well-designed and timely clinical trials as soon as feasible and to finish the trials adequately and as rapidly as possible.

2.7. *Lung Oncology Group in Kyushu*

The Lung Oncology Group in Kyushu (LOGiK) was established in 2004 as a voluntary cooperative group to perform multicenter clinical trials for thoracic malignant diseases, mainly lung cancer, and is headquartered at the Research Institute for Diseases of the Chest at Kyushu University (Fig. 1, Table 1). It comprises a large network of medical oncologists, thoracic surgeons and physicians, radiologists, pathologists, and biostatisticians at public and private institutions across the country, although most LOGiK member institutions are located in Kyushu districts. As of 10 January 2014, the group had 322 members affiliated with 89 medical institutions. The operational policy of the group is decided at regularly held board meetings. Plans for clinical trials can be proposed by any member of the group and are discussed in detail by the protocol committee and, as necessary, by the pathology committee or radiology committee. The activities of the group are funded and supported by the Clinical Research Support Center Kyushu (CReS Kyushu), whose services include various aspects of clinical trials such as registration and assignment of patients, trial monitoring, collection of case report forms, and data cleaning. The biostatistics committee at CReS Kyushu meets regularly with contact biostatisticians to analyze clinical trial data or provide advice for trial planning. LOGiK has conducted various phase II and feasibility trials for lung cancer [17,18] and currently has 13 active clinical trials.

2.8. *North East Japan Study Group*

In January 2006, 35 institutions belonging to four Japanese regional groups in Hokkaido, Tohoku, Saitama, and Tokyo joined together to conduct a phase II study (NEJ001) and a phase III study (NEJ002) of patients with EGFR mutation-positive NSCLC screened with the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method developed by Koichi Hagiwara (Table 1). This North East Japan Study Group (NEJSG) was established with the assistance of Hisanobu Niitani, who was the chairperson of TCOG. Together, NEJ001 and NEJ002 showed that EGFR-TKI treatment conferred long-term PFS and a better quality of life and thereby helped to open the door to personalized medicine in the field of lung cancer [19–21]. NEJSG became an NPO in December 2010 for the performance of clinical studies in which biological investigation is important. The aim of NEJSG is to develop, conduct, coordinate, and stimulate translational and clinical research to improve the management of lung cancer and related problems and to increase the survival and quality of life of affected individuals. At present, 108 institutions located in the original four regions as well as in two additional regions (Tochigi and Niigata) are active in NEJSG studies.

NEJSG is currently conducting a randomized phase III study comparing single-agent gefitinib with the combination of carboplatin-pemetrexed and gefitinib followed by continuation maintenance therapy with pemetrexed and gefitinib in patients with advanced nonsquamous NSCLC positive for activating mutations of EGFR (Fig. 2D). The primary end point of this study is the OS.

3. Conclusions and future perspectives

Although only eight cooperative study groups in Japan are reviewed here because of space limitations, several other Japanese groups are also conducting clinical trials for lung cancer. The establishment of multiple study groups to perform clinical trials for this single disease is indicative of the high priority given to the development of new treatment strategies for lung cancer through such trials in Japan, but it also presents several challenges. First, it may be difficult for all such groups to be associated with a data center that maintains data quality, ensures the scientific integrity of trial results, and minimizes the risk to enrolled patients. Second, the number of clinical trials that target small subsets of patients with specific driver oncogenes, specific histological subtypes of lung cancer, poor performance status, or advanced age is increasing. Overlap in such trials performed by different groups and institutional overlap among clinical trial groups do not represent optimal use of limited resources. Third, the number of groups that are able to complete phase III trials is limited to date, given the large sample size required and the complexity of data management for such trials. The division of roles in each cooperative study groups is essential to improve efficiency of clinical trials in Japan.

To overcome these challenges, Japanese cooperative groups have increased the extent of their collaboration. Indeed, several intergroup clinical trials for advanced NSCLC (including those performed by JCOG and WJOG, NEJSG and TCOG, and OLCSG and LOGiK) are now ongoing (Fig. 3A–C). In addition, seven Japanese cooperative groups are working together to conduct a large randomized phase III trial comparing cisplatin plus vinorelbine with cisplatin plus pemetrexed in patients with completely resected nonsquamous NSCLC of p-stage II or III (Fig. 3D). The primary end point of this study is the OS, and a total of 800 patients will be enrolled. The study, named JIPANG, was designed to test a new application of pemetrexed to adjuvant chemotherapy in Japan. Smooth implementation of such intergroup studies requires abundant funds; however, Japan does not seem to have an effective national funding system for cooperative study groups. In United State of America, the National Cancer Institute has provided enormous funds for the consolidation of several cooperative groups and the merging of groups focused on a single disease site or modality with multidisciplinary groups.

Although institutional barriers to the performance of such large intergroup trials remain, further harmonization and collaboration among cooperative groups will be important in allowing Japanese investigators to generate new data that can change clinical practice and improve the clinical outcome of lung cancer patients.

Conflict of interest

Isamu Okamoto received honoraria from Pfizer Co., Eli Lilly K.K., and Taiho Pharmaceutical Co. Ltd.; Yuichiro Ohe

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received honoraria from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., and Daiichi Sankyo Co., Ltd. and research funding from Chugai Pharmaceutical Co. Ltd., Pfizer Co., AstraZeneca K.K., and Merck Serono, Eisai; Kazuhiko Nakagawa received honoraria from Abbott Japan Co. Ltd., Eli Lilly K.K., Takeda Bio Development Center Ltd., Daiichi Sankyo Co. Ltd., AstraZeneca K.K., Kyowa Hakko Kirin Co. Ltd., and Chugai Pharmaceutical Co. Ltd., and research funding from Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., Nippon Boehringer Ingelheim Co. Ltd., and Daiichi Sankyo Co. Ltd. and subsidies from Daiichi Sankyo Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Ono Pharmaceutical Co. Ltd.; Katsuyuki Kiura received honoraria from Pfizer Co., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd, and Eli Lilly K.K., and research funding from Phizer Co., Chugai Pharmaceutical Co. Ltd., Novartis Pharmaceutical K.K., and Daiichi Sankyo Co. Ltd. and subsidies from Sanofi K.K. and Chugai Pharmaceutical Co. Ltd.; Yuichi Takiguchi received honoraria from AstraZeneca K.K, Chugai Pharmaceutical Co. Ltd., Sanofi K.K., and Titan Ltd.; Koichi Takayama received honoraria from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., Phizer Co., and AstraZeneca K.K. and research grants from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., Kyowa Hakko Kirin Co. Ltd., and Phizer Co.; Masahiro Tsuboi received honoraria from AstraZeneca K.K., Eli Lilly K.K., Johnson and Johnson, Chugai Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd.; Nobuyuki Yamanoto received honoraria from Taiho Pharmaceutical Co. Ltd., Pfizer Co., Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., and Ono Pharmaceutical Co. Ltd.; Toshihiro Nukiwa received honoraria from Shionogi Pharmaceuticals and Boehringer Ingelheim Co. Ltd., research funding from AstraZeneca K.K. and Chugai Pharmaceutical Co. Ltd., and other fees from Sekisui Diagnostics; Hideo Saka received research funding from Daiichi Sankyo Co. Ltd., Ono pharmaceutical Co., AstraZeneca K.K., Novartis Pharmaceutical K.K., Eisai Co., Kyowa Hakko Kirin Co. Ltd., and Eli Lilly K.K.; Hiroaki Okamoto received research funding from Eli Lilly K.K., Chugai Pharmaceutical Co. Ltd., and Dainippon Sumitomo Pharma; the other authors have no conflict of interest.

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ORIGINAL REPORT

Randomized Phase III Trial of Erlotinib Versus Docetaxel As Second- or Third-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA)

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To investigate the efficacy of erlotinib versus docetaxel in previously treated patients with advanced non–small-cell lung cancer (NSCLC) in an epidermal growth factor receptor (EGFR) –unselected patient population.

Patients and Methods
The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), response rate, safety, and analyses on *EGFR* wild-type tumors. Patients with stage IIIB or IV NSCLC, previous treatment with one or two chemotherapy regimens, evaluable or measurable disease, and performance status of 0 to 2 were eligible.

Results
From August 2009 to July 2012, 150 and 151 patients were randomly assigned to erlotinib (150 mg daily) and docetaxel (60 mg/m^2 every 3 weeks), respectively. *EGFR* wild-type NSCLC was present in 109 and 90 patients in the erlotinib and docetaxel groups, respectively. Median PFS for erlotinib versus docetaxel was 2.0 *v* 3.2 months (hazard ratio [HR], 1.22; 95% CI, 0.97 to 1.55; $P = .09$), and median OS was 14.8 *v* 12.2 months (HR, 0.91; 95% CI, 0.68 to 1.22; $P = .53$), respectively. In a subset analysis of *EGFR* wild-type tumors, PFS for erlotinib versus docetaxel was 1.3 *v* 2.9 months (HR, 1.45; 95% CI, 1.09 to 1.94; $P = .01$), and OS was 9.0 *v* 10.1 months (HR, 0.98; 95% CI, 0.69 to 1.39; $P = .91$), respectively.

Conclusion
Erlotinib failed to show an improvement in PFS or OS compared with docetaxel in an EGFR-unselected patient population.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. Non–small-cell lung cancer (NSCLC) comprises more than 80% of all lung tumors. Approximately two thirds of NSCLCs are diagnosed at advanced stages. The standard first-line treatment for NSCLC, platinum-based doublet chemotherapy, has a response rate of approximately 30%, and the response usually lasts only 4 to 5 months.[1] Second- and third-line chemotherapy has been used to further improve survival. A standard regimen of docetaxel has been established based on results from randomized phase III studies of patients with previously treated advanced NSCLC,[2,3] in whom the median progression-free survival (PFS) in response to docetaxel was 2.0 to 2.5 months.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are active against previously treated NSCLC. Erlotinib, an EGFR-TKI, showed a significant survival benefit in a placebo-controlled phase III trial (BR21), with a median PFS of 2.2 months and hazard ratio (HR) of 0.61.[4] The noninferiority of gefitinib, another EGFR-TKI, to docetaxel in patients with previously treated NSCLC was shown in terms of survival in a global phase III study (Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere [INTEREST], n = 1,433)[5]

but not in a smaller phase III study in Japan (V15-32, n = 489).[6] A global phase IV study of erlotinib (Tarceva Lung Cancer Survival Treatment [TRUST], n = 6,580) showed a PFS of 3.3 months[7] and a much longer PFS (5.6 months) in an Asian subset.[8] Although both erlotinib and docetaxel are considered standard therapies for previously treated NSCLC, given the favorable survival in erlotinib-treated Asian patients, erlotinib might produce longer PFS than docetaxel in Asian patients with previously treated NSCLC in an EGFR-unselected population.

The Docetaxel and Erlotinib Lung Cancer Trial (DELTA) is a multicenter, open-label, phase III study from Japan. Because gefitinib failed to show noninferiority to docetaxel in the V15-32 trial, we investigated the efficacy and tolerability of erlotinib versus docetaxel as second- or third-line treatment for *EGFR*-unselected patients with NSCLC.

When this study was initiated, EGFR-TKIs were usually used without testing for EGFR mutational status in clinical practice. Then, the pivotal Iressa Pan-Asia Study (IPASS) study showed that gefitinib was superior to carboplatin and paclitaxel in terms of PFS in patients with *EGFR* mutant tumors (HR, 0.48; 95% CI, 0.36 to 0.64), whereas the opposite results were observed in patients with *EGFR* wild-type tumors (HR, 2.85; 95% CI, 2.05 to 3.98) in the first-line setting.[9] Given the advancement of molecular knowledge, we preplanned an analysis to examine the treatment effect in *EGFR* wild-type and *EGFR* mutant disease.

PATIENTS AND METHODS

Patients

This multicenter, open-label, randomized phase III study was sponsored by the National Hospital Organization, an independent administrative agency in Japan. Patients age 20 years or older were eligible if they met the following criteria: pathologically or histologically proven NSCLC with stage IIIB or IV disease (International Union Against Cancer, version 6); previous treatment with one or two chemotherapy regimens, including at least one platinum agent; evaluable or measurable disease by computed tomography (CT) or magnetic resonance imaging; and Eastern Cooperative Oncology Group performance status (PS) of 0 to 2. The main exclusion criteria were previous exposure to EGFR-TKI or docetaxel, symptomatic brain metastasis, and a second active cancer. Patients were also excluded from the study if they had interstitial pneumonia or pulmonary fibrosis detected by chest CT. All enrolled patients provided written informed consent before entering the study. The protocol was approved by the institutional review boards and ethics committees of the National Hospital Organization.

Treatment

Erlotinib (150 mg per day) was administered orally. Docetaxel was administered every 3 weeks as a 1-hour intravenous infusion of 60 mg/m^2 (ie, the approved dose in Japan). Adverse events were monitored and graded according to the Common Terminology Criteria for Adverse Events (version 3.0). Patients received the study treatment until disease progression or intolerable toxicities. Poststudy treatment was given at the discretion of the physician and patient, and cross-over treatment was allowed in this trial.

Assessments

Tumors assessments were performed via CT, spiral CT, or magnetic resonance imaging, and the same methods of measurement were used throughout the study for each patient. PFS was defined as the time from random assignment to the earliest occurrence of disease progression or death from any cause; patients who had not experienced progression or died at data cutoff were censored at the last tumor assessment. Overall survival (OS) was assessed from the date of random assignment to the date of death as the result of any cause, or data were censored at the last date the patient was confirmed to be alive. Tumor response according to RECIST was assessed at baseline, every month for the first 4 months, and every 2 months thereafter. Investigator assessment of best overall tumor response was used for the analysis. Routine laboratory assessments were performed at baseline, every week for the first month, and every 2 to 4 weeks thereafter. *EGFR* mutations were examined in exons 18 to 21 by a highly sensitive polymerase chain reaction (PCR)–based method (ie, the PCR-invader method, peptide nucleic acid–locked nucleic acid PCR clamp method, or cycleave method). These assays were performed in commercial laboratories to which each institute sent the diagnostic tumor samples.[10]

Statistical Analysis

Eligible patients were randomly assigned 1:1 to erlotinib or docetaxel by the minimization method according to sex, performance status, histology, and institution. Efficacy analyses were completed for the intent-to-treat population. Safety analyses were performed for the population who received at least one dose of the trial medication after random assignment. The primary end point was PFS. Secondary end points were OS, response, safety, and analyses on *EGFR* wild-type and mutant tumors. Median PFS was assumed to be 3.5 months and 2.5 months in patients receiving erlotinib and docetaxel, respectively, based on data from previous clinical trials.[2,7,8] The present study was

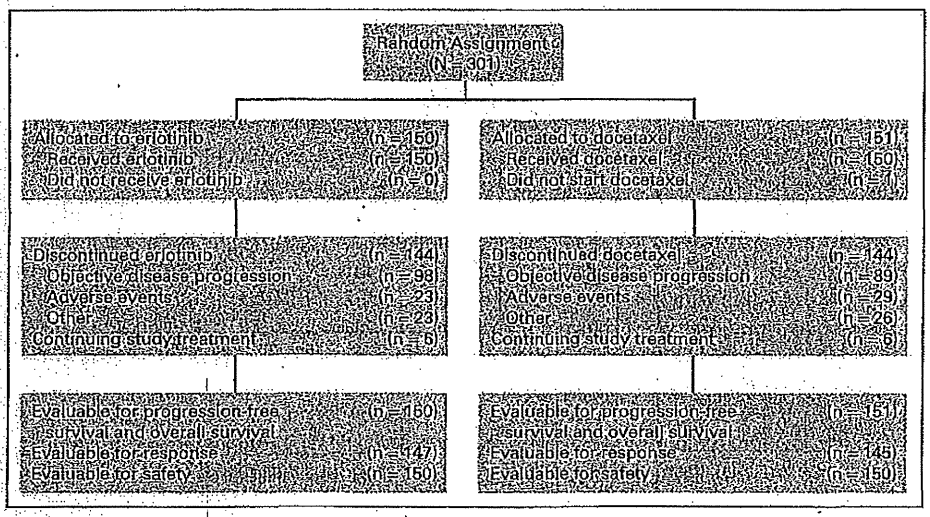

Fig 1. CONSORT diagram.

designed to assess the efficacy of erlotinib versus docetaxel in *EGFR*-unselected patients and to have 80% power to detect a 1-month difference at a two-sided significance level of $P = .05$. A sample size of 300 patients was planned based on these assumptions. Final analysis was planned after 278 events. Survival curves were calculated using the Kaplan-Meier method, and a log-rank test was used to compare treatment groups. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[11] Estimates of the treatment effect were expressed as HRs and two-sided 95% CIs from a Cox regression model for erlotinib versus docetaxel.

Subgroup analyses for PFS were performed to explore the potential interaction effect of the treatment groups with sex (male *v* female), PS (0 *v* 1 or 2), stage (IIIB *v* IV), histology (adenocarcinoma *v* other), and smoking status (ever *v* never). Response, toxicity, and patient characteristics were compared between the treatment groups using Fisher's exact test, and age was compared using the Wilcoxon rank sum test. As secondary end points, we performed similar analyses for PFS and OS in patients with *EGFR* wild-type and *EGFR* mutant tumors. To assess the homogeneity of the treatment effect on PFS and OS, an interaction term of treatment and *EGFR* mutation status (wild-type, exon 19 deletion or L858R, or other) was evaluated in the Cox model using the likelihood ratio test. To correct for potential confounding of patient characteristics other than the *EGFR* mutation status in these subgroup analyses, adjusted HRs were also calculated using the Cox regression model, including stratification factors with the exception of institution. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Table 1. Patient Demographics and Clinical Characteristics for All Study Patients

Demographic or Clinical Characteristic	Erlotinib (n = 150) No. of Patients	%	Docetaxel (n = 151) No. of Patients	%
Sex				
Female	42	28.0	44	29.1
Male	108	72.0	107	70.9
Age, years				
Median	68		67	
Range	37-82		31-85	
Stage				
IIIB	30	20.0	29	19.2
IV	120	80.0	122	80.8
Performance status				
0	77	51.3	78	51.7
1	67	44.7	67	44.4
2	6	4.0	6	4.0
Smoking status				
Ever-smoker	111	74.0	114	75.8
Never-smoker	39	26.0	37	24.5
Histology				
Adenocarcinoma	104	69.3	103	68.2
Squamous cell carcinoma	29	19.3	32	21.2
Others	17	11.3	16	10.6
First-line treatment	150	100	151	100
Platinum doublet	141	94.0	140	92.7
Platinum doublet + bevacizumab	6	4.0	10	6.6
Other	3	2.0	1	0.7
Second-line treatment	29	19.3	21	13.9
Platinum doublet	19	12.7	9	6.0
Platinum doublet + bevacizumab	3	2.0	3	2.0
Other	7	4.7	9	6.0
EGFR status				
Wild-type	109	72.7	90	59.6
Exon 19 deletion or L858R	21	14.0	30	19.9
Other mutations	2	1.3	3	2.0
Insufficient/not examined	18	12.0	28	18.6

Abbreviation: EGFR, epidermal growth factor receptor.

RESULTS

Patients

From August 2009 to July 2012, 301 patients were enrolled from 41 institutions belonging to the National Hospital Organization. In the intent-to-treat population, 150 and 151 patients were randomly assigned to erlotinib and docetaxel, respectively (Fig 1). The baseline characteristics were well balanced between the treatment groups in terms of age, sex, PS, smoking status, histology, first- and second-line chemotherapy regimens, and *EGFR* status (Table 1).

PFS, OS, and Response Rate in EGFR-Unselected Population

Median PFS time was 2.0 months (95% CI, 1.3 to 2.8 months) for erlotinib and 3.2 months (95% CI, 2.8 to 4.0 months) for docetaxel (Fig 2A), but this difference was not significant (HR, 1.22; 95% CI, 0.97 to 1.55; $P = .09$). At data cutoff (January 17, 2013) with median follow-up of 8.9 months, 141 patients (94.0%) in the erlotinib group and 138 patients (91.4%) in the docetaxel group experienced disease

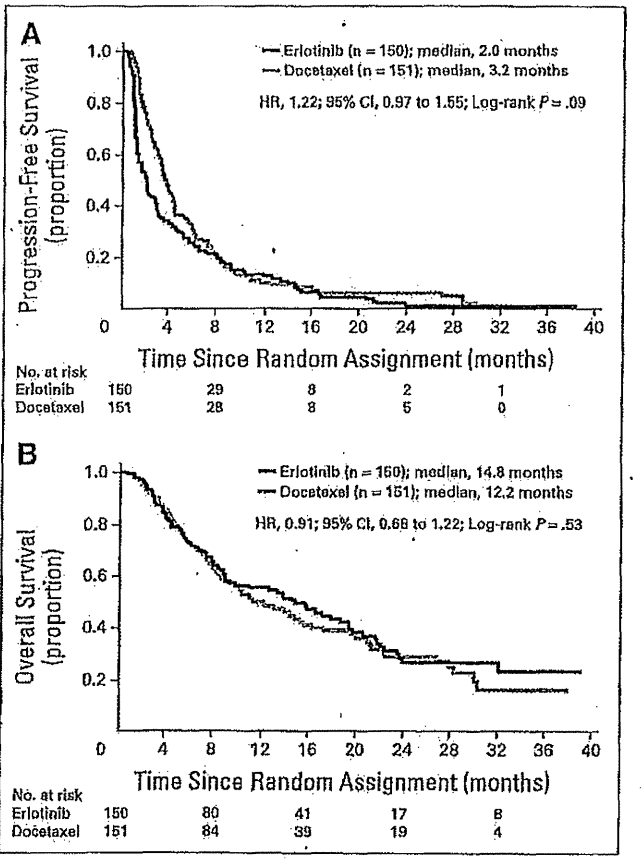

Fig 2. (A) Progression-free survival (all patients). (B) Overall survival (all patients). HR, hazard ratio.

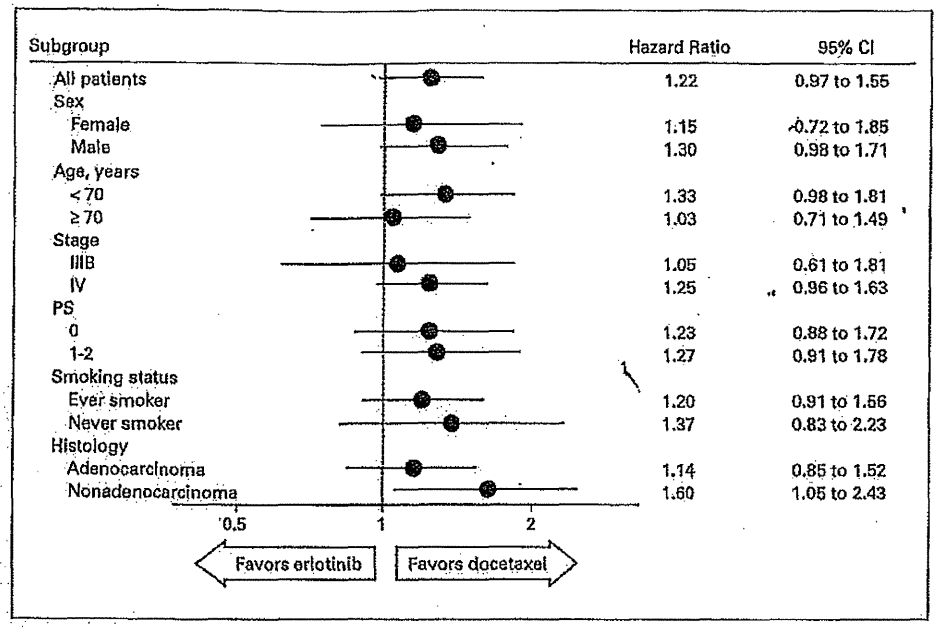

Fig 3. Progression-free survival in clinical subgroups (all patients). PS, performance status.

progression or death. The median OS time was 14.8 months (95% CI, 9.0 to 19.4 months) for erlotinib and 12.2 months (95% CI, 9.0 to 15.5 months) for docetaxel (HR, 0.91; 95% CI, 0.68 to 1.22; $P = .53$; Fig 2B). The number of patients with tumor response was similar in both groups; 25 patients (17.0%; 95% CI, 11.3% to 24.1%) responded in the erlotinib group, and 26 patients (17.9%; 95% CI, 12.1% to 25.2%) responded in the docetaxel group ($P = .88$). A complete response was reported in the erlotinib group in one patient with unknown *EGFR* status. As shown in Figure 3, subgroup analyses for PFS revealed that there was no significant difference between the two drugs, with the exception of nonadenocarcinoma histology (HR, 1.60; 95% CI, 1.05 to 2.43; $P = .03$). All factors numerically favored docetaxel.

PFS, OS, and Response Rate in EGFR *Wild-Type and Mutant Tumors*

EGFR status was determined in 255 (84.7%) of 301 patients, including 199 patients with wild-type *EGFR* NSCLC and 51 patients with active mutant *EGFR* NSCLC. The interaction term between treatment and *EGFR* mutation status was significant for PFS but not for OS ($P = .03$ and $P = .20$, respectively). In patients with *EGFR* wild-type disease, there was no significant difference between the erlotinib and docetaxel groups regarding sex (men and women: 85 and 24 *v* 68 and 22 patients, respectively; $P = .74$), age (median age, 68 *v* 67 years, respectively; $P = .96$), PS (0, 1, and 2: 52, 52, and five *v* 38, 49, and three patients, respectively; $P = .66$), histology (adenocarcinoma and nonadenocarcinoma: 72 and 37 *v* 58 and 32 patients, respectively; $P = .88$), stage (IIIB and IV: 26 and 83 *v* 20 and 70 patients, respectively; $P = .87$), and smoking status (ever-smoker and never-smoker: 87 and 22 *v* 76 and 14 patients, respectively; $P = .46$). In patients with *EGFR* wild-type tumors, the docetaxel group had a significantly longer PFS (2.9 months; 95% CI, 2.1 to 3.3 months) than the erlotinib group (1.3 months; 95% CI, 1.1 to 2.0 months; Fig 4A). A supportive Cox analysis with stratification factors confirmed the significant difference (adjusted HR, 1.57; 95% CI, 1.18 to 2.11; $P < .01$). However, the difference in OS was not statistically significant. The median OS was 9.0 months (95% CI, 7.8 to 14.5 months) in the erlotinib group compared with 10.1 months (95% CI, 7.3 to 12.4 months) in the docetaxel group ($P = .91$; Fig 4B). In terms of tumor response, six patients (5.6%; 95% CI, 2.1% to 11.9%) responded to erlotinib, and 17 patients (20.0%; 95% CI, 12.1% to 30.1%) responded to docetaxel ($P < .01$).

In patients with *EGFR* mutations, median PFS and median OS were longer in the erlotinib group than in the docetaxel group (PFS: 9.3 *v* 7.0 months, respectively; OS: not reached *v* 27.8 months, respectively). However, these differences in PFS (Fig 4C) and OS (Fig 4D) were not statistically significant.

Safety

The safety population included 300 patients: 150 in each group (Table 2). The most common adverse event with erlotinib was rash (92.7%), whereas docetaxel was associated with fatigue (71.3%), nausea (50.0%), and hematologic toxicities. Grade 3 to 4 leukopenia, neutropenia, and febrile neutropenia were significantly more frequent with docetaxel compared with erlotinib (0.7% *v* 64.0%, 0.7% *v* 80.0%, and none *v* 15.3%, respectively; Table 2). Two patients in the erlotinib group died of interstitial lung disease, and one patient in the docetaxel group died as a result of infection.

Poststudy Treatment

The number of patients who received further treatment was similar in the two groups ($P = .22$). Sixty-one patients (42.3%) in the erlotinib group received docetaxel, and 55 patients (37.9%) in the docetaxel group received EGFR-TKIs. Other drugs were administered to 45 patients (31.3%) in the erlotinib group and 41 patients (28.3%) in the docetaxel group. In the unselected population, no difference in OS was observed between the erlotinib and docetaxel arms when comparing patients who went on to receive subsequent chemotherapy (HR, 0.96; 95% CI, 0.62 to 1.49; $P = .84$).

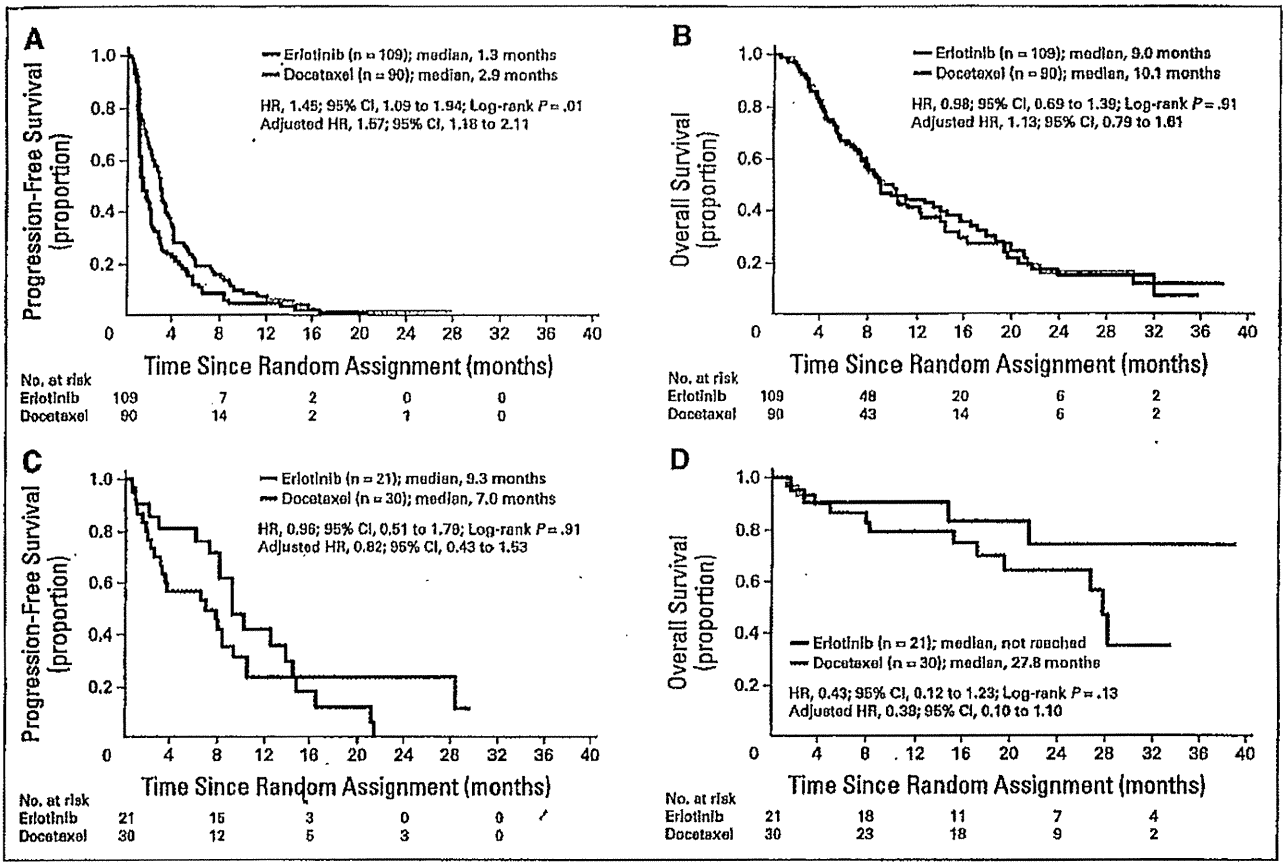

Fig 4. (A) Progression-free survival (PFS) in epidermal growth factor receptor (*EGFR*) wild-type tumors. (B) Overall survival (OS) in *EGFR* wild-type tumors. (C) PFS in *EGFR* mutant tumors (exon 19 deletion or L858R). (D) OS in *EGFR* mutant tumors (exon 19 deletion or L858R). HR, hazard ratio.

Similarly, no difference was observed in the unselected population between the two arms when comparing patients who did not go on to receive subsequent chemotherapy (HR, 1.28; 95% CI, 0.77 to 2.12; $P = .34$). However, patients with *EGFR* wild-type tumors who were treated with docetaxel and did not receive subsequent therapy had a trend toward longer OS when compared with patients treated with erlotinib (HR, 1.79; 95% CI, 0.95 to 3.35; $P = .06$). However, no significant difference in OS was seen between the

Table 2. Common Adverse Events

	All Grades					Grade 3 or 4				
	Erlotinib (n = 150)		Docetaxel (n = 150)			Erlotinib (n = 150)		Docetaxel (n = 150)		
Toxicity	No. of Patients	%	No. of Patients	%	*P*	No. of Patients	%	No. of Patients	%	*P*
Rash	139	92.7	22	14.7	< .01	20	13.3	1	0.7	< .01
Nausea	46	30.7	75	50.0	< .01	3	2.0	5	3.3	.72
Vomiting	13	8.7	25	16.7	.06	1	0.7	0		1.00
Diarrhea	57	38.0	31	20.7	< .01	2	1.3	2	1.3	1.00
Fatigue	80	53.3	107	71.3	< .01	8	5.3	7	4.7	1.00
Anemia	120	80.0	141	94.0	< .01	6	4.0	12	8.0	.22
Thrombocytopenia	31	20.7	48	32.0	.04	0		3	2.0	.245
Leukopenia	19	12.7	140	93.3	< .01	1	0.7	96	64.0	< .01
Neutropenia	15	10.0	136	90.7	< .01	1	0.7	120	80.0	< .01
Neutropenic fever						0		23	15.3	< .01
AST	43	28.7	36	24.0	.43	3	2.0	0		.25
ALT	39	26.0	35	23.3	.69	5	3.3	1	0.7	.21
Pneumonitis	10	6.7	8	5.3	.81	2	1.3	3	2.0	1.00

erlotinib and docetaxel arms in patients who received any subsequent treatment (HR, 0.91; 95% CI, 0.63 to 1.32; $P = .62$).

DISCUSSION

This study showed that there was no significant difference in PFS when comparing erlotinib versus docetaxel as second- or third-line treatment for an *EGFR*-unselected population with NSCLC. In the preplanned subgroup analysis, PFS and response rate were significantly better with docetaxel than erlotinib in *EGFR* wild-type tumors. In contrast, patients with *EGFR* mutant tumors showed longer PFS and OS in the erlotinib group than in the docetaxel group, although these differences did not reach statistical significance, possibly because of the small sample size.

To date, five phase III trials have compared EGFR-TKI and chemotherapy in patients with previously treated and EGFR-unselected NSCLC.[5,6,12-14] INTEREST was the largest study and examined gefitinib versus docetaxel, but there was no significant difference between these two agents in terms of median PFS (2.2 *v* 2.7 months, respectively) and median OS (7.6 *v* 8.0 months, respectively).[5] This trend was also confirmed for Japanese patients in the V15-32 trial.[6] Other drugs examined included erlotinib versus pemetrexed by the Hellenic Oncology Research Group[13] and erlotinib versus docetaxel/pemetrexed in the Tarceva in Treatment of Advanced NSCLC (TITAN) study,[14] and similar results were obtained; there was no difference in PFS and OS between EGFR-TKI and chemotherapy. The findings of DELTA are consistent with the results from these phase III trials in *EGFR*-unselected patients with NSCLC.

Therapy can now be individualized based on the molecular profile of the tumor. Convincing evidence that EGFR-TKIs have marked antitumor activity in patients with activating mutations of exons 19 and 21 of the *EGFR* gene has accumulated.[15,16] This genotyping-guided treatment has been effective in clinical practice. Along with these achievements, the role of EGFR-TKIs in patients with *EGFR* wild-type NSCLC has been discussed.[17] Our prospectively defined analyses included an examination of *EGFR* wild-type NSCLC, revealing 199 patients with wild-type *EGFR* disease (66.1%) among the 255 patients (84.7%) who were assessed for *EGFR* mutations, which is a higher proportion than that assessed in previous studies.[13,14,18] The present analysis showed that docetaxel was superior to erlotinib in terms of PFS in the subset analysis for *EGFR* wild-type NSCLC. To date, three randomized studies have compared EGFR-TKIs and chemotherapy focusing on wild-type *EGFR* tumors.[14,18] However, our data are inconsistent with the subset analyses of the INTEREST[18] and TITAN trials,[14] both of which showed no significant difference in PFS when comparing EGFR-TKIs and chemotherapy. Another recent phase III study, the Tarceva Italian Lung Optimization Trial (TAILOR),[19] in which all the patients had *EGFR* wild-type disease, reported the same results as ours. Because the sample size of the four studies is approximately 200 patients, the discrepancy in PFS among studies might partly be attributable to the methods used for *EGFR* analysis. For example, INTEREST and TITAN used direct sequencing, whereas the TAILOR study used restriction fragment length polymorphism and Sanger sequencing. DELTA adopted highly sensitive PCR-based assays. The TAILOR and DELTA studies used likely more sensitive methods to detect mutations than direct sequencing, particularly for diagnostic tumor samples.[20] The response rates for EGFR-TKI versus docetaxel were 6.6% *v* 9.8%, respectively, in INTEREST; 3.0% *v* 15.5%, respectively, in TAILOR; and 5.6% *v*. 20.0%, respectively, in DELTA (no data available for TITAN). These data support our observations regarding the PFS benefit in the docetaxel group of DELTA.

In contrast to PFS and response rate, there were no differences in OS when comparing EGFR-TKI and chemotherapy in our study as well as in the subset analysis of INTEREST and TITAN. Only the TAILOR study, which did not allow cross-over therapy, showed that docetaxel was better than erlotinib in terms of PFS and OS. In the DELTA study, approximately 40% of patients received cross-over treatments, and other subsequent therapies were similarly delivered in both groups. Therefore, unlike PFS, OS may not be affected by subsequent therapies. In fact, we found a trend toward better OS in the docetaxel group than in the erlotinib group in *EGFR* wild-type patients who received no subsequent chemotherapy in our subset analysis. Given the active drugs available for poststudy chemotherapy that might confer prolonged survival after progression, PFS can be a clinically relevant end point, and further research and discussion are required.[21,22]

The response rate of 20% in the docetaxel arm was higher and hematologic toxicities were more severe compared with the response rate and hematologic toxicities seen in phase III trials in Western countries. There might be some ethnic differences in efficacy and toxicity between white and Asian patients.[23,24] For example, in the Common Arm Trial, which compared clinical outcomes between US and Japanese patients treated with carboplatin and paclitaxel according to identical study design, eligibility criteria, and staging system,[25] the PFS and OS were longer and adverse effects of neutropenia and anemia were more severe in Japanese patients. Although 75 mg/m^2 of docetaxel is more commonly used in Western populations, the absolute response rate and survival in DELTA do not suggest underdosing.

This study has several limitations. First, we failed to detect a significant difference in PFS in the unselected population, which may have been a result of the small sample size. Second, the trial was nonblinded, and the primary end point of PFS was assessed by the individual investigator at each institution. Therefore, caution should be used when comparing our results with those of other studies in which PFS was centrally assessed.

In summary, the present study showed no significant difference in PFS and OS when comparing docetaxel and erlotinib in EGFR-unselected patients with NSCLC. However, docetaxel was superior to erlotinib in terms of PFS and response rate (but not OS) in patients with *EGFR* wild-type disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

epidermal growth factor receptor (EGFR): also known as HER1. Belongs to a family of receptors (HER2, HER3, HER4 are other members of the family) and binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. It also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.

erlotinib: also known as Tarceva (Genentech, South San Francisco, CA). Erlotinib is a small molecule that inhibits the tyrosine kinase activity of epidermal growth factor receptor/HER1 and has been evaluated extensively in clinical trials in patients with non–small-cell lung cancer, pancreatic cancer, and glioblastoma multiforme.

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Adjuvant Chemotherapy in Patients with Completely Resected Small Cell Lung Cancer: A Retrospective Analysis of 26 Consecutive Cases

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Objective: Several clinical studies have demonstrated the efficacy and safety of adjuvant chemotherapy in patients with completely resected small cell lung cancer for a selected limited stage. However, it is unclear whether adjuvant chemotherapy is feasible in clinical practice. The objective of this study was to analyze the efficacy and safety of adjuvant chemotherapy for small cell lung cancer patients retrospectively in clinical practice.
Methods: From January 2002 to March 2012, 56 small cell lung cancer patients underwent surgery as initial therapy in our institute. Of these, 26 patients received adjuvant chemotherapy. The clinical data of patients who received adjuvant chemotherapy were retrospectively analyzed.
Results: The chemotherapy regimens were cisplatin and irinotecan in 16 patients, cisplatin and etoposide in 1 and carboplatin and etoposide in 9. Median follow-up time was 44.8 months. Nineteen (73%) patients received the full course of chemotherapy. Median recurrence-free survival was 21.4 months. Median survival time was not reached. There was no treatment-related death.
Conclusion: Adjuvant chemotherapy may be generally safe and efficacious in selected small cell lung cancer patients.

Key words: small cell lung cancer – surgery – adjuvant chemotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancers. It is a virulent, rapidly growing, early metastasizing and invasive cancer. At diagnosis, approximately 90% of patients with SCLC already have regional or distant spread (1). Furthermore, it is difficult to diagnose SCLC presenting as a solitary small nodule of the lung by transbronchial lung biopsy. As a result, SCLC presenting as a solitary small nodule is often diagnosed at the time of therapeutic surgical resection. In these cases, we commonly administer additional chemotherapy after surgery in clinical practice to control micro metastases. A previous clinical study, case series and a meta-analysis showed that adjuvant chemotherapy might be feasible and reduce the risk of recurrence in SCLC patients (2–4). In addition, Tsuchiya et al. (5) reported that surgical resection followed by cisplatin and etoposide chemotherapy was feasible. The European Society for Medical Oncology (ESMO) and American College of Chest Physicians (ACCP) guidelines recommend adjuvant chemotherapy for SCLC patients. However, it was unclear that adjuvant

chemotherapy for SCLC patients was efficacy and safety in clinical practice. Therefore, the efficacy and safety of adjuvant chemotherapy for SCLC patients were retrospectively analyzed.

PATIENTS AND METHODS

The current study included 56 consecutive patients with histologically proven SCLC who underwent complete resection at the National Cancer Center Hospital (NCCH) from January 2002 to March 2012. The medical records of SCLC patients who received adjuvant chemotherapy were retrospectively reviewed. Patients who had post-operative recurrence before starting adjuvant chemotherapy, patients who had difficulty with adjuvant chemotherapy due to complications, and patients who refused were excluded. No patients had received any treatment such as chemotherapy or irradiation before surgery. Histological diagnoses and tumor grades were determined in accordance with TNM staging (seventh edition) (6). The following data were extracted: (i) patients' characteristics: age, sex and Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the start of adjuvant chemotherapy, clinical stage before surgery, pathological stage after surgery and histological diagnosis before and after surgery; (ii) type of chemotherapeutic agents administered, dose, treatment cycle, relative dose intensity and toxicity; and (iii) patterns of recurrence, recurrence-free survival time (RFS) and overall survival time (OS) data. All the patients gave their written informed consent to analyze their medical records after treatments. This study was approved by the Institutional Review Board of NCCH.

Treatment Schedule

The chemotherapy regimens were cisplatin and irinotecan (IP), cisplatin and etoposide (EP) and carboplatin and etoposide (CE). The doses of the chemotherapeutic agents were: cisplatin (60 mg/m^2 on Day 1) and irinotecan (60 mg/m^2 on Days 1, 8 and 15) repeated every 4 weeks; cisplatin (80 mg/m^2 on Day 1) and etoposide (100 mg/m^2 on Days 1–3) repeated every 3 weeks; and carboplatin (AUC = 5 on Day 1) and etoposide (80 mg/m^2 on Days 1–3) repeated every 3 weeks. All regimens consisted of a total of four cycles. The efficacy and safety of each regimen has been established in previous clinical trials (5,7,8).

Assessment and Analysis

Safety and tolerability were assessed during the adjuvant chemotherapy. Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. RFS and OS were measured from the date of surgery until recurrence and death or the final day of the follow-up period, and median survival was calculated using the Kaplan–Meier method. STATA version 12 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Table 1. Patients' characteristics

Characteristic	*N*
Twenty-six patients received adjuvant chemotherapy	
Total	26
Sex	
Male/female	19/7
Age	
Median (range)	67 (46–84)
ECOG PS	
0/1	21/5
Clinical stage	
I (T1N0M0/T2aN0M0)	22 (17/5)
II (T1N1M0/T2aN1M0/T3N0M0)	4 (1/2/1)
III 0	
Pathological stage	
I (T1N0M0/T2aN0M0)	10 (6/4)
II (T2bN0M0/T1N1M0/T2N1M0/T3N0M0)	9 (1/2/4/2)
III (T1N2M0/T2N2M0/T3N2M0)	7 (4/2/1)
Pathological histology	
Small cell carcinoma	18
Combined small cell carcinoma	
With adenocarcinoma	4
With large cell carcinoma	4
Thirty patients received surgery alone	
Total	30
Sex	
Male/female	25/5
Age	
Median (range)	71 (57–89)
ECOG PS	
0/1	13/17
Clinical stage	
I (T1N0M0/T2aN0M0)	25 (21/4)
II (T1N1M0/T2N1M0)	4 (2/2)
III (T3N1M0)	1 (1)
Pathological stage	
I (T1N0M0/T2aN0M0)	18 (15/3)
II (T1N1M0/T2N1M0/T3N0M0)	7 (3/2/2)
III (T1N2M0/T2N2M0/T3N2M0/T4N2M0/T3N3M0)	5 (1/1/1/1 /1)
Pathological histology	
Small cell carcinoma	19
Combined small cell carcinoma	
With adenocarcinoma	4
With large cell carcinoma	4
With squamous cell carcinoma	3

ECOG PS, Eastern Cooperative Oncology Group Performance Status; *N*, number of patients.

RESULTS

Patient Characteristics

A total of 56 consecutive patients with SCLC were sampled from the hospital-based registry of the NCCH between January 2002 and March 2012. The characteristics of the patients are listed in Table 1. All patients underwent surgery as initial treatment. The surgical procedures were pulmonary lobectomy in 55 patients and partial resection in one patient. Thirty patients were excluded for reasons such as death not relevant to surgery ($n = 1$), early post-operative recurrence ($n = 2$), thoracic empyema after surgery to need antibiotics for long periods ($n = 2$), severe complications ($n = 4$) and poor general condition including old age ($n = 5$) (Fig. 1). As a result, 26 patients who received adjuvant chemotherapy were reviewed in this study.

Discrepancy Between Clinical and Pathological Histology Findings and Stages

Only 9 patients had a confirmed diagnosis of SCLC and 13 patients did not have a confirmed diagnosis before surgery. On the other hand, in four patients, the confirmed diagnosis was changed to SCLC. Their pre-operative diagnoses included one adenocarcinoma, one squamous cell carcinoma, one large cell carcinoma and one carcinoma not otherwise specified, respectively. As a consequence of surgery, combined SCLC types with adenocarcinoma or squamous cell carcinoma were found in 8 (30.8%) patients. Twenty-two patients had pre-operative clinical Stage I disease and four had Stage II disease. However, post-operative pathological Stage I, II and III disease was found in 10, 9 and 7 patients, respectively (Table 1).

Chemotherapy Regimens

The chemotherapy regimen was selected by each physician. Sixteen patients received IP, one received EP and nine received CE (Table 2). The median age of the patients who received IP was 65 years (range, 47–72 years), while that of patients who received CE was 75 years (range, 62–84 years). Most patients who were 70 years of age or older received CE (88.9%).

Treatment Delivery and Relative Dose Intensity

The median duration from surgery to starting chemotherapy was 51 days (range, 26–78 days). Table 3 shows treatment delivery for each regimen. Nineteen (73%) patients received four cycles of chemotherapy. Seven (27%) patients did not

Table 2. Regimen selected

	Number of patients	Median age (range)	ECOG PS 0/1 (*N*)
IP	16	65 (47–72)	10/6
EP	1	46	1/0
CE	9	75 (62–84)	4/5

IP, cisplatin and irinotecan; EP, cisplatin and etoposide; CE, carboplatin and etoposide.

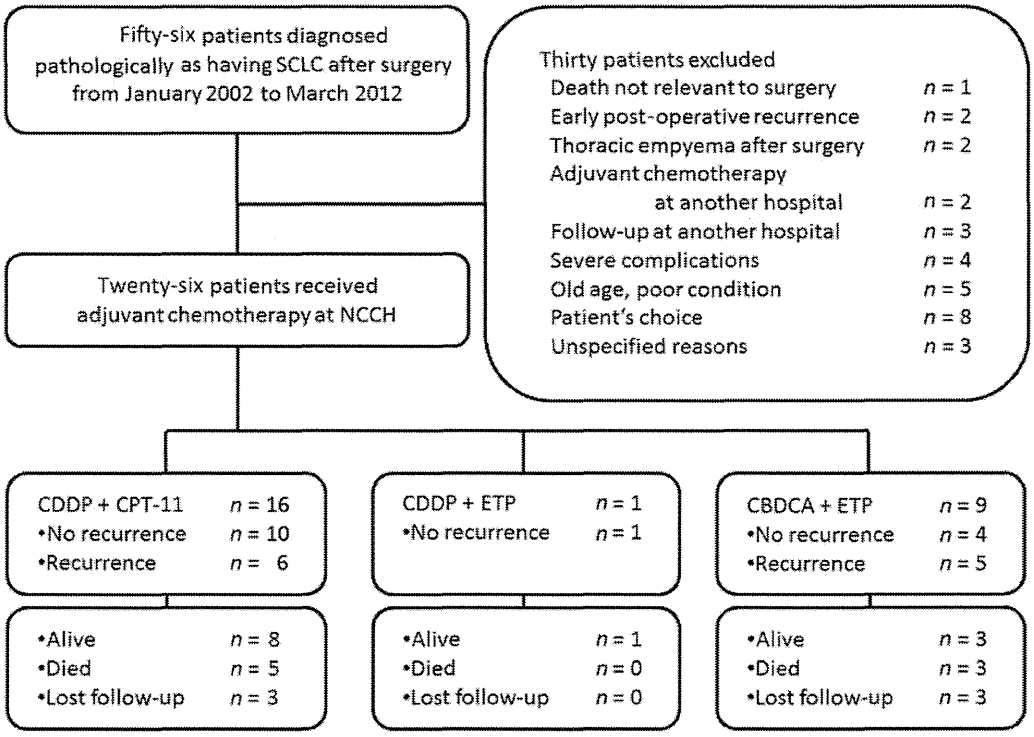

Figure 1. Follow-up of the study patients by treatment group after surgery.

complete the initially planned chemotherapy because of adverse events (AE). The relative dose intensity was 83.6% in IP, 87.5% in EP, and 86.8% in CE.

Safety Analysis

Chemotherapy-related toxicity is shown in Table 4. Grade 4 AEs were found in 14 (53.8%) patients: neutropenia in 11 patients, thrombocytopenia in 2 patients and febrile neutropenia in 1 patient. Adjuvant chemotherapy for completely resected SCLC patients was feasible. All AEs were manageable, and there was no treatment-related death. We had to stop or change chemotherapy regimens due to AEs in four patients received IP and three patients received CE. In IP, two patients were changed to EP due to hepatic toxicity, one patient was changed to CE due to kidney failure and one patient could not continue to receive chemotherapy due to brain bleeding. In CE, all three patients discontinued chemotherapy due to fatigue and allergy. These three patients were over the age of 70 years (Table 3).

Efficacy Analysis

Of the 26 patients, 18 (69.2%) were still alive after the median follow-up of 44.8 months (range, 2.8–78.1 months). The median RFS of all patients was 21.4 months (95% CI: 14.6–41.3 months); the median RFS was 17.8 months (95% CI: 12.8–46.5 months) with IP and 23.0 months with CE (95% CI: 10.2–61.9 months) (Fig. 2A). The median survival time of all patients could not be calculated due to the insufficient follow-up time. The estimated 3-year and 5-year survivals were 68.9% (95% CI: 42.3–84.6%) and 51.7% (95% CI: 24.0–73.2%), respectively (Fig. 2B). On the other hand, the estimated 3-year and 5-year survivals of 30 patients received surgery alone were 60.5% (95% CI: 39.9–76.0%) and 45.4% (95% CI: 25.0–63.8%), respectively.

Table 3. Treatment delivery

Number of treatment cycles	IP ($N = 16$)	EP ($N = 1$)	CE ($N = 9$)	Total ($N = 26$)
4	12 (75%)	1 (100%)	6 (67%)	19 (73%)
3	–	–	1 (11%)	1 (4%)
2	–	–	1 (11%)	1 (4%)
1	4 (25%)	–	1 (11%)	5 (19%)

Table 4. Chemotherapy-related toxicity by CTC-AE ver. 4.0

	Grade				
Toxicity	1	2	3	4	3/4
Anemia	10	3	2	0	2 (8)
Neutropenia	1	0	3	11	14 (54)
Febrile neutropenia	0	0	2	1	3 (12)
Thrombocytopenia	1	3	3	2	5 (19)
Nausea	12	3	1	0	1 (4)
Appetite loss	11	5	0	0	0 (0)
Diarrhea	7	5	1	0	1 (4)
Fatigue	8	2	1	0	1 (4)
Hepatic dysfunction	1	0	2	0	2 (8)
Renal failure	1	1	0	0	0 (0)

Values are N (%).

Patterns of Recurrence

Recurrence was confirmed in 10 (38.5%) patients, and the initial recurrence site was mediastinal lymph nodes in three patients, lung in three, bone in three and abdominal lymph node in one. Recurrence was found in two patients with pathological Stage I, four patients with Stage II, and four patients with Stage IIIA.

DISCUSSION

Although the standard treatment for most cases of limited SCLC is considered to be chemoradiotherapy, clinical T1 and T2 SCLC without evidence of lymph node involvement (N0) can be considered for surgical resection. Previous reports suggested that these selected patients might benefit from surgery expecting radical cure (9–11). In addition, combination surgery and adjuvant chemotherapy or post-operative irradiation has a 5-year survival of approximately 40–70% (2–5). However, it is difficult to diagnose T1 and T2 SCLC presenting as a solitary pulmonary nodule prior to surgery despite development of less invasive diagnostic methods such as transbronchial lung biopsy, endobronchial ultrasonography and CT-guided lung biopsy (12). As a result, SCLC presenting as a solitary pulmonary nodule is often diagnosed at the time of therapeutic resection. In the present analysis, 13 patients underwent surgery with uncertain pathological diagnoses. Furthermore, four patients had a diagnosis of NSCLC before surgery. According to previous reports, approximately 5–10% of patients diagnosed with SCLC will have other pathologies such as adenocarcinoma or squamous cell carcinoma within the surgically resected specimens (13,14). As a consequence of surgery, combined SCLC types with adenocarcinoma or squamous cell carcinoma were found in 8 (30.8%) patients. We have no defined treatment strategy for combined SCLC (containing any other NSCLC component). However, it has been reported that there is no difference in the prognosis between SCLC and combined SCLC (15). In our perspective, surgery would be the best treatment choice for early stage combined SCLC.

There have been no Phase III trials of adjuvant chemotherapy for SCLC. A previous clinical study, a case series, and a meta-analysis showed that adjuvant chemotherapy including cisplatin may be feasible and reduce the risk of recurrence in SCLC patients (2–4). The feasibility of EP after surgical resection has

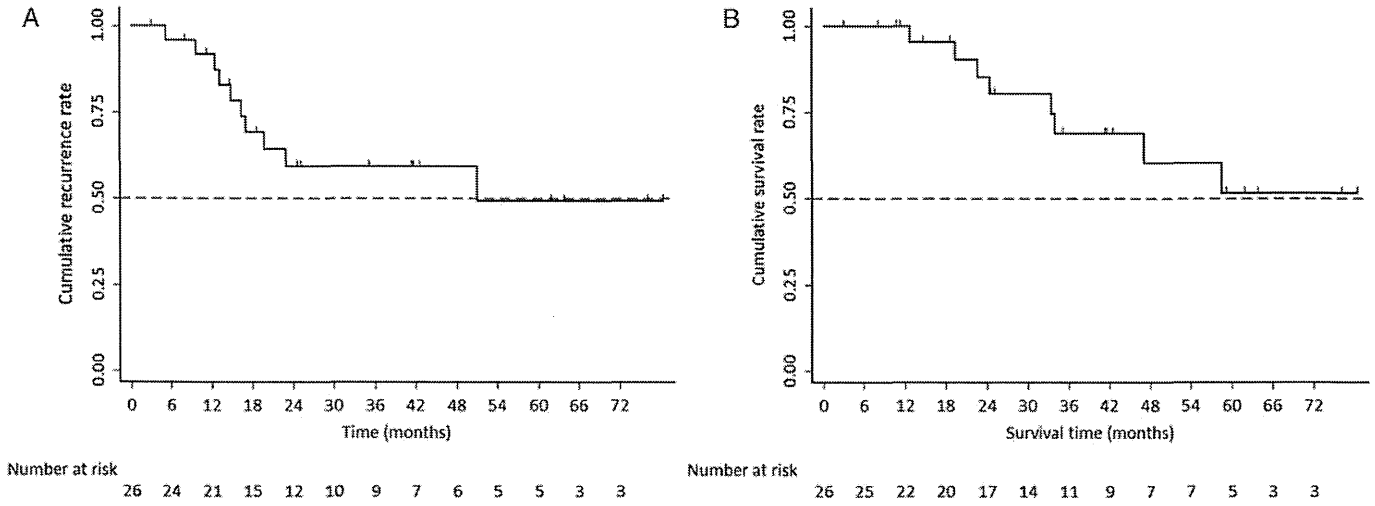

Figure 2. (A) Recurrence-free survival among the study patients. Kaplan–Meier curves for recurrence-free survival are shown for the recurrence-free survival population. (B) Overall survival among the study patients. Kaplan–Meier curves for overall survival are shown for the overall survival population.

been reported from Japan (2,5). Therefore, it remains unclear which regimen is appropriate. According to previous clinical trials of extensive disease-SCLC (7,8), EP, IP and CE were selected for adjuvant chemotherapy regimens. In the present analysis, the choice of regimen was left to the physician by reference to previous clinical trials (5,7,8). Regarding efficacy, we consider that IP and CE were not apparently inferior to EP in a previous Phase II study (JCOG 9101) in which the estimated 3-year and 5-year survivals were 61 and 57%, respectively.

The CE regimen has been used in elderly or poor-risk patients with extensive disease-SCLC (8). In the present analysis, CE had acceptable toxicities and reproducible efficacy in this population. In the period of the present analysis, surgery was performed as initial therapy for 56 SCLC patients at the NCCH. Of these, 30 patients could not receive adjuvant chemotherapy for any reason. Therefore, those who received surgery and adjuvant chemotherapy in this study were highly selected. Thirty patients received surgery alone tended to be in higher median age and in poor PS compared with these received adjuvant chemotherapy. But, we could not show clearly-defined cut-off line of adjuvant chemotherapy. It is the limitation of this retrospective study.

A phase III trial of EP versus IP for adjuvant chemotherapy (UMIN 000010298) is now ongoing in patients diagnosed with high-grade pulmonary neuroendocrine carcinoma (large cell neuroendocrine carcinoma and small cell lung cancer) by the Japan Clinical Oncology Group (JCOG).

Adjuvant chemotherapy of selected SCLC patients may be generally safe and efficacious. Further studies should be considered to evaluate the therapeutic possibility of adjuvant chemotherapy in SCLC patients.

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Conflict of interest statement

None declared.

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Cyclooxygenase-2 inhibitors for non-small-cell lung cancer: A phase II trial and literature review

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Abstract. Several preclinical and clinical studies have demonstrated that cyclooxygenase-2 (COX-2) inhibitors are efficient for the treatment of non-small-cell lung cancer (NSCLC). However, two recent phase III clinical trials using COX-2 inhibitors in combination with platinum-based chemotherapy failed to demonstrate a survival benefit. Thus, validation and discussion regarding the usefulness of COX-2 inhibitors for patients with NSCLC are required. We conducted a prospective trial using COX-2 inhibitors for the treatment of 50 NSCLC patients accrued between April, 2005 and July, 2006. Patients with untreated advanced NSCLC received oral meloxicam (150 mg daily), carboplatin (area under the curve = 5 mg/ml x min on day 1) and docetaxel (60 mg/m^2 on day 1) every 3 weeks. The primary endpoint was response rate. The response and disease control rates were 36.0 and 76.0%, respectively. The time-to-progression (TTP) and overall survival (OS) were 5.7 months [95% confidence interval (CI): 4.6-6.7] and 13.7 months (95% CI: 11.4-15.9), respectively. The 1-year survival ratio was 56.0%. Grade 3 neuropathy was observed in only 1 patient. We performed tumor immunohistochemistry for COX-2 and p27 and investigated the correlation between their expression and clinical outcome. COX-2 expression in the tumor tended to correlate with a higher response rate (50.0% in the high- and 18.2% in the low-COX-2 group; P=0.092). Based on our results and previous reports, various trial designs, such as the prospective use of COX-2 inhibitors only for patients with COX-2-positive NSCLC, including the exploratory analysis of biomarkers associated with the COX-2 pathway, may be worth further consideration.

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Key words: non-small-cell lung cancer, cyclooxygenase-2, p27, carboplatin, docetaxel

Introduction

Cyclooxygenase-2 (COX-2), the enzyme that converts arachidonic acid to prostaglandins (PGs), is expressed in a number of solid tumors and is associated with carcinogenesis, tumor proliferation, infiltration, metastasis, angiogenesis and resistance to anticancer drugs (1). In lung cancer cells, COX-2, which is particularly overexpressed in adenocarcinoma (2), is considered to be a negative predictor of survival in this subpopulation (3-7). Based on these reports, several clinical trials have been conducted for the potentiation of targeting COX-2 in lung cancer (8).

The cyclin-dependent kinase (Cdk) inhibitor p27 plays a critical role in cell cycle regulation from the G1 to the S phase by inhibiting Cdk4/6-cyclin D1 and Cdk2-cyclin E (9). Loss of p27 expression tends to be an unfavorable prognostic factor in patients with non-small-cell lung cancer (NSCLC) (10). Increased p27 expression is attributed to COX-2-independent mechanisms of G0/G1 arrest driven by COX-2 inhibitors (11). Thus, p27 expression may be another predictive factor of the response to COX-2 inhibitors.

Taxanes, such as paclitaxel and docetaxel, are microtubule-stabilizing agents that act by interfering with spindle microtubule dynamics, causing cell cycle arrest and apoptosis through activating a number of molecular pathways (12,13). Taxanes are able to drive COX-2 expression, which is followed by increased prostaglandin E_2 (PGE_2) production (14); therefore, a complementary and additive or synergistic effect with COX-2 inhibitors may be expected. Moreover, the response to carboplatin plus docetaxel in Asian patients was reported to be statistically superior to that in Caucasian patients (15).

Based on the abovementioned findings, we projected a prospective phase II trial using carboplatin, docetaxel and a

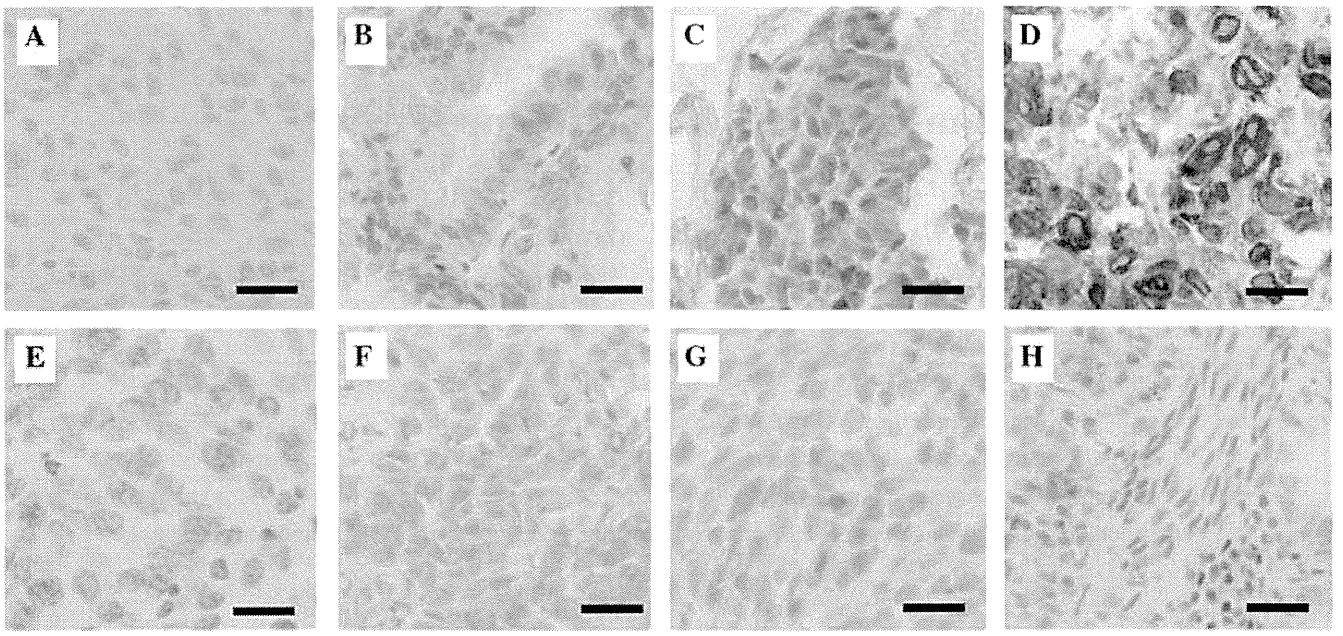

Figure 1. Representative immunohistochemical staining of (A-D) cyclooxygenase-2 and (E-H) p27 in lung cancer tissues obtained from the patients in this study. (A and E) 0, no expression; (B and F) 1+, weak expression; (C and G) 2+, moderate expression; and (D and H) 3+, strong expression. Scale bars, 250 μm.

selective COX-2 inhibitor for patients with advanced NSCLC. We also investigated the p27 and COX-2 expression levels in the tumors, so as to determine the correlation between these molecules and the clinical outcome of the combined treatment.

Materials and methods

Patient characteristics. The eligibility criteria included histologically or cytologically confirmed stage IIIB/IV NSCLC, a patient age of 20-75 years and a life expectancy of >3 months. The patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.0, had received no prior chemotherapy or radiotherapy for target lesions and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The required laboratory criteria were white blood cell (WBC) count >4,000/mm^3, neutrophil count >2,000/mm^3, platelet count >100,000/mm^3, hemoglobin >9.0 g/dl, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <1.5-fold of the upper limit of the normal range (ULN), total bilirubin <1.5 mg/dl and creatinine clearance (CCr) >50 ml/min. The exclusion criteria were active infection or fibrosis on chest X-ray, significant cardiovascular disease, uncontrolled diabetes mellitus or hypertension, peripheral nervous disorders of grade ≥2 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, active secondary malignancy, central nervous system symptoms due to metastasis, uncontrolled pleural or pericardial effusion, history of severe drug hypersensitivity, recent or current use of non-steroidal anti-inflammatory drugs, pregnancy, or patients deemed inappropriate for the study by the participating physicians.

This study was performed in accordance with the Declaration of Helsinki and all the patients signed an informed consent prior to inclusion. The study protocol was approved by the Institutional Review Board of each participating institution.

Study design and treatment protocol. This was a single-arm prospective phase II study. The dose of carboplatin was determined using the Calvert formula with a target area under the curve (AUC) of 5 mg/ml x min. All the patients received docetaxel (60 mg/m^2) and carboplatin at an AUC of 5 mg/ml x min on day 1 every 3 weeks. Oral meloxicam at a dose of 10 mg daily was administered on days 1-21. We investigated p27 and COX-2 expression levels in tumors by immunohistochemistry (IHC). Dose reduction was permitted in the case of grade 4 neutropenia for 3 consecutive days, febrile neutropenia, or patient-physician's decision. The next course of chemotherapy was postponed in case of bone marrow suppression (WBC count <3,000/mm^3, or neutrophil count <1,500/mm^3, or platelet count <100,000/mm^3), non-hematological events (total bilirubin >1.5 mg/dl, AST >1.5 x ULN, ALT >1.5 x ULN, or CCr <50 ml/min) and any non-hematological grade 2 adverse events. The clinical, hematological and biochemical status was assessed on days 1, 8 and 15 in all the courses. Chest radiographs and computed tomography were performed at least once per month. The toxicities were graded using CTCAE, version 3.0.

IHC. IHC was centrally performed at SRL, Inc. (Tokyo, Japan). First, 5-μm sections of the specimens were deparaffinized and hydrated. For antigen retrieval, the slides were microwaved 4 times in 1 mM EDTA (pH 8.0) for 5 min. For COX-2 detection, staining was performed on an automated immunostainer (Ventana NX system; Ventana Medical Systems, Inc., Tucson, AZ, USA). The Endogenous Biotin Blocking kit (Ventana) was used to reduce non-specific staining caused by endogenous biotin present in the tissues. Subsequently, primary antibody (C295; anti-human COX-2 rabbit IgG polyclonal antibody; IBL Co., Ltd., Nagoya, Japan) diluted 1:25 was used for 30 min at 37˚C, followed by biotinylated goat anti-rabbit immunoglobulins (E0432; Dako, Glostrup, Denmark) diluted 1:500 and the 3-3'-diaminobenzidine tetrahydrochloride (DAB) kit (Ventana).

The sections were then counterstained with hematoxylin for 1 min. For p27 detection, following antigen retrieval as described above, endogenous peroxidase activity was blocked by 3% hydrogen peroxidase in phosphate-buffered saline (PBS) for 10 min. The sections were washed in water. After blocking non-specific binding with 10% porcine serum in PBS for 10 min, the sections were incubated with the primary antibody (F-8; anti-human p27 mouse IgG1 monoclonal antibody; Santa Cruz, Dallas, TX, USA) diluted 1:50 in a humid chamber at 4˚C overnight. After washing with water, the sections were incubated with biotinylated rabbit anti-mouse immunoglobulins (E0464) (dilution, 1:500; Dako, Glostrup, Denmark) for 30 min at room temperature, washed in water again and then incubated with peroxidase-conjugated streptavidin (dilution, 1:500; Dako) for 30 min at room temperature. Following an additional wash in water, DAB was applied for 5 min and the sections were counterstained with hematoxylin for 1 min.

All the slides were reviewed by two pulmonary oncologists who were blinded to the clinical information. The slides were scored in a method similar to that previously described (weighted index) (16,17). Five random fields per slide at x200 magnification were evaluated to determine the ratio (%) of stained cells and intensity. The estimated ratios of stained cells were between 0% (0) and 100% (1.0), with intervals at a 10% grade. Intensity was scored using a numerical scale (0, no expression; 1+, weak expression; 2+, moderate expression; and 3+, strong expression, Fig. 1). The index (0-3) was calculated as % positive staining x intensity score.

Statistical analysis. The primary endpoint was overall response rate (ORR), defined as the proportion of patients whose best response was either complete or partial response (PR) in the intent-to-treat (ITT) analysis. Assuming that an ORR of 45.0% in eligible patients would indicate potential usefulness, whereas an ORR of 25.0% would be the lower limit of interest, with α=0.05 and β=0.20, 45 patients were required. The secondary endpoints were safety, time-to-progression (TTP), overall survival (OS), OS rate at 1 year and correlation between OS and the expression level of COX-2 and p27. The TTP and OS were estimated using the Kaplan-Meier method. Log-rank tests were used to evaluate the differences in TTP and OS between patients with positive and those with negative COX-2 and p27 expression, as determined by IHC. The association between the protein levels of COX-2 and p27 was evaluated using the Pearson's product-moment correlation coefficient. The correlation between COX-2 and p27 expression and the response rate was evaluated using the Fisher's exact probability test. The statistical analysis was performed using SPSS software, version 20 (IBM Corporation, Armonk, NY, USA). P≤0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics. Between April, 2005 and July, 2006, 50 NSCLC patients were enrolled from 5 institutions. The patients' baseline characteristics are summarized in Table I. The median age was 65 years (range, 44-78 years), 17 patients were female and 24 had an ECOG PS of 1. One patient did not undergo treatment, due to disease progression after registration. The median number of treatment courses was 3 (range, 0-6).

Table I. Patient characteristics.

Characteristics	Patients (n=50) No.	%
Age, years [median (range)]	65 (44-78)	
Gender		
Female	17	34.0
Male	33	66.0
ECOG PS		
0	24	48.0
1	26	52.0
Histology		
Adenocarcinoma	29	58.0
Squamous cell carcinoma	18	36.0
Large-cell carcinoma	2	4.0
Adenosquamous cell carcinoma	1	2.0
Clinical stage (TNM, version 6)		
IIIA	1	2.0
IIIB	15	30.0
IV	32	64.0
Postoperative recurrence	2	4.0
Courses of chemotherapy		
0	1	2.0
1	5	10.0
2	11	22.0
3	9	18.0
4	19	38.0
5	3	6.0
6	2	4.0

ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis.

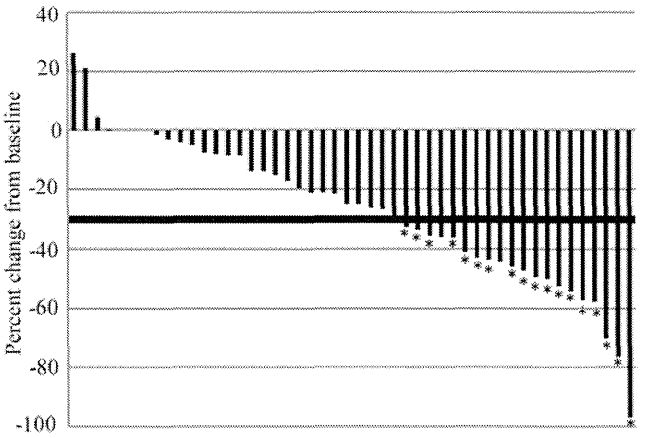

Figure 2. Waterfall plot for the extent of tumor shrinkage. The asterisks represent patients exhibiting a partial response.

Efficacy. A total of 49 patients were evaluable for response to treatment. The majority of the patients achieved tumor shrinkage (Fig. 2). According to the ITT analysis, the ORR

Table II. Objective response (RECIST, version 1.0).

Type of response	No.	%
Number of patients evaluated	50	100.0
Complete response	0	0.0
Partial response	18	36.0
Stable disease	20	40.0
Progressive disease	9	18.0
Not evaluable	3	6.0
Response rate (95% CI)	36.0 (24.1-49.9)	
Disease control rate (95% CI)	76.0 (62.5-85.8)	

RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval.

was 36.0 (95% CI: 24.1-49.9) and the disease control rate (DCR) was 76.0 (95% CI: 62.5-85.8) (Table II). The median follow-up time was 12.9 months (range, 2.1-26.2 months). The TTP and OS were 5.7 months (95% CI: 4.6-6.7) and 13.7 months (95% CI: 11.4-15.9), respectively (Fig. 3). The OS rate at 1 year was 56.0%.

Safety. The incidence of treatment-related adverse events is presented in Table III. The grade 3/4 hematological adverse events were leukopenia (58.0%), neutropenia (80.0%), anemia (16.0%), thrombocytopenia (4.0%) and febrile neutropenia (8.0%). The grade 3/4 non-hematological toxicities were anorexia (12.0%), nausea/vomiting (8.0%), diarrhea (4.0%), fever (4.0%), alopecia (2.0%), neuropathy (2.0%) and myopathy (2.0%). One patient (2.0%) had grade 3 angina pectoris: the patient experienced chest pain on day 3 during the first course of the treatment, which was relieved by immediate infusion of heparin and coronary vasodilator for 6 days; however, the patient's treatment was terminated. Another patient (2.0%) suffered from febrile neutropenia and pneumonia followed by septic shock, requiring treatment with antibiotics and catecholamines on day 12 and developed deep vein thrombosis (DVT) in the left leg on day 26 during the second course of the treatment. The DVT was controlled using heparin followed by warfarin; however, the treatment protocol was discontinued.

Association between expression of p27 and COX-2 and clinical outcome. Tissue samples were obtained from 34 (68.0%) of the 50 patients. Of the 34 samples, 32 were considered adequate for IHC. Of the 32 patients, 2 were not evaluable and one did not undergo treatment after registration. The expression of COX-2 and p27 was tabulated with clinical outcome and cut-off points were established by visual inspection of the data. We did not identify a correlation between the weighted index of COX-2 and that of p27. There was a trend of correlation between the level of COX-2 expression and ORR (50.0% in the high- and 18.2% in the low-COX-2 group; P=0.092) when the cut-off value of the index was 0.2 (Table IV). The level of p27 expression was not associated with ORR (54.5% in the high- and 27.8% in the low-p27 score group; P=0.24). The TTP and OS of the patients with positive and negative COX-2 expression were estimated by the Kaplan-Meier method; however there was no significant difference between the two groups (TTP: 6.0 vs. 4.9 months, P=0.357; and OS: 14.9 vs. 13.9 months; P=0.372, respectively). There was also no significant difference in either TTP or OS between patients whose tumors were positive and those whose tumors were negative for p27 (TTP: 6.0 vs. 5.1 months, P=0.613; and OS: 14.9 vs. 13.4 months, P=0.438, respectively).

Table III. Adverse events (CTCAE, version 3.0).

	Grade		
Adverse events	1-2 (%)	3 (%)	4 (%)
Leukopenia	26.0	50.0	8.0
Neutropenia	6.0	14.0	66.0
Anemia	62.0	10.0	6.0
Thrombocytopenia	30.0	4.0	0.0
Febrile neutropenia	0.0	6.0	2.0
Anorexia	55.0	12.0	0.0
Nausea/vomiting	48.0	8.0	0.0
Diarrhea	18.0	4.0	0.0
Fever	28.0	4.0	0.0
Alopecia	44.0	2.0	0.0
Neuropathy	10.0	2.0	0.0
Myopathy	0.0	2.0	0.0
Angina pectoris	0.0	2.0	0.0
Aphtha	16.0	0.0	0.0
Skin rash	2.0	0.0	0.0
Arthralgia	2.0	0.0	0.0
Thrombosis	2.0	0.0	0.0

CTCAE, Common Terminology Criteria for Adverse Events.

Table IV. Correlation between COX-2 expression and response.

COX-2 IHC index	PR	SD+PD	Total
High	9	9	18
Low	2	9	11
Total	11	18	29

COX-2, cyclooxygenase-2; PR, partial response; SD, stable disease; PD, progressive disease; IHC, immunohistochemistry.

Discussion

In this trial, we investigated the effectiveness and toxicity of COX-2 inhibitors administered with carboplatin plus docetaxel in Japanese NSCLC patients and the association between tumor COX-2 and p27 expression and clinical outcome. There was a trend of correlation between the level of COX-2 expression and ORR. We first attempted to determine how p27 expression, which involves COX-2-independent mechanisms of G0/G1 arrest driven by COX-2 inhibitors, affects patient survival. However, the results revealed no statistical correlation. The