Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer

By Masahiro Fukuoka, Seiji Yano, Giuseppe Giaccone, Tomohide Tamura, Kazuhiko Nakagawa, Jean-Yves Douillard, Yutaka Nishiwaki, Johan Vansteenkiste, Shinzoh Kudoh, Danny Rischin, Richard Eek, Takeshi Horai, Kazumasa Noda, Ichiro Takata, Egbert Smit, Steven Averbuch, Angela Macleod, Andrea Feyereislova, Rui-Ping Dong, and José Baselga

Purpose: To evaluate the efficacy and tolerability of two doses of gefitinib (Iressa [ZD1839]; AstraZeneca, Wilmington, DE), a novel epidermal growth factor receptor tyrosine kinase inhibitor, in patients with pretreated advanced non–small-cell lung cancer (NSCLC).

Patients and Methods: This was a randomized, double-blind, parallel-group, multicenter phase II trial. Two hundred ten patients with advanced NSCLC who were previously treated with one or two chemotherapy regimens (at least one containing platinum) were randomized to receive either 250-mg or 500-mg oral doses of gefitinib once daily.

Results: Efficacy was similar for the 250- and 500-mg/d groups. Objective tumor response rates were 18.4% (95% confidence interval [CI], 11.5 to 27.3) and 19.0% (95% CI, 12.1 to 27.9); among evaluable patients, symptom improvement rates were 40.3% (95% CI, 28.5 to 53.0) and 37.0% (95% CI, 26.0 to 49.1); median progression-free survival times were 2.7 and 2.8 months; and median overall survival times were 7.6 and 8.0 months, respectively. Symptom improvements were recorded for 69.2% (250 mg/d) and 85.7% (500 mg/d) of patients with a tumor response. Adverse events (AEs) at both dose levels were generally mild (grade 1 or 2) and consisted mainly of skin reactions and diarrhea. Drug-related toxicities were more frequent in the higher-dose group. Withdrawal due to drug-related AEs was 1.9% and 9.4% for patients receiving gefitinib 250 and 500 mg/d, respectively.

Conclusion: Gefitinib showed clinically meaningful antitumor activity and provided symptom relief as second- and third-line treatment in these patients. At 250 mg/d, gefitinib had a favorable AE profile. Gefitinib 250 mg/d is an important, novel treatment option for patients with pretreated advanced NSCLC.

J Clin Oncol 21:2237-2246.

LUNG CANCER is the most common cause of cancer deaths in both men and women worldwide.[1] Despite advances in treatment, such as combination chemotherapy and chemoradiation, survival has improved very little over the past few decades.[2] A meta-analysis demonstrated that the median survival time for patients with advanced disease receiving cisplatin-based chemotherapy is around 6 months.[3] The 5-year survival rate for all stages is less than 15%.[4] Prognosis is particularly poor for patients who have progressive disease following chemotherapy; for non–small-cell lung cancer (NSCLC) patients receiving best supportive care (BSC) after 1 or more prior chemotherapy regimen, median survival time is just 16 weeks, with a 1-year survival rate of 16%.[5]

Recently, it has become generally accepted that systemic chemotherapy is beneficial in terms of improved survival and quality of life (QoL) in those with advanced NSCLC.[3,6] As more patients receive first-line chemotherapy, the need for effective second-line therapy is increasing. Currently, docetaxel, having demonstrated survival benefits over BSC, is the only approved treatment in the United States and the European Union for patients who have been failed by previous platinum-based chemotherapy.[7]

Patients with late-stage NSCLC are often symptomatic, with specific pulmonary problems (eg, cough, breathlessness, hemotypsis) and general symptoms (eg, fatigue, weight loss) that can

From the Kinki University School of Medicine, Osaka City University School of Medicine, and AstraZeneca, Osaka, Tokushima University School of Medicine, Tokushima, National Cancer Center, Central Hospital, and Japanese Foundation for Cancer Research, Tokyo, National Cancer Center, East Hospital, Chiba, Kanagawa Cancer Center, Yokohama, and National Shikoku Cancer Center, Matsuyama, Japan; C.R.L.C.C. Rene Gauducheau, Saint-Herblain, France; University Hospital Gasthuisberg, Leuven, Belgium; Centre for Developmental Cancer Therapeutics, Melbourne, Australia; Mary Potter Oncology Centre, Pretoria, South Africa; Academic Hospital Free University, Amsterdam, the Netherlands; AstraZeneca, Wilmington, DE; AstraZeneca, Alderley Park, United Kingdom; and Vall d'Hebron University Hospital, Barcelona, Spain.

Submitted October 4, 2002; accepted January 28, 2003.

The authors wish to disclose the following conflicts of interest statement: José Baselga has been in receipt of a research grant from AstraZeneca and honoraria to attend advisory boards and to give talks on ZD1839; Johan Vansteenkiste has received honoraria from AstraZeneca to attend advisory boards; Jean Yves Douillard has received honoraria for participating in advisory boards or symposia; Giuseppe Giaccone has received honoraria and research grants; and Danny Rischin has been in receipt of honoraria and travel grants from AstraZeneca. Steven Averbuch, Angela Macleod, Andrea Feyereislova, and Rui-Ping Dong were employed by AstraZeneca at the time of study completion, and as such, may hold stock in the company. All other authors have nothing to declare.

Address reprint requests to Masahiro Fukuoka, MD, Fourth Department of Internal Medicine, Kinki University School of Medicine, 377-2 Ohnohigashi Osakasayama, Osaka 589, Japan; email: mfukuoka@med.kindai.ac.jp.

0732-183X/03/2112-2237/$20.00

cause extreme distress to the patient. Therefore, improvements in disease-related symptoms and QoL are the key desired outcomes of medical management.[8] Effective, palliative, low-toxicity treatments for patients with advanced NSCLC are needed.

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because it is expressed or highly expressed in a variety of tumors, including NSCLC.[9,10] Furthermore, high levels of EGFR expression have been associated with a poor prognosis in lung cancer patients in several studies.[11-13] EGFR-targeted cancer therapies are currently being developed; strategies include inhibition of the intracellular tyrosine kinase domain of the receptor by small molecules such as gefitinib (Iressa [ZD1839]; AstraZeneca, Wilmington, DE).[14] Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells.[15,16]

Four phase I studies assessed gefitinib tolerability and pharmacokinetics in pretreated patients with solid tumors, including 100 patients with heavily pretreated advanced NSCLC.[17] Evidence of major tumor regression was seen in 10 patients with NSCLC; a number of other patients had nonprogressive disease lasting for 6 months or longer; and palliation of specific symptoms was also frequently observed. In these trials, responses were seen across the dose range 150 to 800 mg/day, while the majority of dose interruptions and reductions due to toxicity were required in patients receiving more than 600 mg/d. From these data, two doses (250 and 500 mg/d) were selected for investigation in phase II and phase III trials. The 250 mg/d dose is higher than the lowest dose level at which objective tumor regression was seen, while 500 mg/d is the highest dose that was well tolerated when taken over an extended period in phase I trials.

The aims of this Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL 1) trial were to further investigate the efficacy and safety of oral gefitinib in patients with advanced NSCLC who had previously received one or two chemotherapy regimens, with at least one containing platinum. The population was prospectively stratified into Japanese and non-Japanese patients to investigate whether there were any differences between the two patient populations with respect to efficacy.

PATIENTS AND METHODS

Study Design

This randomized, double-blind, parallel group, phase II multicenter trial recruited patients at 43 centers across Europe, Australia, South Africa, and Japan. Primary objectives were to evaluate the objective tumor response rate (RR) for gefitinib doses of 250 and 500 mg/d and to further characterize the safety profile of these doses. Secondary objectives were to estimate disease-related symptom improvement rate, disease control rate (response + stable disease), progression-free survival (PFS), and overall survival (OS); to evaluate changes in QoL; and to assess any differences between Japanese and non-Japanese patients with respect to efficacy and safety.

Patient Eligibility

Eligibility criteria were histologic or cytologic confirmation of locally advanced or metastatic NSCLC; stage III or stage IV disease not curable with surgery or radiotherapy at study entry; recurrent or refractory disease following one or two previous chemotherapy regimens (at least one containing platinum); at least one bidimensionally measurable or radiographically assessable lesion; age of 18 years or older; World Health Organization performance status (PS) of 0 to 2; and life expectancy of 12 weeks or longer. Patients with stable brain metastases were eligible. Exclusion criteria were more than two previous chemotherapy regimens, systemic anticancer therapy within 21 days, or radiotherapy within 14 days before the start of treatment; unresolved chronic toxicity higher than the National Cancer Institute common toxicity criteria (NCI-CTC, version 2) grade (G) of 2 (excluding cases of alopecia); ALT or AST levels greater than 2.5 times the upper limit of reference range (ULRR; more than 5 times the ULRR in the presence of liver metastases); serum creatinine levels greater than 1.5 times the ULRR; serum bilirubin levels greater than 1.25 times the ULRR; and neutrophils less than 1.5×10^9/L or platelets less than 75×10^9/L. Patients gave informed consent, and trial document approval was obtained from the ethics committee or institutional review board at each trial center. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Treatment

Patients were randomly assigned to receive double-blind gefitinib doses at 250 or 500 mg/d. Tablets were administered once daily, except on day 1 when patients received two doses approximately 12 hours apart. Patients continued uninterrupted treatment until disease progression, intolerable toxicity, withdrawal of consent, or trial closure (4 months after the last patient was recruited). Patients without progression were permitted to continue gefitinib treatment in a further study.

One dose reduction per patient was permitted in the event of unacceptable toxicity. New blinded treatment supplies, decreasing the dose from 500 mg to 250 mg or from 250 mg to 100 mg, were dispensed. Gefitinib administration could be interrupted for a maximum of 14 days.

No systemic anticancer treatment was permitted during the trial, except for palliative radiotherapy in patients with isolated symptomatic bone metastases, and as long as trial drug administration was not interrupted for longer than 14 days.

Efficacy

We assessed objective tumor response as complete response (CR), partial response (PR), partial response in nonmeasurable disease (PRNM), stable disease (SD), or progressive disease (PD) in accordance with the Southwest Oncology Group modification of Union Internationale Contre le Cancer/WHO criteria.[18] Baseline assessments were performed within 14 days before randomization. After the start of treatment, assessments were performed every 4 weeks, then every 8 weeks following the fourth month. An independent response evaluation committee consisting of three radiologists/oncologists at each session reviewed images of patients with CR, PR, and SD; reviewers were blinded to the investigators' assessment and dose of gefitinib. Duration of response was defined as the time from the first objective assessment of CR or PR to the first instance of progression or death.

Disease Control

Disease control was defined as the best tumor response of CR, PR, or SD that was confirmed and sustained for 4 weeks or longer.

Disease-related symptom improvement was measured using the Lung Cancer Subscale (LCS), a validated subscale of the QoL instrument, the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire (Fig 1).[19] Patients completed a weekly diary card rating the severity of each of the following seven LCS items on a scale of 0 to 4: shortness of breath, weight loss, lack of clear thinking, coughing, loss of appetite, tightness in the chest, and difficulty breathing. On day 28, the LCS was completed as part of the entire FACT-L questionnaire. The maximum (asymptomatic) attainable score was 28. Patients with a baseline LCS score of 24 or lower were evaluable for symptom improvement. This information was used to determine symptom improvement rate, time to symptom improvement, and

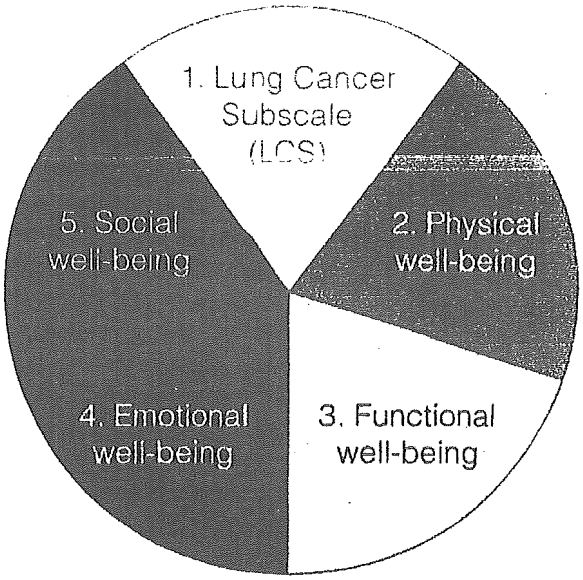

Fig 1. The five components of the Functional Assessment of Cancer Therapy - Lung (FACT-L). Component 1 is measured by the Lung Cancer Subscale itself; components 1 through 3, by the Trial Outcome Index; and components 1 through 5, by FACT-L.

duration of symptom improvement. Based on data showing that a 2-point change in LCS score is clinically meaningful for patients and is significantly associated with Eastern Cooperative Oncology Group performance status, weight loss, objective tumor response, and time to progression,[20] symptom improvement was prospectively defined as a 2-point (or greater) improvement in LCS score sustained for 4 weeks or longer, with no worsening at any interim weekly time points. Duration of symptom improvement was defined as the interval between the first visit presenting with symptom improvement and a subsequent visit at which symptoms had worsened. Missing data points were counted as no change in symptoms.

QoL Assessment

Patients completed the FACT-L questionnaire to assess QoL. The FACT-L assessment has been validated with respect to its psychometric properties and sensitivity to clinical changes.[19] FACT-L was completed at baseline and then every 28 days after the start of treatment. The questionnaire was administered before clinical assessment and before patients heard news about their disease status. The Trial Outcome Index (TOI) of FACT-L (Fig 1) measures the more physical aspects of patient QoL that are shown to be sensitive to chemotherapy.[19] TOI and FACT-L scores were derived in a similar manner to the LCS scores; the highest scores attainable for TOI and FACT-L were 84 and 136, respectively. TOI and FACT-L responses were prospectively defined as a 6-point (or greater) improvement (for 4 weeks or longer), a change that has been shown to be clinically meaningful.[20]

PFS and OS

PFS was defined as the period from the randomization date to the date when disease progression (or death) was observed. OS was defined as the period from the randomization date to the date of death. Patients alive at data cutoff were censored at the last date the patient was known to be alive.

Safety and Tolerability

All adverse events (AEs) were reported, and severity was assessed by the NCI-CTC (version 2.0) grading system. Data were collected on therapy interruptions and withdrawals due to AEs. Routine clinical and laboratory assessments were performed. ECGs and complete ophthalmic evaluations, including slitlamp examination, were performed at baseline, at 4 months, and on completion of or withdrawal from the trial.

Statistical Methods

Patients were randomized to receive oral gefitinib at doses of 250 or 500 mg/d, and were stratified by ethnicity as Japanese and non-Japanese. Randomization and allocation were performed by a centralized registration or randomization center using dynamic balancing[21] with factors for country and WHO-PS of 0 to 1 versus 2. Patients were categorized at randomization with respect to prior taxane therapy (docetaxel ± paclitaxel *v* paclitaxel alone *v* no taxane) and number of prior regimens (one *v* two).

The target sample population of 200 patients (100 in each dose group and 100 in each ethnic group) was chosen to enable the tumor lower limit for RR to be independently evaluated in the four strata defined by dose and ethnicity. Within each stratum, the goal was to have 90% power for a two-sided 5% significance test to show that the RR was greater than 5% assuming that the actual RR was 20%, which required 45 or more evaluable patients per stratum.

RRs and disease control rates were compared between strata using Fisher's exact test. Logistic regression models were used to further explore observed differences and to identify baseline factors that may independently predict for tumor response and disease control. PFS and OS were compared between strata using the log-rank test. Further analyses were conducted on these data using Cox's proportional hazard modeling.

RESULTS

Patients

A total of 210 patients were randomized within 4 months (October 2, 2000 to January 30, 2001). Of these, 208 patients were evaluable for efficacy, and 209 patients were evaluable for safety (Fig 2). The two dose groups were well balanced for most baseline demographic factors, with the exception of sex (Table 1). As planned, approximately half of the patients randomized were Japanese. There were some demographic imbalances between the Japanese and non-Japanese populations (62.7% *v* 77.8% male; 20.6% *v* 15.7% PS of 0; 8.8% *v* 16.7% PS of 2; and 76.5% *v* 50.0% adenocarcinoma, respectively).

Efficacy

The investigator assessments of the best overall tumor responses are shown in Table 2. RR was 18.4% for the 250-mg/d group, which was not statistically different from that of the 500-mg/d group (RR, 19.0%; Table 2). The independent response evaluation committee reviewed 107 of the 110 patients whom the investigator considered to have CR, PR, PRNM or SD. These included 38 of the 39 responders. There was a high concordance in tumor response evaluation between investigators and independent reviewers (73.8%; Table 3). In addition, the response evaluation committee evaluated an additional 25 patients who were assessed by the investigators as having a best response of PD. Of these 25 patients, the response evaluation committee considered 7 patients to have had a best response of SD.

Of the patients who responded, most showed rapid tumor regression, with 68% meeting the criteria for objective response by the first postbaseline assessment. The remaining patients met the criteria in the second, third, or fourth month following randomization. Furthermore, across both doses, most responders (87.2%) still had a response at the data cutoff, with a median follow-up of 6.3 months (range, 4.0–7.9 months). For patients who responded, median duration of response was more than 3 months (ranges: 250-mg/d group, 1–5 months; 500-mg/d group, 1–5.5 months). RRs were similar irrespective of whether

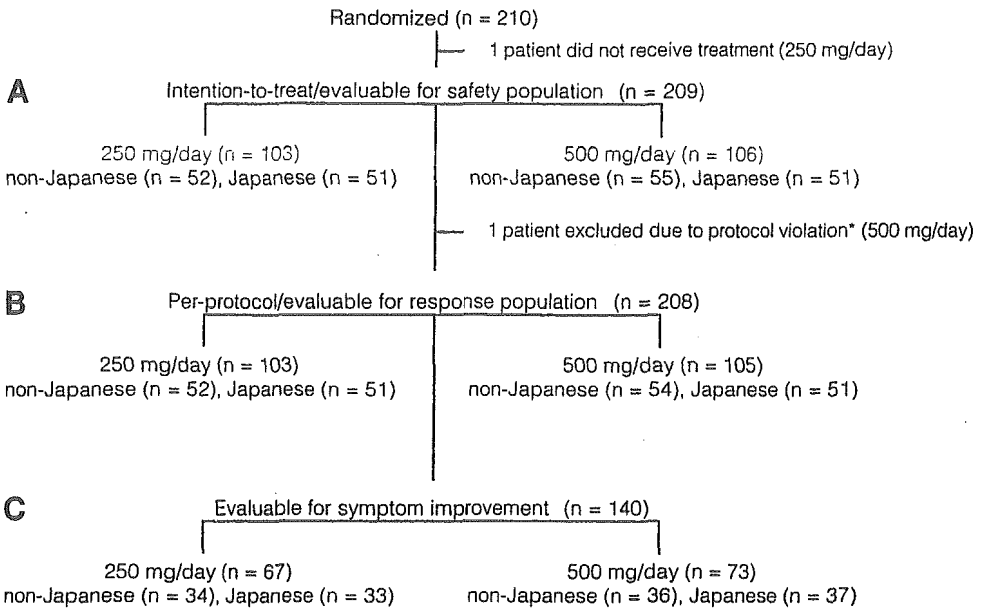

Fig 2. Number of patients included in the analysis populations. (A) Patients who received 1 or more doses of trial treatment. (B) Patients who received 14 or more days of trials treatment in each 28-day treatment period before the first tumor assessment recorded their best tumor response. (C) Patients with a Lung Cancer Subscale score of 24 or lower. Asterisk indicates that this patient's last dose of systemic anticancer therapy was received within 21 days prior to the start of trial treatment.

gefitinib was used as second-line (17.5%, 250 mg/d; 18.3%, 500 mg/d) or third-line treatment (19.6%, 250 mg/d; 20.0%, 500 mg/d). A post hoc nonrandomized analysis showed that RRs for the subgroup of patients who had previously received a platinum and a taxane were 24.0% at 250 mg/d and 28.0% at 500 mg/d. Similarly, RRs for patients previously given platinum and docetaxel were 24.0% at 250 mg/d and 26.0% at 500 mg/d. RRs for patients who had progressed on two prior chemotherapy regimens were 13.6% at 250 mg/d and 7.9% at 500 mg/d.

Table 1. Baseline Demography of the Randomized Population

	Gefitinib			
	250 mg/d		500 mg/d	
	No.	%	No.	%
No. of patients randomized	104		106	
Age				
Median	61.0		60.0	
Range	28 to 85		37 to 78	
Sex (male:female)	78:26	75:25	70:36	66:34
Performance status				
0	18	17.3	20	18.9
1	73	70.2	72	67.9
2	13	12.5	14	13.2
Disease stage at study entry				
IIIA	4	3.8	2	1.9
IIIB	19	18.3	16	15.1
IV	81	77.9	88	83.0
Tumor histology				
Adenocarcinoma*	67	64.4	71	67.0
Squamous	25	24.0	18	17.0
Large-cell	9	8.7	9	8.5
Undifferentiated	3	2.9	8	7.5
Previous cancer treatment				
Failed 1 previous chemotherapy regimen	104	100.0	106	100.0
Failed 2 previous chemotherapy regimens	46	44.2	46	43.4
Radiotherapy	52	50.0	48	45.3
Surgery	32	30.8	25	23.6
Immuno/hormonal therapy	4	3.8	9	8.5
Symptomatic at entry	67	64.4	73	68.9

*Bronchioloalveolar carcinomas were included in this group. Three patients in each dose group had adenosquamous histology.

Table 2. Best Overall Objective Response

	Gefitinib			
	250 mg/d		500 mg/d	
	No.	%	No.	%
No. of patients evaluable	103		105	
Complete response	0	0	1	1.0
Partial response	18	17.5	19	18.1
Partial response in nonmeasurable disease	1	1.0	0	0.0
Stable disease	37	35.9	34	32.4
Progressive disease	42	40.8	44	41.9
Unknown*	5	4.9	7	6.7
Response rate				
%	18.4		19.0	
95% CI	11.5 to 27.3		12.1 to 27.9	
Disease control rate				
%	54.4		51.4	
95% CI	44.3 to 64.2		41.5 to 61.3	

Abbreviation: CI, confidence interval.

*No conclusion was reached about the best overall tumor response (eg, because of missing scans or relevant x-ray films).

As expected, the mean number of days under treatment was higher for responders than for nonresponders (150 *v* 68 days, respectively); however, the number of days under treatment, as compared with the number of days under the trial was 95% versus 96% in both groups.

Disease Control

The disease control rate was 54.4% for the 250-mg/d group, which was not statistically different from that of the 500-mg/d group, 51.4% (P = .68; Table 2). Median duration of disease control for patients who responded or had stable disease was 3.2 and 4.6 months, respectively. Disease control was similar for second-line (59.6%, 250 mg/d; 50.0%, 500 mg/d) and third-line treatment (47.8%, 250 mg/d; 53.3%, 500 mg/d). SD rate was 35.9% at 250 mg/d and 32.4% at 500 mg/d.

Disease-Related Symptom Improvement

Evaluable baseline questionnaires were received from 80 and 81 patients from the 250- and 500-mg/d groups, respectively. Of these, 67 and 73 patients, respectively, were evaluable for symptom improvement. Median baseline scores for LCS were 18.0 (ranges: 250 mg/d, 4–24; 500 mg/d, 2–24) for each dose group, indicating that this was a symptomatic population. The symptom improvement rate was 40.3% (95% confidence interval [CI], 28.5 to 53.0) for the 250-mg/d group and 37.0% (95% CI, 26.0 to 49.1) for the 500-mg/d group. Most patients with a tumor response who were evaluable for symptom improvement also showed an improvement in their disease-related symptoms, and more than 50% of the patients with SD also had symptom improvement (Fig 3).

The median of the maximum change in LCS score for the patients with symptom improvement was 7.0 points (range, 3–17 points) during the first interval of improvement (time between the first visit response of improved, to the subsequent response of worsened). Importantly, median time to symptom improvement was only 8 days (the time of first postbaseline assessment) for both doses. Median duration of symptom improvement was 5.1 month (range, 1.1–5.6+ months) at 500 mg/d. At 250 mg/d, the median duration of symptom improvement was not calculable because patients were still responding at the time of data cutoff; symptom improvement lasted for at least 3 months in 75% of patients and for 6 months in 65% of patients. Median time to

Table 3. Tumor Response Evaluation by Investigators and Independent Response Evaluation Committee

	Investigator Evaluation	
REC Evaluation	PR (n = 38)	SD (n = 69)
PR (n = 34)	31	3
SD (n = 53)	5	48
PD (n = 18)	1	17
UK (n = 2)	1	1

NOTE. Complete response and partial response in nonmeasurable disease are indicated by PR for the purpose of calculating concordance rates.

Abbreviations: REC, response evaluation committee; PR, partial response; SD, stable disease; PD, progressive disease; UK, unknown due to missing slides or scans.

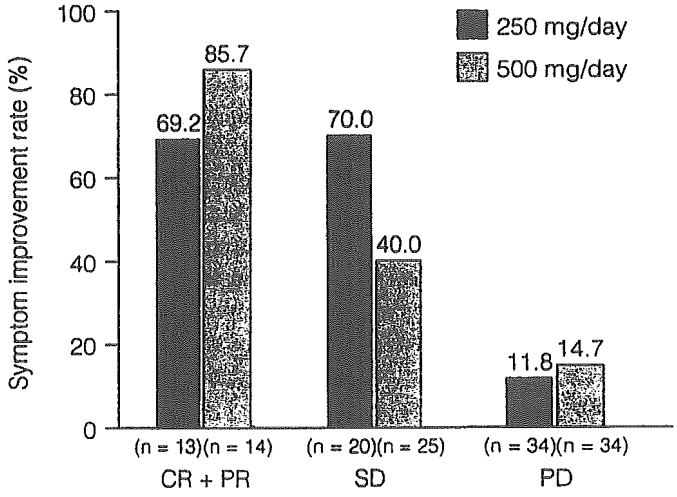

Fig 3. Symptom improvement benefits by tumor response. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

symptom worsening, for all patients, was longer for the 250-mg/d group (4.1 months) than for the 500-mg/d group (2.8 months).

Generally, more patients showed an improvement in the pulmonary items of the LCS than in the nonpulmonary items. Improvements in shortness of breath, cough, and breathing were each seen in 78% of LCS responders, while appetite, weight loss, and clear thinking improved in 54% to 57% of LCS responders.

PFS and OS

Median PFS was 2.7 months (95% CI, 2.0 to 2.8) for the 250-mg/d group and 2.8 months (95% CI, 1.9 to 3.8) for the 500-mg/d group (Fig 4a), with 29% and 39% of patients, respectively, progression-free after 4 months of therapy. Median overall survival times were 7.6 months (95% CI, 5.3 to 10.1) and 8.0 months (95% CI 6.7 to 9.9) for the 250- and 500-mg/d groups, respectively (Fig 4b); 1-year survival rates were 35% and 29%, respectively.

Tumor response was associated with improved OS. For patients with either CR or PR, the median OS was 13.3 months for 250-mg/d group and 10.6 months for the 500-mg/d group (Fig 4c).

QoL Assessed by TOI and FACT-L

Median baseline scores were 53 for TOI (range, 15–75) and 85 (range, 32–125) for FACT-L, indicating that this population had compromised QoL.

QoL improvement rate measured by TOI was 20.9% (95% CI, 11.9 to 32.6) for the 250-mg/d group and 17.8% (95% CI, 9.8 to 28.5) for the 500-mg/d group. QoL improvement rate measured by FACT-L was 23.9% (95% CI, 14.3 to 35.9) and 21.9% (95% CI, 13.1 to 33.1) at 250 and 500 mg/d, respectively. The median time to improvement (measured by TOI and FACT-L) for both doses was 29 days, the time of the first postbaseline assessment.

Efficacy in Japanese and Non-Japanese Patients

In this trial, the RR was higher for Japanese patients than non-Japanese patients (27.5% *v* 10.4%; odds ratio = 3.27; P = .0023). A population pharmacokinetic analysis of steady-state trough gefitinib plasma concentrations did not reveal any differences between Japanese and non-Japanese patients that might explain the difference in RR (data not shown). To further investigate this difference in RR observed between Japanese and non-Japanese patients, a planned multivariate logistic analysis was performed. Twenty-two baseline factors were evaluated independently to assess their value in predicting response. Using a 10% significance level, only seven factors were found to be predictive of response (baseline LCS, body mass index, PS, prior radiotherapy, histology, prior immuno/hormonal therapy, and sex). To ensure that only relevant baseline factors were retained in the multivariate model, the backward regression technique was employed at the 10% significance level. This resulted in only four factors being retained in the model: PS, sex, histology, and prior immuno/hormonal therapy (Table 4).

The final multivariate model, including all four significant baseline prognostic factors and the factor for ethnicity, resulted in a Japanese:non-Japanese odds ratio of 1.64 (95% CI, 0.71 to 3.93; P = .25), which is not considered to be statistically significant.

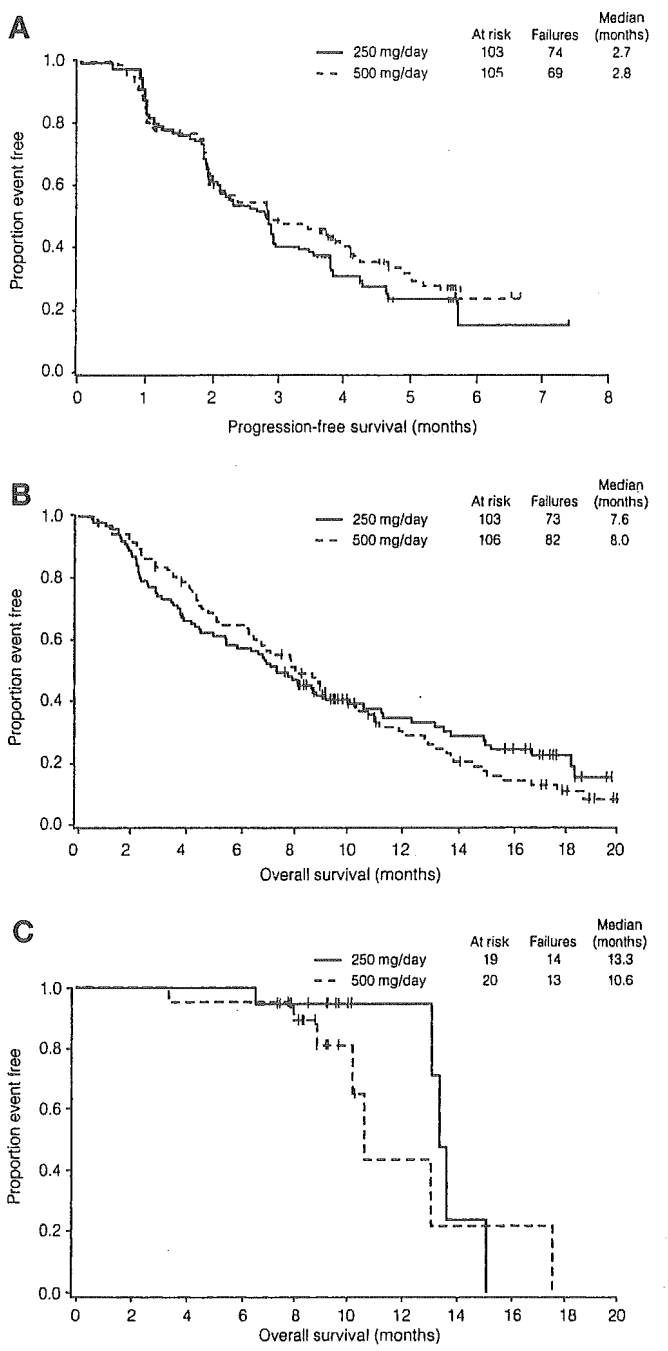

Fig 4. Kaplan-Meier plots showing (A) progression-free survival, (B) overall survival and (C) overall survival in patients with a complete or partial tumor response by dose.

Safety and Tolerability

A total of 209 patients were evaluable for safety and tolerability. Most AEs seen in this trial were mild (CTC, G1 or G2), there was no evidence of cumulative toxicity, and most events were reversible. Drug-related AEs observed in more than 10% of patients on either dose are shown in Table 5. The first occurrence of most AEs was seen before the end of the first month of treatment. In the 250-mg/d group, 15.5% of patients had AEs requiring a short treatment interruption, and none required a dose

Table 4. Final Adjusted Model of Prognostic Factors Associated With an Objective Response According to a Multivariate Analysis

Parameter	Odds Ratio	95% CI	P	Interpretation
Performance status (PS)	6.26	1.20 to 115.36	.081	The odds of responding is over 6 times higher for PS 0 or 1 patients compared with PS 2 patients.
Received prior immuno/hormonal treatment*	6.01	1.58 to 26.15	.011	The odds of responding is 6 times higher for patients who received immuno/hormonal treatments prior to entry compared with those who did not.
Histology	3.45	1.29 to 11.02	.021	The odds of responding is almost 3.5 times higher for patients with adenocarcinoma than for patients with other tumor histologies.
Sex	2.65	1.19 to 5.91	.017	The odds of responding is over 2.5 times higher for females than males.
Ethnicity	1.64	0.71 to 3.93	.25	After accounting for all baseline imbalances, the odds ratio indicates that the chance of responding is just over 1.5 times higher for Japanese patients compared with non-Japanese patients.

Abbreviation: CI, confidence interval.
*Immuno/hormonal treatments include picibanil, investigational drugs, minomycin, marimastat, and tamoxifen citrate.

reduction. At 500 mg/d, 28.3% of patients required a treatment interruption, and 10.4% required a dose reduction. The main reasons for dose interruptions were skin reactions, gastrointestinal disturbances, and elevated transaminases. Mean time on treatment was similar for the 250- and 500-mg/d groups, at 85.1 and 81.5 days, respectively, which corresponds to 97.8% and 93.8% of the total days on trial. Withdrawal due to drug-related AEs was 1.9% and 9.4% for patients receiving gefitinib doses at 250 and 500 mg/d, respectively. The main reasons for withdrawal mirrored reasons for drug interruption.

Of all the drug-related AEs reported, CTC G3 or G4 was seen in only 1.5% of patients receiving 250 mg/d and in 4.7% of those receiving 500 mg/d; no G4 drug-related AEs were reported at 250 mg/d. The most frequent drug-related G3 or G4 AEs included diarrhea, rash, and ALT elevation (Table 5). The AE profile and the incidence of G3 or G4 drug-related AEs were similar for the Japanese and non-Japanese populations.

Diarrhea could be controlled, if necessary, with antidiarrheal agents such as loperamide. Twenty-four percent of 250-mg/d patients and 43% of 500-mg/d patients took antipropulsives or antidiarrheal agents. Furthermore, diarrhea resolved in 84% (250 mg/d) and 83% (500 mg/d) of patients. Of these patients, resolution occurred during treatment (with or without dose reduction) or during temporary therapy interruption in 47.6% (250 mg/d) and 57.6% (500 mg/d) of patients, or following treatment cessation in 19.0% (250 mg/d) and 15.3% (500 mg/d). We did not record the exact time at which the event resolved in 33.3% of the 250-mg/d group and in 27.1% of the 500-mg/d group. Only one patient, receiving 500 mg/d, was withdrawn from the trial due to drug-related gastrointestinal disturbance (combination of G3 diarrhea, G3 nausea, and G2 vomiting).

Skin disorders, including rash, pruritus, dry skin, and acne, were generally mild (Table 5). Patients with rash also frequently reported other skin-related symptoms, including acne (10.6%), pruritus (45.5%), and dry skin (30.8%). In most patients, these skin disorders resolved either during treatment or temporary therapy interruption, or following treatment cessation. Two 500-mg/d patients withdrew from the trial due to skin disorders after 7 and 10 days of treatment (one with G3 rash; one with G1 rash). Concurrent rash and diarrhea was seen in 15.5% and 25.5% of patients receiving gefitinib at 250 and 500 mg/d, respectively.

Two patients experienced interstitial lung-disease–type events during the study (interstitial pneumonia and pneumonitis). Both patients were receiving 500 mg/d of gefitinib. One patient recovered from the event following withdrawal from treatment due to disease progression; in the other patient, the pneumonitis occurred 3 days after stopping gefitinib treatment because of severe fatigue, and was ongoing at the time of death due to disease progression 5 weeks later. A computed tomography scan for this patient showed progression of carcinomatous pleuritis. Both patients received antibiotics, steroids, and oxygen therapy.

Most patients had no deterioration in hepatic function during the trial, and occurrences of elevated levels of transaminases were generally G1 and asymptomatic. Four patients (three at 500 mg/d) were withdrawn from the trial due to G3 or G4 elevations in hepatic enzymes. No clinically significant deterioration in renal function was observed during the trial, even in patients who entered the trial with mild or moderate renal impairment. The incidence of cardiovascular events was low; seven patients (one at 250 mg/d; six at 500 mg/d) had G1 or G2 cardiovascular events. Two patients in the 250-mg/d group had a G3 drug-related AE (atrial fibrillation and bundle branch block), and one patient in the 500-mg/d group had G4 deep thrombophlebitis.

Ophthalmic monitoring did not reveal any significant drug-related abnormalities and no drug-related G3 or G4 events were reported. G1 or G2 drug-related ophthalmic AEs were reported in 43 patients (21%), but none of these events required withdrawal from therapy. These events included conjunctivitis, blepharitis, keratitis, eye pain, dry eyes, and corneal erosion.

No clinically significant changes in hematology parameters were observed during the trial; most patients experienced no changes from baseline in CTC grade for hemoglobin, platelets, or WBC values. The only drug-related G3 or G4 hematologic AE

Table 5. Patients With Drug-Related Adverse Events That Occurred in More Than 10% of Patients in Either Dose Group

Adverse Event	CTC Grade*	Gefitinib 250 mg/d (n = 103) No.	%	Gefitinib 500 mg/d (n = 106) No.	%
Skin					
Rash	1	27	26.2	31	29.2
	2	20	19.4	35	33.0
	3	1	1.0	6	5.7
	4	0	0	1	0.9
Pruritus	1	26	25.2	34	32.1
	2	5	4.9	3	2.8
	3	0	0	1	0.9
Dry skin	1	25	24.3	23	21.7
	2	3	2.9	8	7.5
Acne	1	10	9.7	5	4.7
	2	3	2.9	8	7.5
	3	0	0	2	1.9
Digestive					
Diarrhea	1	33	32.0	36	34.0
	2	8	7.8	18	17.0
	3	0	0	7	6.6
Nausea	1	11	10.7	17	16.0
	2	1	1.0	7	6.6
	3	1	1.0	1	0.9
Anorexia	1	8	7.8	11	10.4
	2	1	1.0	8	7.5
	3	0	0	1	0.9
Vomiting	1	4	3.9	14	13.2
	2	2	1.9	7	6.6
Metabolic					
ALT increased	1	10	9.7	14	13.2
	2	1	1.0	5	4.7
	3	2	1.9	5	4.7
	4	0	0	1	0.9
AST increased	1	9	8.7	15	14.2
	2	2	1.9	6	5.7
	3	0	0	2	1.9
	4	0	0	1	0.9
Whole Body					
Pain	1	9	8.7	15	14.2
	2	1	1.0	2	1.9
Asthenia	1	7	6.8	7	6.6
	2	1	1.0	3	2.8
	3	0	0	1	0.9

Abbreviation: CTC, common toxicity criteria.
*Adverse events were not observed at CTC grades higher than those presented.

reported was anemia, which was seen in three 500-mg/d patients (G3, one patient; G4, two patients), but no patients were withdrawn due to anemia.

DISCUSSION

This multicenter, randomized, double-blind, parallel-group trial conducted in Europe, Australia, South Africa, and Japan evaluated the efficacy and safety of daily oral doses of 250 and 500 mg of gefitinib in patients with locally advanced or metastatic NSCLC who had previously received either one, or a maximum of two, chemotherapy regimens (at least one of which had contained platinum). The major aim of the randomization was to identify the optimal dose for patients in this setting. In 103 patients treated with gefitinib at 250 mg/d, the RR was 18.4%, with a median PFS of 2.7 months and a median OS of 7.6 months, suggesting that gefitinib is an effective treatment for previously treated patients with advanced NSCLC. The RR was similar for the 500-mg dose and for patients receiving gefitinib as second- and third-line treatment.

With respect to safety, drug-related AEs at both doses were generally mild (G1 or G2), consisting mainly of skin reactions and diarrhea, but the incidence of AEs, dose modifications, and withdrawals was lower for 250-mg/d group than for 500-mg/d group. Additionally, gefitinib was not associated with common conventional chemotherapy AEs such as neutropenia, thrombocytopenia, or neuropathy. Less than 1% of patients experienced interstitial lung-disease–type events during the study. The data from this trial suggest that treatment with gefitinib at 250 mg/d does not require any special clinical or laboratory monitoring beyond the usual standards of care in this patient population.

Overall, 250 mg/d was as effective as, and better tolerated than, 500 mg/d, and is thus the recommended dose for patients with NSCLC who have previously received platinum-based chemotherapy. This dissociation of the efficacy and safety dose-response relationships was predicted for molecularly targeted anticancer agents such as gefitinib.[22]

Following inevitable first progression or recurrence after first-line chemotherapy, the current therapeutic option for patients with advanced NSCLC is additional chemotherapy. In the second-line setting, numerous phase II trials of one or more chemotherapy agents have reported widely varying RRs and little or no data concerning other efficacy end points.[23] The notable exception is docetaxel, the only approved chemotherapy agent for treatment of previously treated patients and the only agent for which phase III data exists in a large number of patients with prior platinum therapy. In the first of two randomized phase III trials, median survival with docetaxel was significantly better than the supportive care arm (7.0 *v* 4.6 months; $P = .047$).[7] The RR for the 55 patients who received docetaxel at 75 mg/m^2 was 5.5%, and the overall disease control rate was 52.8%. In the second trial, the median survival with 75 mg/m^2 of docetaxel was 5.7 months, the RR was 6.7%, and the disease control rate was 42.7%.[24] These trials also demonstrated that docetaxel has a positive impact on QoL.[25]

A key therapeutic aim in patients with NSCLC is to palliate disease-related symptoms without compromising overall QoL. Patients with progressive NSCLC who have been failed by previous chemotherapy have an extremely poor prognosis and often exhibit severe symptoms. The patient population in this study was symptomatic, with median baseline LCS and TOI scores of 18.0 and 53.0, respectively. This is comparable with a randomized trial comparing three first-line chemotherapeutic regimens in patients with advanced NSCLC, which reported mean baseline LCS and TOI scores of 18.7 and 56.4, respectively.[20] Our study provided a unique demonstration of clinically significant improvement in disease-related symptoms, which was documented both in patients with tumor regression and in those with stable disease. The rate of disease-related symptom improvement was high, with approximately 40% of the patients in the

250-mg/d group experiencing improvement for at least 1 month. The median time to symptom improvement was short, occurring within 8 days, and QoL improvements also appeared rapidly.

The statistically significant difference in RR between Japanese and non-Japanese patients could not be explained on the basis of pharmacokinetic differences in the two populations. However, it was possible to identify baseline prognostic factors that accounted for these results (PS of 0–1, receipt of prior immuno/hormonal treatment, female sex, and adenocarcinoma histology). After accounting for baseline imbalances between the populations, the odds ratio for ethnicity was 1.64, which is not considered to be statistically significant ($P = .25$). Performance status and sex have been previously identified as prognostic factors for RR and survival following first-line chemotherapy in individuals with NSCLC.[23] In this study, the better outcome in women could not be accounted for by sex differences in pharmacokinetic parameters. It is interesting that adenocarcinoma is a prognostic factor, given that EGFR is more frequently expressed in squamous cell carcinoma[26]; it may be that the relatively slow growth of adenocarcinoma cells renders them more sensitive to gefitinib, or there might be an unknown factor at the protein level that determines sensitivity to gefitinib rather than the level of EGFR expression. We do not yet know whether the EGFR status of tumors influences the efficacy of gefitinib. However, tissue samples have been retained to assess EGFR status by immunohistochemistry, and analysis of these samples is underway.

A second phase II trial of gefitinib monotherapy for the treatment of advanced NSCLC in patients who have received at least two previous chemotherapy agents, including platinum and docetaxel, has been completed and confirms the activity of gefitinib in heavily pretreated patients.[27]

In conclusion, oral gefitinib at 250 or 500 mg/d provides clinically significant durable antitumor activity, accompanied by rapid, clinically meaningful symptom relief and improvements in QoL as second- and third-line treatment in patients with advanced NSCLC who have received previous platinum-based therapy. The 250-mg/d dose of gefitinib has a more favorable safety profile and better tolerability than the 500-mg/d dose and is, therefore, the recommended dose in this clinical setting. The data from this multi-institutional, randomized phase II trial suggest that oral gefitinib is an important, novel treatment option for patients with previously treated advanced NSCLC.

ACKNOWLEDGMENT

We would like to acknowledge the assistance of the Clinical Study Leader, Sally Sambrook; the Clinical Team Leader, Yuhiko Nogi; the Clinical Research Leader, Sue Hunter; and the Clinical Strategy Manager, Masaru Hirose.

APPENDIX

The appendix is available online at www.jco.org.

REFERENCES

1. Ferlay J, Bray F, Pisani P, et al: GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0 (IARC, CancerBase No 5). Lyon France, IARC Press, 2001

2. Schiller J: Current standards of care in small-cell and non-small-cell lung cancer. Oncology 61:3-13, 2001 (suppl 1)

3. Non-small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899-909, 1995

4. Ries L, Eisner M, Kosary C, et al: SEER Cancer Statistics Review, 1973-1998. Bethesda, MD, National Cancer Institute, 2001

5. Fossella FV, Lee JS, Hong WK: Management strategies for recurrent non-small cell lung cancer. Semin Oncol 24:455-462, 1997

6. Klastersky J, Paesmans M: Response to chemotherapy, quality of life benefits and survival in advanced non-small cell lung cancer: Review of literature results. Lung Cancer 34:95-101, 2001 (suppl 4)

7. Shepherd F, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000

8. American Society of Clinical Oncology: Clinical practice guidelines for the treatment of unresectable non- small-cell lung cancer: Adopted on May 16, 1997 by the American Society of Clinical Oncology. J Clin Oncol 15:2996-3018, 1997

9. Salomon D, Brandt R, Ciardiello F, et al: Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 19:183-232, 1995

10. Rusch V, Baselga J, Cordon-Cardo C, et al: Differential expression of the epidermal growth factor receptor and its ligands in primary non-small cell lung cancers and adjacent benign lung. Cancer Res 53:2379-2385, 1993

11. Fujino S, Enokibori T, Tezuka N, et al: A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. Eur J Cancer 32A:2070-2074, 1996

12. Pavelic K, Banjac Z, Pavelic J, et al: Evidence for a role of EGF receptor in the progression of human lung carcinoma. Anticancer Res 13:1133-1137, 1993

13. Volm M, Rittgen W, Drings P: Prognostic value of ERBB-1, VEGF, cyclin A, FOS, JUN and MYC in patients with squamous cell lung carcinomas. Br J Cancer 77:663-669, 1998

14. Lawrence D, Niu J: Protein kinase inhibitors: the tyrosine-specific protein kinases. Pharmacol Ther 77:81-114, 1998

15. Negoro S, Nakagawa K, Fukuoka M, et al: Final results of a phase I intermittent dose-escalation trial of ZD1839 (Iressa) in Japanese patients with various solid tumours. Proc Am Soc Clin Oncol 20:324a, 2001 (abstr 1292)

16. Ranson M, Hammond L, Ferry D, et al: ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: Results of phase I trial. J Clin Oncol 20:2240-2250, 2002

17. Kris M, Herbst R, Rischin D, et al: Objective regressions in non-small cell lung cancer patients treated in phase I trials of oral ZD1839 (Iressa), a selective tyrosine kinase inhibitor that blocks the epidermal growth factor receptor (EGFR). Lung Cancer 29:72, 2000 (suppl 1, abstr 231)

18. Green S, Weiss G: Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 10:239-253, 1992

19. Cella D, Bonomi A, Lloyd S, et al: Reliability and validity of the Functional Assessment of Cancer Therapy - Lung (FACT-L) quality of life instrument. Lung Cancer 12:199-220, 1995

20. Cella DF, Eton DT, Fairclough DL, et al: What is a clinically meaningful change on the Functional Assessment of Cancer Therapy - Lung (FACT-L) questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol 55:285-295, 2002

21. Pocock S, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-115, 1975

22. Rowinsky EK: The pursuit of optimal outcomes in cancer therapy in a new age of rationally designed target-based anticancer agents. Drugs 60:1-14, 2000 (suppl 1)

23. Huisman C, Smit EF, Giaccone G, et al: Second-line chemotherapy in relapsing or refractory non-small-cell lung cancer: a review. J Clin Oncol 18:3722-3730, 2000

24. Fossella F, DeVore R, Kerr R, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol 18:2354-2362, 2000

25. Shepherd FA, Fossella FV, Lynch T, et al: Docetaxel (Taxotere) shows survival and quality-of-life benefits in the second-line treatment of non-small cell lung cancer: a review of two phase III trials. Semin Oncol 28:4-9, 2001

26. Rusch V, Klimstra D, Venkatraman E, et al: Overexpression of the epidermal growth factor receptor and its ligand transforming growth factor α is frequent in resectable non-small cell lung cancer but does not predict tumor progression. Clin Cancer Res 3:515-522, 1997

27. Kris M, Natale RB, Herbst R, et al: A phase II trial of ZD1839 ('Iressa') in advanced non-small cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2). Proc Am Soc Clin Oncol 21:292, 2002 (abstr 1166)

Lung Cancer (2003) 42, 103–111

ELSEVIER

LUNG CANCER
IASLC

www.elsevier.com/locate/lungcan

Phase II clinical study of photodynamic therapy using mono-L-aspartyl chlorin e6 and diode laser for early superficial squamous cell carcinoma of the lung

Harubumi Kato[a], Kinya Furukawa[a,*], Masami Sato[b], Tetsuya Okunaka[a], Yohko Kusunoki[c], Masaaki Kawahara[d], Masahiro Fukuoka[e], Teruomi Miyazawa[f], Takashi Yana[g], Kaoru Matsui[h], Takeshi Shiraishi[i], Hirohisa Horinouchi[j]

[a] *Department of Surgery, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan*
[b] *Department of Surgery for Thoracic Surgery, Institute of Development, Aging and Cancer Affiliated Hospital, Tohoku University, Miyagi, Japan*
[c] *Department of Internal Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*
[d] *Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, Osaka, Japan*
[e] *Department of Internal Medicine, Kinki University School of Medicine Affiliated Hospital, Osaka, Japan*
[f] *Department of Respiratory Medicine, Hiroshima City Hospital, Hiroshima, Japan*
[g] *Department of Respiratory System, Rinku General Medical Center, Izumisano Municipal Hospital, Osaka, Japan*
[h] *Department of Internal Medicine, Osaka Prefectural Habikino Hospital, Osaka, Japan*
[i] *Department of Surgery, Fukuoka University Hospital, Fukuoka, Japan*
[j] *Department of Surgery for Respiratory Organs, Keio University Hospital, Tokyo, Japan*

Received 11 November 2002; received in revised form 10 April 2003; accepted 29 April 2003

KEYWORDS
Photodynamic therapy;
PDT;
Mono-L-aspartyl chlorin e6;
Talaporfin;
Diode laser;
Occult lung cancer

Summary Photofrin is the most commonly used photosensitizer for photodynamic therapy (PDT). The major side effect of Photofrin is cutaneous photosensitivity. A second generation photosensitizer, mono-L-aspartyl chlorin e6 (NPe6) has shown anti-tumor efficacy and rapid clearance from skin. Therefore, we conducted a phase II clinical study to investigate the anti-tumor effects and safety of NPe6 in patients with early superficial squamous cell carcinoma of the lung. Enrollment criteria consisted of endoscopically evaluated early stage lung cancer with normal chest X-ray and CT images, no lymph node or distant metastasis. Tumors were located no more peripherally than subsegmental bronchi, the peripheral margin had to visible, and the tumor size had to not more than 2 cm in diameter. The histologic type of the

*Corresponding author. Present address: Department of Chest Surgery, Kasumigaura Hospital, Tokyo Medical University, 3-20-1 Chuou, Ami-machi, Inashiki-gun, Ibaraki 300-0395, Japan. Tel.: +81-298-87-1161; fax: +81-298-87-1266.
E-mail address: k-furu@tokyo-med.ac.jp (K. Furukawa).

0169-5002/03/$ - see front matter
doi:10.1016/S0169-5002(03)00242-3

tumor had to squamous cell carcinoma. Laser irradiation (100 J/cm^2) using a diode laser was performed at 4 h after administration of NPe6 (40 mg/m^2). Among 41 patients with 46 lesions, 40 with 45 lesions were eligible for safety evaluation, and 35 patients with 39 lesions were judged as eligible for efficacy evaluation. No serious adverse drug reactions were observed. Disappearance of skin photosensitivity was recognized within 2 weeks in 28 of 33 patients (84.8%) and in all the other seven patients first tested at 15–18 days. Complete response (CR) was seen in 84.6% of lesions (82.9% of patients). This study demonstrated excellent anti-tumor effects and safety, especially low skin photosensitivity in patients with early stage lung cancer. PDT using the second generation photosensitizer NPe6 and a diode laser will likely become a standard modality of PDT for central type early superficial squamous cell carcinoma of the lung.

1. Introduction

Photodynamic therapy (PDT) is a form of cancer treatment which offers palliative therapy for advanced cancer with obstructive tumors and the possibility of curing minimally invasive disease when treated in its earliest stages. PDT is a two stage process with the first stage consisting of an injection of a photosensitizer. Photofrin (porfimer sodium) is the most commonly used photosensitizer for this process. The major side effect of Photofrin itself is cutaneous photosensitivity, which lasts approximately 4–6 weeks [1]. Photofrin is mostly cleared from a variety of tissues at 24–72 h following a period of time after injection. However, this photosensitizer is retained in tumor, skin, and organs of the reticuloendothelial systems [2]. In the second and final stage of the tumor is illuminated with 630 nm red light emanating from a laser. Tumor selectivity in treatment occurs through a combination of selective retention of photosensitizer, selective delivery of light, and drug/light dose selection such that normal tissues are relatively spared [3]. However, the effectiveness of PDT is known to be limited because the maximal therapeutic depth of penetration by activating light is no more than 2 cm. Therefore, the main application of PDT for lung cancer to obtain complete remission is for carcinoma in situ or early invasive squamous cell carcinoma [4].

Because of the skin photosensitivity of Photofrin, many investigators have shown interest in the synthesis of new photosensitizers, which possess lower skin photosensitivity for use in PDT. Among those photosensitizers, mono-L-aspartyl chlorin e6 (NPe6) is considered as a promising photosensitizer. This compound has shown anti-tumor efficacy with laser irradiation in a murine tumor model and rapid clearance from skin [5]. We performed a phase I clinical study using NPe6 and a diode laser for bronchogenic early superficial squamous cell carcinoma from April 1995 to December 1996. When the results were analyzed in eight eligible patients (eight lesions), the rate of complete response (CR) was 87.5% (7/8), and neither particularly serious adverse reactions nor abnormal clinical laboratory findings were noted [6]. Therefore, we conducted a phase II clinical study to investigate anti-tumor effects and the safety of NPe6 in patients with endoscopically evaluated early stage lung cancer using the same dosage shown to be safe and effective in the previous phase I clinical study.

2. Patients and methods

The type of study was nation-wide multi-center study funded by Ministry of Health and Welfare. This study was designed as an open-labeled clinical trial. A total of ten institutions were enrolled in this study from October 1997 through March 2000.

2.1. Inclusion criteria

(1) Patients with endoscopically evaluated early stage lung cancer. (2) Patients with normal chest X-ray and CT images. (3) No metastasis to lymph nodes and no distant metastasis revealed by routine clinical diagnostic methods (N0M0). (4) Tumors located from the bifurcation of the trachea to subsegmental bronchi, with the peripheral margin of the lesions endoscopically visible. (5) Tumor size not more than 2 cm in diameter, measured by forceps endoscopically. (6) Histological type should be early superficial squamous cell carcinoma. (7) Patients to whom a sufficient dose of laser transmission can be irradiated endoscopically. (8) Patients who are not surgical candidates because of underlying cardiopulmonary dysfunction or who refuse surgery, in principal. However,

patients who have received sufficient information concerning surgery and PDT and wish to receive PDT can be enrolled. (9) WBC $\geq$ 4000 per mm^3, Hb $\geq$ 10 g/dl, platelet $\geq 10 \times 10^4$ per mm^3, AST (GOT), ALT (GPT) $\leq$ 60 U/l, T-bil. $\leq$ 20 mg/dl, BUN $\leq$ 25 mg/dl, creatinine $\leq$ 1.5 mg/dl. (10) No history of acute myocardial infarction or unstable angina pectoris within 3 months prior to the PDT. (11) PaO_2 greater than 60 mmHg. (12) Patients with an ECOG performance status of 0–2. (13) Patients with a life expectancy of more than 3 months. (14) If the patients had a previous treatment history (surgery, chemotherapy, radiotherapy, PDT using Photofrin, etc.) for other synchronous or metachronous lesions, the patients should have a more than 4-week wash-out period after the completion of the previous treatment. (15) Patients who have given informed consent to participate in writing.

2.2. Exclusion criteria

(1) Pregnant women or women likely to be pregnant during the study period, and lactating women. (2) Patients with active multiple carcinomas. (3) Patients with serious concomitant diseases (uncontrolled diabetes mellitus, serious hypertension or serious infection etc.) (4) Patients with a history of photosensitivity. (5) Patients with a history of porphyria.

2.3. Number of patients planned

Based on the results of the phase I clinical study in early stage lung cancer patients (rate of CR: 87.5% = 7/8) [6], the expected efficacy rate of this study was set at 90.0%. Setting the range of the 95.0% confidence interval of the expected efficacy rate at 0.2, the number of necessary patients was calculated as 35 cases. Furthermore, assuming 10.0–15.0% of the number of necessary patients would be incomplete, the planned number of patients was set at 40 cases.

2.4. Photosensitizer and laser delivery system

NPe6 (lyophilized talaporfin sodium, Meiji Seika Kaisha, Ltd., Tokyo, Japan) is an effective photosensitizer possessing high chemical purity and a major absorption band at 664 nm. NPe6 has a molecular weight of 799.69, and its structure is shown in Fig. 1 [7]. NPe6 (99% purity) was provided by Meiji Seika Kaisha, Ltd. as a dark blue–green, water-soluble compound. It was reconstituted as a 1.0 mg/ml solution in physiological saline immediately before administration in order to avoid degradation by light, due to its photochemical activity.

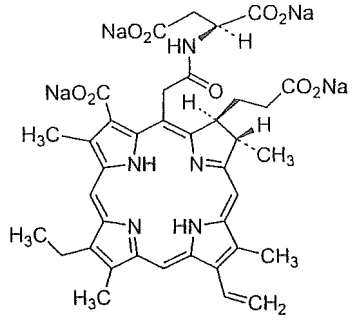

Fig. 1 Chemical structure of NPe6 (talaporfin sodium). This compound is an effective photosensitizer and a major absorption band at 664 nm. NPe6 has a molecular weight of 799.69.

A new diode laser system (Panalas 6405, Matsushita Industrial Equipment Co., Ltd., Osaka, Japan) was used in this study. This laser device is Aluminum Gallium Indium Phosphorus (AlGaInP). The laser wavelength was adjusted to 664 nm and the power output was variable in the range of 50–500 mW at the fiber tip in a continuous wave (CW) mode. The laser system weighs 20 kg, and is portable. It runs on 100 V current. This system generates a laser beam with a wavelength (664 ± 2 nm) suitable for the light activation of NPe6 and yields high therapeutic efficiency.

2.5. Administration and laser irradiation method

In the phase I clinical study conducted previously, the optimal conditions yielding high safety and efficacy were suggested to be intravenous administration of NPe6 (40 mg/m^2) and irradiation of laser (100 J/cm^2) at 4 h after administration, using a diode laser apparatus [6]. The dosage and administration were, therefore, set accordingly. One vial of NPe6 containing 100 mg was dissolved in 4 ml of physiological saline and the defined dose (40 mg/m^2) was slowly injected intravenously. At 4 h after administration, a wavelength 664 nm laser beam was irradiated to the tumor site endoscopically using a directional quartz fiber (power density: 150 mW/cm^2, energy level: 100 J/cm^2). The output power and wavelength of laser were determined before and after irradiation using an optical power meter and an optical spectrum analyzer in order to confirm the performance of the laser apparatus.

2.6. Skin photosensitivity test

The back of the hand should be exposed to sunlight for 5 min to observe photosensitivity (e.g. erythema), followed by photography for the records at 1 h after the exposure. The test should be performed before administration and 2 weeks after administration. If photosensitivity is observed, the same test should be conducted within several days until it disappears, with the patient avoiding direct sunlight and intense incandescent light in the interim. The results of the skin photosensitivity test should be classified as "0: no reaction, 1: minimum visible erythema, 2: deep clearly defined erythema, 3: intense erythema or edema" according to the criteria specified for this study (*Guidelines for Assessment of NPe6 Test Value*).

Since patients receiving NPe6 may have a photochemical reaction to intense light, the indoor light intensity should be adjusted below 500 lux, using a digital lux meter, for 2 weeks from immediately after administration, using blackout curtains, etc., and the patients should be made to wear sunglasses, long sleeves, gloves and mask after administration. The patient is prohibited from going out into direct sunlight for 2 weeks after administration.

2.7. Safety evaluation

Severity grades of general findings, symptoms and signs as well as abnormal clinical laboratory findings are to be measured according to the "*Guidelines for Assessment of Adverse Drug Reactions*" instituted by the Japan Society of Clinical Oncology [8] which closely resemble the WHO criteria. Since severity grades of coughing, increased sputum, bloody sputum and C-reactive protein (CRP) increases are not specified in the "*Guidelines for Assessment of Adverse Drug Reactions*", these items were also categorized according to the criteria specified for this study (*Guidelines for Assessment of NPe6 Test Value*). The severity grades of coughing, increased sputum, bloody sputum were classified by a 4-grade scale of "1: mild, 2: moderate, 3: severe and 4: serious". The severity grades of CRP were classified by a 3-grade scale of "1: < 1.5 mg/dl, 2: 1.5–6.5 mg/dl, 3: > 6.5 mg/dl".

The causal relationship was graded by a 4-grade scale of "1: Definitely, 2: Probably, 3: Possibly and 4: None", and the adverse events corresponding to 1–3 were treated as adverse drug reactions.

2.8. Efficacy evaluation

The antitumor effect was rated, based on endoscopic measurement of tumor size using forceps, morphological observation and histopathological examination by biopsy, according to the "Criteria for the Evaluation of the Clinical Effects of Solid Cancer Chemotherapy" defined by the Japan Society of Clinical Oncology and the "General Rules for Clinical and Pathological Records of Lung Cancer" of the Japan Lung Cancer Society (4th edition) [9]. The antitumor effect was rated at 1 and 2 months after PDT. If it was difficult to evaluate the efficacy at 2 months, it was rated again up to 3 months after PDT. Antitumor effect was rated as CR (no demonstrable tumor for 4 weeks), partial response (PR: 50% or greater reduction in tumor size), no change (NC: less than 50% reduction or less than 25% increase in tumor size), progressive disease (PD: more than 25% increase in tumor size) or not evaluable (NE).

3. Results

Among 41 patients (46 lesions) registered, one patient refused to receive NPe6. Therefore, NPe6 was given to 40 patients (45 lesions, Table 1). All except one were male, and the median age was 67 years old. Performance status was 0 or 1 in all except one patient. The histological type was squamous cell carcinoma in all patients and all were carcinomas in situ (CIS) or early invasive carcinomas. There were 19 clinical stage 0 (CIS) cases (23 lesions), and 21 stage I cases (22 lesions). Fifteen cases were thought not to be surgical candidates because of underlying cardiopulmonary dysfunction, and 25 cases refused surgery and wished to receive PDT. Previous therapy had not been performed in 21 patients and 15 patients had received surgery before PDT. The maximum tumor dimensions were less than 1.0 cm in 33 lesions, more than 1.0 cm but less than 2.0 cm in ten lesions, and 2.0 cm in two lesions.

The evaluation committee judged five patients (six lesions) as ineligible for efficacy evaluation based on inclusion criteria, so there were 35 eligible patients (39 lesions). Among those, one patient who had two lesions was handled as an eligible patient with one eligible lesion, since one of the two lesions given PDT was an eligible lesion but the other lesion was ineligible because it was a benign tumor.

Table 1 Backgrounds of the patients

Total number of patients treated	40 patients (45 lesions)	
Age (years)	Mean: 65.9, Median: 67 (48–77)	
Height (cm)	Mean: 162.3 (143.8–180)	
Weight (kg)	Mean: 56.8 (39.0–76)	
Sex	Male	39 patients (44 lesions)
	Female	1 (1)
Performance status (ECOG PS)	0	26 patients
	1	13
	2	1
Disease stage	0	19 patients (23 lesions)
	I	21 (22)
Previous therapy for other lesion	None	21 patients
	Surgery	9
	Surg. + Rad. + Chemo.	1
	Surg. + Chemo.	1
	Surg. + Chemo. + PDT	2
	Surg. + PDT	2
	Rad.	1
	PDT	2
	Rad. + Chemo. + Electric cauterization	1
Maximum tumor size (cm)	< 0.5	7 lesions
	0.5–0.9	26
	1.0–1.4	10
	1.5–1.9	0
	2.0	2

3.1. Adverse drug reactions

The adverse drug reactions to this therapy (signs, symptoms and abnormal values of clinical laboratory measurements) are shown in Tables 2 and 3. No serious adverse drug reactions were observed. None of the symptoms were graded as grade 3 or more, and those showing grade 2 reactions had either increased CRP (four patients), increased sputum (2), cough (1), fever (1) and neutropenia (1), and all other reactions were of grade 1.

3.2. Skin photosensitivity test

The results of the skin photosensitivity test are shown in Table 4. Twenty eight of 33 patients (84.8%) in whom the first skin photosensitivity test was performed had no photosensitivity by 14 days after drug administration. Five patients showed reaction to light (minimal visible erythema in three patients, deep clearly defined erythema in one patient and blister formation in one patient), but on a second additional test performed within 7 days thereafter, disappearance of the photosensitivity was confirmed in all five patients. Seven patients in whom the first skin photosensitivity test was performed 15–18 days after administration showed no reaction at the time of testing.

3.3. Efficacy

The antitumor effects of PDT according to lesion and patient are shown in Table 5. A verification study was conducted in patients with endoscopically evaluated early stage lung cancer by setting the expected rate of CR at 90.0% with the range of 95.0% confidence interval at 0.2. On a per lesion basis, the CR rate was 84.6% (33/39 lesions) and the overall response rate was 94.9% (37/39 lesions). On a per patient basis, the CR rate was 82.9% (29/35 patients) and the overall response rate was 94.3% (33/35 patients). Since the rate of CR exceeded the lower limit of the expected rate of CR (80.0%), the efficacy of NPe6 was confirmed.

4. Discussion

PDT was first applied clinically for endoscopically early stage lung cancer at our institution using an argon dye laser combined with a tumor-specific photosensitizer, hematoporphyrin derivative (HpD) in March 1980 [10], and subsequently Kato et al. reported the first case of 5-year disease-free survival in a case of early stage lung cancer treated only by PDT [11]. In 1988, a multicentric study on PDT for early stage lung cancer performed by the PDT cancer group of the Ministry of Health and Welfare demonstrated that the rate of CR was 77.3% (51/66 lesions) and 100% in the cases less than 1.0 cm in diameter (28 lesions), and the recurrence rate was 15.7% (8/51 lesions) [12].

Thereafter, a prospective phase II study on PDT with Photofrin for centrally located early stage lung cancer was conducted using either an argon dye laser or excimer dye laser from June 1989 to February 1992 [13], and demonstrated excellent PDT efficacy (CR rate: 84.8%, recurrence rate: 10.0%). The Japanese government approved the use of this modality using an excimer dye laser combined with Photofrin for early stage lung cancer in October 1994, and reimbursement

Table 2 Adverse drug reactions (signs and symptoms)

Item	Number of patients evaluated	Incidence (%)	Grade			
			1	2	3	4
Pruritus cutaneous [c]	40	2 (5.0)	2	0	0	0
Itching of forehead and backs of both hands[c]	40	1 (2.5)	1	0	0	0
Blisters[c]	40	1 (2.5)	1	0	0	0
Coughing[b]	40	6 (15.0)	5	1	0	0
Increased sputum[b]	40	11 (27.5)	9	2	0	0
Bloody sputum[b]	40	10 (25.5)	10	0	0	0
Sorethroat[c]	40	2 (5.0)	2	0	0	0
Chest discomfort[c]	40	1 (2.5)	1	0	0	0
Fever[a]	40	4 (10.0)	3	1	0	0
Abnormal ECG	37	1 (2.5)	–	–	–	–

–, Not graded.
[a] The item was graded according to the *"Guidelines for Assessment of Adverse Drug Reactions"* established by the Japan Society of Clinical Oncology.
[b] These items were graded according to the 4-grade scale specified in the protocol, since those are not specified in the *"Guidelines for Assessment of Adverse Drug Reactions"* established by the Japan Society of Clinical Oncology.

through the National Health Insurance began in April 1996. After the approval of PDT, the number of cases treated by PDT gradually increased year by year (20–30 cases per year at Tokyo Medical University).

While the effectiveness of PDT using Photofrin has been recognized clinically, it is not widely employed, partly because of the cost and the large size of the laser equipment and the problems posed by skin photosensitization. The incidence of cutaneous phototoxic reactions induced by Photofrin (0.5–2.0 mg/kg, iv) was assessed in a series of 180 patients by Dougherty et al. [1]. Overall, 20–40% of patients reported some type of phototoxic response. Many of the clinical reviews of PDT written in the past few years have concluded that this promising approach to the treatment of solid malignant tumors requires better photosensitizers which may be more efficient than Photofrin and which will not induce prolonged cutaneous photo-

Table 3 Abnormal changes in clinical laboratory measurements

Item	Number of patients evaluated	Incidence (%)	Grade[a]			
			1	2	3	4
Leukocytosis	40	1 (2.5)	–	–	–	–
Decreased hemoglobin	40	1 (2.5)	1	0	0	0
Leucopenia	40	1 (2.5)	0	1	0	0
Neutropenia	40	1 (2.5)	0	1	0	0
Lymphocytosis	40	2 (5.0)	–	–	–	–
Monocytosis	40	1 (2.5)	–	–	–	–
Thrombocytopenia	40	1 (2.5)	1	0	0	0
AST (GOT) increased	40	1 (2.5)	1	0	0	0
ALT (GPT) increased	40	4 (10.0)	4	0	0	0
Al-P increased	40	1 (2.5)	1	0	0	0
Serum calcium decreased	40	1 (2.5)	1	0	0	0
Urinary protein increased	39	1 (2.6)	1	0	0	0
CRP increased[b]	37	8 (21.6)	4	4	0	0

–, No grading scale.
[a] Each item was graded according to the *"Guidelines for Assessment of Adverse Drug Reactions"* established by the Japan Society of Clinical Oncology, except for leukocytosis, lymphocytosis and monocytosis.
[b] CRP was classified by a 3-grade scale of "1: < 1.5 mg/dl, 2: 1.5–6.5 mg/dl, 3: > 6.5mg/dl".

Table 4 Results of the first skin photosensitivity test

Item	Days after administration (days)										Total
	9	10	11	12	13	14	15	16	17	18	
Number of patients tested	1	–	–	1	1	30	1	4	1	1	40
Negative reaction	1	–	–	1	0	26	1	4	1	1	35
Positive reaction	0	–	–	0	1	4	0	0	0	0	5

sensitivity [14,15]. There is, therefore, great interest in the synthesis of new sensitizing agents for use in PDT.

Among the second generation photosensitizers, NPe6 is considered as a promising photosensitizer and has shown antitumor efficacy in a murine tumor model and rapid clearance from skin [5]. This compound has a major absorption peak at 664 nm, i.e. 34 nm longer than the treatment wavelength of Photofrin. As a result, greater photodynamic efficacy with a slight gain in penetration depth of light is possible. The synthesis of NPe6 was first described by Bommer et al. in 1985 [16], and this new compound was considered as a candidate photosensitizer of PDT for tumors [17]. The characteristics of this compound include a low degree of skin photosensitivity [18], and a high degree of affinity for malignant tissues [19]. Kessel demonstrated that the kinetics of NPe6 elimination from plasma is consistent with a half-life (T1/2ß) of approximately 134 h [20] which agrees with the data of our phase I study [6], which is much shorter than the approximately 250 h of Photofrin. NPe6 is eliminated almost twice as rapidly as Photofrin. Wong et al. compared NPe6 in animal experiments to HpD, which is a proto-drug of Photofrin, and demonstrated the superiority of NPe6 to HpD in terms of tumor volume reduction, inhibition of tumor regrowth, depth of tissue necrosis and duration of cutaneous photosensitization [21].

Commonly used laser systems are the argon dye laser in Europe and North America and excimer dye laser in Japan. The argon dye laser or excimer dye laser systems are costly and bulky, therefore, these systems are not portable, lack convenience and a special laser suite is necessary. The prolonged skin photosensitivity of Photofrin and high cost and bulky size of laser systems have limited the widespread acceptance of PDT. Therefore, the ideal laser system for PDT would be compact, easy to handle, almost maintenance free and inexpensive. A small size diode laser is considered as a candidate laser system for PDT instead of the bulky gas dye laser system. A low cost diode laser system is commonly used as a light source for pain control in Japan, but it is normally impossible to use this diode laser for PDT with commonly available photosensitizers, because its wavelength is too long to activate the photosensitizers. The absorption wavelength of NPe6 is longer than those for excitation of other commonly used photosensitizers. Recently, a new diode laser system has been developed and this system is considered to have potential for PDT applications with NPe6.

As mentioned above, second generation PDT using NPe6 combined with a diode laser was developed to solve the problems of the initial PDT approach using Photofrin and a dye laser system. The phase II clinical study was conducted to investigate the efficacy and safety of NPe6 in patients with endoscopically evaluated early stage lung cancer using the dosage, the safety and efficacy of which had been verified in the previous phase I clinical study. The previous phase II clinical study on Photofrin performed by Furuse et al. demonstrated that the longitudinal length of tumor extent was the only independent prognostic factor for CR [13], therefore, we decided that tumor size should be not more than 2.0 cm in greatest dimension and that the peripheral margin of these lesions must be accessible for observation in order to irradiate sufficient laser light. In our study, CRs were obtained in 84.6% of lesions and 82.6% of cases. These encouraging results are similar to the data of the previous phase II clinical study on Photofrin (84.8% of lesions) and the data of Tokyo Medical University (81.1% of cases) [22].

Table 5 Anti-tumor effects by lesion and by patient

Classification	Eligible	CR	PR	NC	PD	NE	CR rate (%)	95.0% confidence rate (%)	Response rate (%)
Lesion	39	33	4	2	0	0	84.6	69.5–94.1	94.9
Patient	35	29	4	2	0	0	82.9	66.4–93.4	94.3

There were no serious adverse effects of grade 3 or more. The few cases showing grade 2 reactions included increased CRP, increased sputum, coughing, fever and neutropenia. These reactions seemed to be due to the photodynamic reaction and bronchoscopic examinations, and were considered not to be directly related to NPe6 of diode laser irradiation. Among the grade 1 reactions, the "itching of the forehead and the backs of both hands" in one patient occurred since the patient exposed himself to direct sunlight before the skin photosensitivity test. Blisters in one patient and cutaneous pruritus in two patients were observed in the skin photosensitivity test conducted soon after administration. In the phase II study on Photofrin, toxicity assessment showed grade 2 adverse reactions of transient elevation of ALT (1.9%), allergic reaction (3.8%), pulmonary toxicity including exertional dyspnea and fever due to bronchitis and obstructive pneumonia (7.7%) and sunburn (1.9%). These reactions of ALT elevation and allergy might be derived from the hydrophobic property of Photofrin, but our study showed no liver dysfunction and no allergic reaction more than grade 2 due to the effects of the hydrophilic property of NPe6.

Grade 2 pulmonary toxicity was seen in 7.5% (three out of 40 cases) in our study, which is similar to the study on Photofrin. The most frequent adverse effect of Photofrin was skin photosensitization, which was recognized in 28.8% (grade 1) and 1.9% (grade 2). However, our study showed very low skin photosensitivity, 10.0% (four out of 40 cases) grade 1 and 0.0% grade 2–4, compared with Photofrin, and there was no skin photosensitization in any case. It was confirmed that the reactivity to light disappeared in most patients by 2 weeks after administration (84.8%) and also disappeared in the remaining patients by 3 weeks after administration. The number of days required for disappearance of the reaction to light was consistent with the results obtained in the skin photosensitivity test conducted in the phase I clinical study by irradiating imitation sunlight on the back of each patient. In PDT using NPe6, the incidence of hypersensitivity to light was very low and hyperpigmentation was not observed, while hypersensitivity to light was seen frequently with Photofrin [1].

The present study demonstrated the excellent anti-tumor effects and safety of NPe6 according to the administration dosage verified in the previous phase I clinical study, in patients with endoscopically evaluated early stage lung cancer. PDT using this newly developed second generation photosensitizer, NPe6, and a diode laser was proven safe and effective and will likely be a standard modality of PDT for central type early superficial squamous cell lung carcinoma in the next several years.

Acknowledgements

The authors wish to thank Professor J.P. Barron of the International Medical Communications Center of Tokyo Medical University for his review of the manuscript.

References

[1] Dougherty TJ, Cooper MT, Mang TS. Cutaneous phototoxic occurrence in patients receiving Photofrin. Lasers Surg Med 1990;10:485–8.
[2] Bellnier DA, Ho Y, Pandey RK, et al. Distribution and elimination of Photofrin II in mice. Photochem Photobiol 1987;50:221–8.
[3] Potter WR, Mang TS, Dougherty TJ. The theory of photodynamic therapy dosimetry: consequences of photodestruction of sensitizer. Photochem Photobiol 1987;46:97–101.
[4] Edell ES, Cortese CA. Photodynamic therapy in the management of early superficial squamous cell carcinoma as an alternative to surgical resection. Chest 1992;102:1319–22.
[5] Katsumi TA, Aizawa K, Kuroiwa Y, et al. Photodynamic therapy with a diode laser for implanted fibrosarcoma in mice employing mono-L-aspartyl chlorin E6. Photochem Photobiol 1996;64:671–5.
[6] Furukawa K, Okunaka T, Tsuchida T, et al. A phase I clinical study of photodynamic therapy for early stage lung carcinoma using ME2906 and a diode laser system. Porphyrins 1998;7:199–206.
[7] Gomi S, Nishizuka T, Ushiroda O, et al. The structure of mono-L-aspartyl chlorin e6 and its related compounds. Heterocycles 1998;48:2231–43.
[8] Niiya H, Abe R, Ibuti K, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. Int J Clin Oncol 1997;32:61–5.
[9] General rules for clinical and pathological records of lung cancer. 4th ed., The Japan Lung Cancer Society, editors. Tokyo: Kanehara & Co. Ltd., 1995. p. 123–33.
[10] Hayata Y, Kato H, Konaka C, et al. Hematoporphyrin derivative and laser photoradiation in the treatments of lung cancer. Chest 1982;81:269–77.
[11] Kato H, Konaka C, Kawate N, et al. Five-year disease-free survival of a lung cancer patient treated only by photodynamic therapy. Chest 1986;90:768–70.
[12] Kato H. Study on photodynamic therapy by laser. Annual report of the Cancer Research Ministry of Health and Welfare. National Cancer Center, 1988. p. 62–30:255–261, in Japanese.
[13] Furuse K, Fukuoka M, Kato H, et al. A prospective phase II study on photodynamic therapy with Photofrin II for centrally located early-stage lung cancer. J Clin Oncol 1993;11:1852–7.
[14] Dougherty TJ, Marcus SL. Photodynamic therapy. Eur J Cancer 1992;28A:1734–42.
[15] Marcus SL. Clinical photodynamic therapy: the continuing evolution. In: Henderson BW, Dougherty TJ, editors. Photodynamic therapy, basic principles and clinical applications. New York: Dekker, 1992:219–68.

[16] Bommer JC, Svejda AJ, Petryka ZJ, et al. The relationship between the structure of a tetrapyrrole and the selective fluorescence in tumors. In: Jori G, Perria C, editors. Photodynamic therapy of tumors and other diseases. Padova: Libreria Progretto, 1985:204–6.
[17] Spikes JD, Bommer JC. Photosensitizing properties of mono-L-aspartyl chlorin e6 (NPe6): a candidate sensitizer for the photodynamic therapy of tumors. J Photochem Photobiol B 1993;17:135–43.
[18] Nelson J, Roberts WG, Berns MW. In vivo studies on the utilization of mono-L-aspartyl chlorin (NPe6) for the photodynamic therapy. Cancer Res 1987;47:4681–5.
[19] Aizawa K, Okunaka T, Ohtani T, et al. Localization of mono-L-aspartyl chlorin e6 (NPe6) in mouse tissues. Photochem Photobiol 1987;46:789–94.
[20] Kessel D. Pharmacokinetics of *N*-aspartyl chlorin e6 in cancer patients. J Photochem Photobiol B 1997;39:81–3.
[21] Wong K, Song LM, Wang KK, et al. Mono-L-aspartyl chlorin e6 (NPe6) and hematoporphyrin derivative (HpD) in photodynamic therapy administered to a human cholangiocarcinoma model. Cancer 1998;15(82):421–7.
[22] Kato H. Photodynamic therapy for lung cancer—a review of 19 years' experience. J Photochem Photobiol B 1998;42:96–9.

Original article

Annals of Oncology 14: 709–714, 2003
DOI: 10.1093/annonc/mdg213

Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI)

I. Sekine[1]*, Y. Nishiwaki[2], K. Noda[3], S. Kudoh[4], M. Fukuoka[5], K. Mori[6], S. Negoro[7], A. Yokoyama[8], K. Matsui[9], Y. Ohsaki[10], T. Nakano[11] & N. Saijo[11]

On behalf of the Japan Clinical Oncology Group (JCOG) Lung Cancer Study Group

[1]*Department of Internal Medicine, National Cancer Center Hospital, Tokyo;* [2]*Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa;* [3]*Division of Internal Medicine, Kanagawa Cancer Center, Yokohama;* [4]*First Department of Internal Medicine, Osaka City University Medical School, Osaka;* [5]*Department of Internal Medicine, Kinki University School of Medicine, Osaka;* [6]*Division of Internal Medicine, Tochigi Prefectural Cancer Center, Utsunomiya;* [7]*Department of Pulmonary Medicine, Osaka City General Hospital, Osaka;* [8]*Division of Internal Medicine, Niigata Cancer Center Hospital, Niigata;* [9]*Department of Internal Medicine, Osaka Prefectural Habikino Hospital, Osaka;* [10]*First Department of Medicine, Asahikawa Medical College, Asahikawa;* [11]*Third Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan*

Received 7 October 2002; revised 9 December 2002; accepted 23 January 2003

Background: The purpose of this study was to evaluate the toxicity and antitumor effect of cisplatin, irinotecan and etoposide combinations on two schedules, arms A and B, for previously untreated extensive small-cell lung cancer (E-SCLC), and to select the right arm for phase III trials.

Patients and methods: Sixty patients were randomized to receive either arm A (cisplatin 25 mg/m^2 day 1, weekly for 9 weeks, irinotecan 90 mg/m^2 day 1, on weeks 1, 3, 5, 7 and 9, and etoposide 60 mg/m^2 days 1–3, on weeks 2, 4, 6, 8), or arm B (cisplatin 60 mg/m^2 day 1, irinotecan 60 mg/m^2 days 1, 8, 15, and etoposide 50 mg/m^2 days 1–3, every 4 weeks for four cycles). Prophylactic granulocyte colony-stimulating factor support was provided in both arms.

Results: Full cycles were delivered to 73% and 70% of patients in arms A and B, respectively. Incidences of grade 3–4 neutropenia, anemia, thrombocytopenia, infection and diarrhea were 57, 43, 27, 7 and 7%, respectively, in arm A, and 87, 47, 10, 13 and 10%, respectively, in arm B. A treatment-related death developed in one patient in arm A. Complete and partial response rates were 7% and 77%, respectively, in arm A, and 17% and 60%, respectively, in arm B. Median survival time was 8.9 months in arm A, and 12.9 months in arm B.

Conclusions: Arm B showed a promising complete response rate and median survival with acceptable toxicity in patients with E-SCLC, and should be selected for the investigational arm in phase III trials.

Key words: cisplatin, etoposide, irinotecan, randomized phase II, small-cell lung cancer

Introduction

Small-cell lung cancer (SCLC), which accounts for approximately 12% of all malignant pulmonary tumors in Japan [1], pursues an aggressive clinical course with rapid growth and early widespread metastases. Whereas chemotherapy combined with thoracic radiotherapy yields a high response rate and significant prolongation of survival in patients with limited disease, treatment of extensive disease remains palliative, and long-term survivors beyond 2 years are extremely rare [2]. A combination of cisplatin and etoposide (PE) has been the standard treatment, with response rates ranging from 60% to 90% and median survival times (MSTs) from 8 to 11 months in this patient population [3–5].

Irinotecan, a water-soluble camptotheçin derivative, has been shown to exhibit excellent antitumor activity against SCLC in monotherapy and in combination with cisplatin [6, 7].

A previous phase III trial of the PE regimen versus a combination of cisplatin and irinotecan (PI) in patients with extensive SCLC showed that the PI regimen produced an MST of 12.8 months and a 2-year survival of 21%, which were significantly better than the results with the PE regimen [8]. However, since etoposide is still considered one of the key drugs for the treatment of SCLC, a combination of these three drugs, cisplatin, irinotecan and etoposide (PIE), seemed to be a promising strategy for advanced SCLC. We previously determined the recommended doses of the PIE regimens for two schedules, weekly and every 4 weeks, independently [9, 10]. In this phase II study, we evaluated the two PIE regimens.

Correspondence to: Dr I. Sekine, Department of Internal Medicine, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: isekine@ ncc.go.jp