34/131)
Other	78	198 (129–232)		6.5 (5/77)
Smoking history				
Yes	104	186 (127–241)	<0.0001	12.5 (13/104)
No	53	414 (357–534)		37.7 (20/53)

MST mean survival time, *ORR* overall response rate

[a] Log-rank test

EGFR tyrosine kinase domain, are missense or deletion mutations causing substitution or partial deficiency of amino acid. Based on the results of basic studies, structural changes of the ATP binding site were found to increase binding affinity for ATP and gefitinib. In other words, under physiological conditions *EGFR* mutations are activating mutations that constitutively increase tyrosine kinase activity, and it is speculated that signals via EGFR are thereby abnormally enhanced and have greater impact on malignant transformation such as cancer cell proliferation. Fortunately, since these mutations are thought to have more highly augmented binding affinity for gefitinib than for ATP, they may display overwhelmingly high sensitivity induced by EGFR-TKIs. What is surprising is the correlation between frequency of *EGFR* mutations and clinical antitumor effects. We compared mutation rates and projected response rates obtained from IDEAL 1 and 2 and from 154 subjects in the clinical study in which our institute participated, and found that the *EGFR* mutation was highly correlated with clinical response (Table 3). In addition, it was reported at the American Society of Clinical Oncology (ASCO) meeting 2005 that *EGFR* gene mutation is closely related to

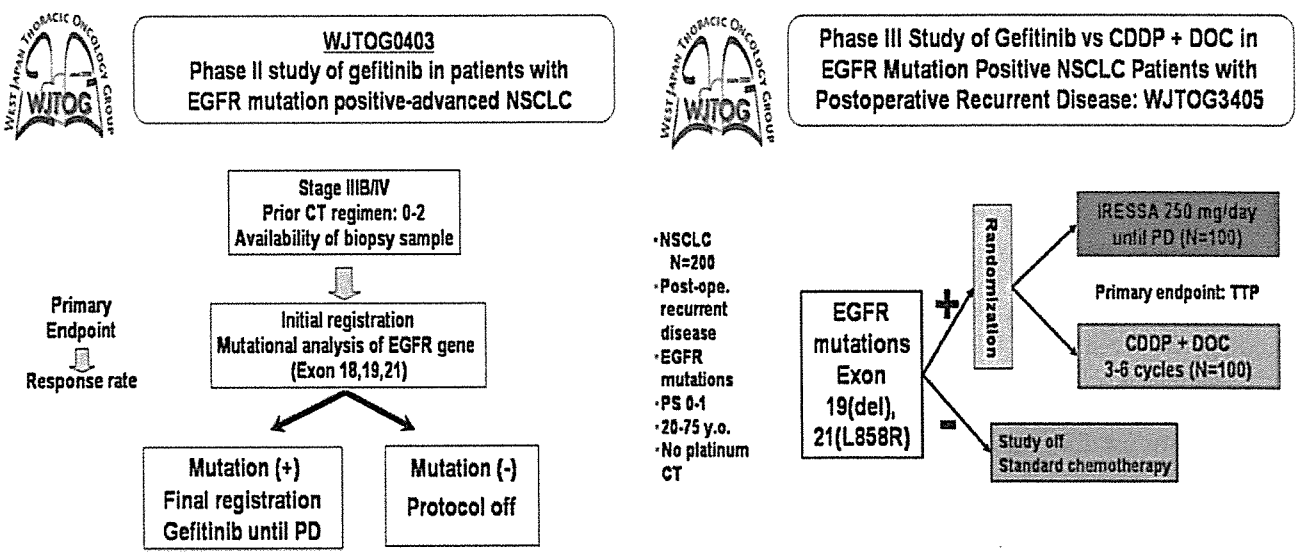

Fig. 1 Trial design of two ongoing prospective phase II (WJTOG0403) and phase III (WJTOG3405) studies investigating clinical benefit of EGFR-TKIs in *EGFR* mutation-positive NSCLC