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# Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer

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**KEYWORDS**
Non-small-cell lung cancer;
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Skin reaction;
Brain metastasis;
Extracranial disease

**Summary**

*Background:* Gefitinib ('Iressa', ZD1839), an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI), has shown antitumor activity in refractory patients with non-small-cell lung cancer (NSCLC) in clinical trials. We have retrospectively analyzed the efficacy and tolerability of gefitinib in patients with advanced NSCLC treated at Okayama University Hospital.
*Methods:* We reviewed the clinical records of 57 patients with advanced NSCLC who had received 250 mg/day gefitinib at our hospital between November 2000 and May 2003. Correlations between the sensitivity of brain metastases and extracranial disease following treatment with gefitinib were also investigated.
*Results:* Extracranial objective responses were observed in 15 (27%; 95% confidence interval 15.8–40.3%) patients. Fourteen out of 57 patients had brain metastases; six experienced objective responses (one complete response, CR and five partial responses, PR) and eight had stable disease (SD) in the brain. Seven out of 14 patients with brain metastases experienced objective responses in their extracranial tumors and, interestingly, objective responses in the brain were observed in six (86%) of these patients. Multivariate analysis found that advanced age (≥70 years) and the presence of brain metastases were associated with clinical response to gefitinib ($P = 0.01$ and 0.05, respectively), and that female patients were more likely to respond. Median survival and median duration of response were 9.1 and 7.7 months, respectively. The majority of adverse events (AEs) were mild and reversible skin and gastrointestinal disorders, with grade 3 adverse events observed in six (11%) patients.

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*Conclusions:* This retrospective analysis has found that gefitinib is effective and well tolerated in patients with refractory NSCLC, confirming previous phase II trial data. Interestingly, gefitinib appeared to be effective for brain metastases as well as extracranial tumors. Further prospective trials are warranted to evaluate the efficacy of gefitinib in elderly patients and in patients with brain metastases.
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## 1. Introduction

Lung cancer is the leading cause of cancer deaths in many countries. Non-small-cell lung cancer (NSCLC) accounts for approximately 75% of lung cancer cases, with the majority of patients having inoperable locally advanced or metastatic disease at the time of diagnosis, reflected by the low 5-year survival rate for all stages (currently 13%) [1]. Although cisplatin-based chemotherapy has been used extensively for the past two decades to treat patients with advanced NSCLC, the survival benefit remains modest [2]. A recent analysis of large phase III trials has shown that the impact of new chemotherapy combinations on survival is minimal compared with older regimens, with overall response rates of approximately 30%, median survival benefits of 8–9 months, and 1-year survival rates of approximately 30% [3]. New therapies are required that are effective against locally advanced or metastatic NSCLC.

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because it is expressed in a variety of tumors, including NSCLC [4], and elevated EGFR expression levels have been associated with a poor prognosis in lung cancer patients [5]. Several EGFR-targeted agents have been developed, including gefitinib ('Iressa', ZD1839), an orally active anilinoquinazoline compound that inhibits EGFR tyrosine kinase activity [6]. In two large, well-designed, phase II clinical trials, refractory patients with NSCLC experienced overall response rates of 11.8–18.4%, median survival benefits of 6.5–7.6 months, and 1-year survival rates of 29–35% [7,8].

At present, it remains unclear whether gefitinib is effective against brain metastases and whether the sensitivity of brain metastases to gefitinib correlates with the sensitivity of extracranial disease. Therefore, we have retrospectively reviewed the efficacy of gefitinib in patients with advanced NSCLC treated at our hospital, and have focused specifically on the response of brain metastases to gefitinib.

## 2. Patients and methods

### 2.1. Patients

Between November 2000 and May 2003, 57 patients were treated with 250 mg/day gefitinib in Okayama University Hospital. All patients had been diagnosed with advanced NSCLC; the staging procedure included medical history, physical examination, laboratory tests, chest radiograph, fiberoptic bronchoscopy, computed tomographic scans of the chest and abdomen, magnetic resonance imaging of the brain, and a radionuclide bone scan (if medically indicated). Written, informed consent was obtained from each patient before gefitinib treatment began.

### 2.2. Assessment of antitumor activity and toxicity

Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) in accordance with the standard Response Evaluation Criteria in Solid Tumors [9]. Extracranial disease was defined as the primary tumor plus extracranial metastases; tumor responses of extracranial disease and brain metastases were also assessed separately. Tumor responses were assessed every 4 weeks. Adverse events (AEs) were graded according to a modified version of the National Cancer Institute Common Toxicity Criteria [10]. Subjective symptoms were assessed based on routine interview every 2 weeks.

### 2.3. Statistical analysis

Statistical analyses were performed using the StatView® 5.0 program (BrainPower Inc., Calabasas, CA, USA). The association between the response to gefitinib of extracranial disease and brain metastases was evaluated using Fisher's exact test. Multivariate analysis was performed with a logistic regression model for potential factors linked to gefitinib sensitivity; these included performance

status, age, gender, histology, smoking history, and disease stage. Survival curves were calculated using the Kaplan–Meier method and *P*-values of <0.05 were considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

Table 1 summarizes the characteristics of the 57 patients analyzed. The median age was 58 (range 29–82) years and the majority of patients had non-squamous histology (89%), a history of smoking (70%), and metastatic disease (79%); one patient with multiple primary NSCLC (stage IA) was also included. Median follow-up time was 11.8 months. Six patients (11%) had not received any prior chemotherapy: one with poor pulmonary function due to severe chronic obstructive pulmonary disease, one with chronic heart failure, one with poor performance status, one who had been enrolled in a clinical trial, and two who had refused other treatment options. All patients had extracranial disease, except for one patient who received gefitinib as postoperative adjuvant therapy without any evaluable lesions. Out of the 57 patients, 14 (25%) had brain metastases.

**Table 1** Patient characteristics

| | |
|---|---|
| Number of patients | 57 |
| Age, median (range) | 58 (29–82) |
| Gender, male/female | 38/19 |
| Performance status | |
| 0 | 9 |
| 1 | 32 |
| 2 | 10 |
| 3 | 4 |
| 4 | 2 |
| Stage | |
| IA | 1 |
| IIIA | 3 |
| IIIB | 7 |
| IV | 45 |
| Postoperative recurrence | 1 |
| Histology | |
| Adenocarcinoma | 45 |
| Squamous cell carcinoma | 6 |
| Large-cell carcinoma | 2 |
| Large-cell neuroendocrine carcinoma | 2 |
| Adenosquamous-cell carcinoma | 1 |
| Bronchioalveolar carcinoma | 1 |
| Smoking | |
| Never | 17 |
| Former | 13 |
| Current | 27 |
| Number of prior chemotherapy regimens | |
| 0 | 6 |
| 1 | 19 |
| 2 | 16 |
| ≥3 | 16 |
| Prior cisplatin-based chemotherapy | |
| Yes | 45 |
| No | 12 |
| Prior thoracic irradiation | |
| Yes | 35 |
| No | 22 |
| Brain metastases | |
| Yes | 14 |
| No | 43 |

### 3.2. Treatment administration

All patients received 250 mg/day gefitinib, which continued uninterrupted until PD, unacceptable toxicity, or withdrawal from treatment. Median duration of treatment was 3.1 (range 0.2–23.9) months and was, as expected, longer for responders than for nonresponders (8.4 versus 1.9 months, respectively).

### 3.3. Response and overall survival

Fifty-six patients (98%) were evaluable for efficacy of gefitinib in extracranial disease and/or brain metastases. Fifteen patients achieved PR (27%; 95% confidence interval 15.8–40.3%) and SD was observed in 27 patients (46%). The median duration of objective tumor response was 7.7 months with a range from 4.1 to 24.0 months. Forty-six out of 57 patients (81%) were symptomatic at the start of treatment, mainly with specific pulmonary problems. Nearly one-third (32.6%) of symptomatic patients experienced symptom improvement (median time to symptom improvement was 18 days), and those who experienced tumor response were more likely to experience improvements in disease-related symptoms (nine out of 15 patients who experienced tumor response versus six out of 14 patients who did not experience tumor response; $P = 0.002$). The median survival has not been reached, while the median follow-up time was 11.8 months.

### 3.4. Effect of gefitinib on brain metastases

Fourteen out of 57 patients (25%) had brain metastases (Table 2); of these, 12 had adenocarcinoma and six had received prior cranial irradiation. The median maximum size of brain metastases

**Table 2** Clinical characteristics of 14 patients with brain metastasis

| Case number | Age | Gender | Smoking | Histology | PS | Prior chemo | Extracranial disease | Prior brain RT | Interval between RT and gefitinib treatment (months) | Objective response | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Extracranial disease | Brain |
| 1 | 40 | M | Never | Ad | 1 | Yes | Lung, liver | Yes | 4.9 | PR | CR |
| 2 | 29 | F | Never | Ad | 1 | Yes | Lung | No | – | PR | PR |
| 3 | 60 | F | Never | Ad | 2 | Yes | LN | Yes | 1.9 | PR | PR |
| 4 | 73 | M | Former | Ad | 2 | Yes | Lung, bone | No | – | PR | PR |
| 5 | 54 | F | Never | Ad | 4 | Yes | Lung, LN, liver | Yes | 7.1 | PR | PR |
| 6 | 59 | F | Never | Ad | 1 | Yes | Lung, bone | Yes | 2.0 | PR | PR |
| 7 | 71 | M | Current | Ad | 1 | Yes | Lung, LN, pleura | No | – | PR | SD |
| 8 | 69 | M | Former | Ad | 1 | Yes | Lung, LN, pleura | No | – | SD | SD |
| 9 | 59 | F | Never | Ad | 1 | Yes | Bone | No | – | SD | SD |
| 10 | 42 | F | Never | Ad | 1 | Yes | Lung, LN, bone | No | – | SD | SD |
| 11 | 33 | M | Current | La | 1 | Yes | Lung, adrenal | No | – | PD | SD |
| 12 | 68 | M | Former | LC | 3 | Yes | Lung, LN | Yes | 0.4 | PD | SD |
| 13 | 44 | F | Former | Ad | 1 | Yes | Lung, LN, liver | Yes | 1.1 | PD | SD |
| 14 | 55 | M | Current | Ad | 1 | Yes | Lung, LN, bone | No | – | PD | SD |

PS, performance status; RT, radiation; M, male; F, female; Ad, adenocarcinoma; La, large-cell carcinoma; LC, large-cell neuroendocrine carcinoma; LN, lymph node; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

Table 3 Multivariate analysis of the hazard ratios for various factors on objective response to gefitinib

| Factors | Tumor response, *n* (%) | Odds ratio (95% CI) | *P*-value |
|---|---|---|---|
| Tumor histology | | | |
| Non-adenocarcinoma | 2 (18) | 0.51 (0.06–4.35) | 0.54 |
| Adenocarcinoma | 13 (29) | 1 | |
| Disease stage | | | |
| I–IV | 10 (26) | 0.23 (0.04–1.56) | 0.13 |
| Postoperative recurrence | 5 (28) | 1 | |
| Performance status | | | |
| 2–4 | 5 (31) | 2.94 (0.47–18.3) | 0.25 |
| 0–1 | 10 (25) | 1 | |
| Smoking status | | | |
| BI ≥ 600 | 7 (25) | 7.27 (0.60–88.3) | 0.12 |
| BI < 600 | 8 (29) | 1 | |
| Gender | | | |
| Female | 6 (32) | 10.6 (0.89–125.3) | 0.06 |
| Male | 9 (24) | 1 | |
| Brain metastasis | | | |
| Yes | 7 (50) | 7.28 (0.98–54.2) | 0.05 |
| No | 8 (19) | 1 | |
| Age (years) | | | |
| ≥70 | 5 (36) | 26.9 (2.19–331.1) | 0.01 |
| <69 | 10 (24) | 1 | |

CI, confidence interval; BI, Brinkman index.

was 3.0 cm, with a median of four metastases per patient. The median interval between cranial irradiation and gefitinib treatment was 2.0 months (range; 0.4–7.1 months) and the median delivered dose was 30 Gy. Control of brain metastases was achieved in all 14 patients; one (7.1%) had a CR, five (35.7%) had PR, and eight (57.1%) had SD. Seven out of 14 patients with brain metastases experienced objective responses in their extracranial tumors, six of whom also experienced objective responses in the brain (four out of six patients (67%) had received prior cranial radiotherapy, but three out of four patients (75%) had shown definite disease progression in the brain before gefitinib treatment was started). The median duration of tumor response in the brain was 8.8 months.

### 3.5. Analysis of factors affecting gefitinib sensitivity

The association between several clinicopathologic factors and response to gefitinib was evaluated with a logistic regression model. Multivariate analysis found that patients aged ≥70 years and those with brain metastases were more sensitive to gefitinib ($P = 0.01$ and 0.05, respectively); in addition, female patients tended to respond well to gefitinib ($P = 0.06$) (Table 3); however, in our series, there were no other possible factors affecting the sensitivity to gefitinib.

### 3.6. Toxicity

All 57 patients were evaluable for safety. The most common AE was mild to moderate, reversible, grade 1/2 skin rash (67%); grade 1/2 diarrhea (44%), hepatotoxicity (elevated ALT/AST, 25%), and nausea and vomiting (16%) were also observed. Grade 3 toxicity was observed in six patients (11%); three had skin rash, two had hepatotoxicity and one had diarrhea. No grade 4 AEs were observed. No patients experienced interstitial lung disease; the condition was suspected in two patients, but autopsy revealed disease progression due to lymphangitis carcinomatosa. Sixteen out of 57 patients required a treatment interruption (median duration 15 days), which was due to AEs in 14 patients (88%) and withdrawal from treatment in two patients (12%). The main AEs included hepatotoxicity (four patients), infection (four patients), skin reaction (three patients), nausea/vomiting (two patients), and diarrhea (one patient). By June 2003, gefitinib treatment had been discontinued in 39 out of 57 patients; disease had progressed

in 33 patients (85%) and six patients (15%) had had treatment withdrawn due to gefitinib-related AEs (grade 3 infection [four patients], grade 2 nausea/vomiting and grade 2 hepatotoxicity [one patient each]). No treatment-related death was encountered.

## 4. Discussion

We previously published the first case report to suggest that gefitinib might be effective in patients with brain metastases [11], and Cappuzzo et al recently described a small case series of patients whose brain metastases, as well as extracranial disease, responded to gefitinib (although no details were given of whether there was any correlation between the efficacy of gefitinib for brain metastases and extracranial disease) [12]. In this retrospective analysis of 57 patients with advanced NSCLC, we have shown that gefitinib is effective against brain metastases, with a response rate equivalent to that obtained against extracranial disease. Furthermore, patients with brain metastases whose extracranial disease did not respond to gefitinib were highly unlikely to experience objective responses in the brain.

To our knowledge, this is the first time that the sensitivity of brain metastases to gefitinib has been strongly correlated to that of extracranial disease. Preclinical studies have shown that gefitinib has therapeutic activity against brain tumors in mice [13], although data on non-tumor-bearing rats showed that distribution of [$^{14}$C] gefitinib in the central nervous system of rats was low [14]. Of the 14 patients in our retrospective analysis with brain metastases, six patients had received cranial irradiation before gefitinib therapy was started and four of these patients responded to gefitinib (in one patient gefitinib was sequentially administered after radiotherapy). However, three patients with progressive disease of brain metastases and two patients with asymptomatic brain metastases who had not received cranial irradiation responded to gefitinib. Therefore, it remains unclear whether sensitivity to gefitinib might be influenced by cranial irradiation. Further prospective clinical trials may be warranted to clarify the role of gefitinib in patients with brain metastasis.

Factors that definitely predict response to gefitinib have yet to be identified, unlike HER-2/neu for trastuzumab and c-kit or BCR-ABL for imatinib [15,16]. Factors that may predict response to gefitinib include female gender and adenocarcinoma [7], along with bronchioalveolar histology and smoking history [17]. In contrast, our analysis revealed that neither tumor histology nor smoking history influenced response to gefitinib, a discrepancy that might result from differences in (i) patient population (an especially small population in our study), (ii) ethnicity, (iii) response criteria, or (iv) treatment schedule. We found that patient age significantly affected sensitivity to gefitinib, an observation that supported the findings of Gridelli et al., who found gefitinib to be active in elderly patients [18]. Interestingly, we also demonstrated that the presence of brain metastases was one of the predictive factors for gefitinib sensitivity, although the reasons why these two factors influenced sensitivity to gefitinib in our analysis remain to be determined.

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ORIGINAL ARTICLE

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# Clinical and pharmacokinetic study of docetaxel in elderly non-small-cell lung cancer patients

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**Abstract** *Purpose*: To evaluate the usefulness and pharmacokinetics of docetaxel in the treatment of elderly patients with advanced non-small-cell lung cancer. *Patients and methods*: Chemotherapy-naive elderly patients (aged at least 76 years) with locally advanced or metastatic non-small-cell lung cancer were accrued. Eligible patients received at least two cycles of docetaxel at a dose of 60 mg/m$^2$ on day 1 over 1 h every 3 weeks. Patients who were considered ineligible for this study were also registered. Symptom control was assessed using a questionnaire during the treatment period. The pharmacokinetics of docetaxel were evaluated in the first cycle of chemotherapy. *Results*: Of 35 elderly patients, 15 (43%) met the study eligibility criteria. The reasons for ineligibility consisted mainly of poor performance status, poor bone marrow function, and hypoxemia (six patients each). A total of 49 cycles of chemotherapy (median 2 cycles, range 1–12 cycles) were administered to the eligible patients, six of whom achieved a partial response (overall response rate 40%, 95% confidence interval 15–65%). The major toxicity was hematologic, with grade 3 or greater neutropenia and grade 3 neutropenic fever developing in 13 patients (87%) and five patients (33%), respectively. Symptoms, as assessed in terms of the symptom control score, did not clearly decline during the treatment period. The values (mean ± SD) of $C_{max}$, $AUC_{0 \rightarrow inf}$, and $t_{1/2}$ were 1.35 ± 0.32 μg/ml, 1.79 ± 0.52 μg h/ml, and 4.1 ± 2.3 h, respectively. *Conclusions*: Although the validity of the results of this study is limited due to the small sample size, docetaxel appears effective in selected elderly patients with advanced non-small-cell lung cancer.

**Keywords** Docetaxel · Elderly · Non-small-cell lung cancer · Pharmacokinetics · Symptom control assessment

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## Introduction

The incidence and mortality rate of lung cancer are increasing in Western countries and Japan. In the United States, the incidences of lung cancer per 100,000 persons from 1994 through 1997 were 565.5 for men and 294.1 for women, and peaked between the ages of 75 and 79 years [18]. In Osaka prefecture, Japan, the incidence also peaked above 74 years of age in the same period [18]. In addition, the mortality rates of lung cancer patients older than 74 years were 42.2% for men and 53.4% for women in Japan in 1999 [14]. Accordingly, treatment of elderly patients with lung cancer is of particular concern.

Cisplatin-based chemotherapy has been proven to improve survival of patients with advanced non-small-cell lung cancer (NSCLC) compared to best supportive care [11]. However, this benefit is modest and is limited to patients who have favorable conditions such as good performance status (PS) and younger age. In clinical trial, the upper age limit is usually set at 65 or 70 years, or 75 years at most; therefore, patients older than 75 years have been excluded from clinical trials.

The diversity of the elderly population makes it particularly difficult to determine the appropriateness of chemotherapy. The prevalence of comorbidity, functional limitations, socioeconomic restrictions, and geriatric syndromes appears to increase in patients greater than 74 years of age. Although no precise formulae are available for determining the physiologic age of patients, Balducci and Extermann have noted that an age of 75 years might represent a reasonable cut-off point to define older individuals [1]. In addition, it remains unclear how many patients can be treated with chemotherapy among all elderly patients with NSCLC, since there have been few reports on the proportion of patients eligible for chemotherapy among all elderly individuals with advanced NSCLC.

New anticancer agents such as vinorelbine, gemcitabine, and taxanes were developed and introduced for the treatment of NSCLC in the 1990s [2]. Among these agents, docetaxel is the first agent to be approved in Japan. The approved dose (60 mg/m$^2$) in Japan is lower than that (100 mg/m$^2$) in the United States and European countries [4]. However, this low dose of docetaxel is sufficiently effective with a low incidence of toxicities such as hypersensitivity and peripheral edema [4, 9].

On the basis of these considerations, a phase II study of docetaxel in elderly patients with advanced NSCLC was conducted in order to (1) evaluate the proportion of patients eligible for this study among all elderly patients with advanced NSCLC, (2) assess the efficacy and safety of docetaxel in the treatment of selected elderly patients, (3) examine the tolerability of this treatment from the view point of symptom control assessment during the treatment period, and (4) examine the pharmacokinetic profile of docetaxel in the elderly.

## Patients and methods

### Eligibility criteria

Chemotherapy-naive elderly patients (aged at least 76 years) with histologically or cytologically confirmed locally advanced (stage IIIA with N2 or IIIB) or metastatic (stage IV) NSCLC were accrued to this study. Eligibility criteria included an Eastern Cooperative Oncology Group PS of two or less, at least one measurable or assessable lesion, and life expectancy of 3 months or longer. Before enrollment, a complete medical history was obtained from each patient, and each underwent physical, laboratory, and staging work-up examinations. Laboratory examinations included complete blood cell counts with differential, routine serum chemistry and tumor marker analyses, 24-h creatinine clearance evaluation, arterial blood gas analysis, urinalysis, electrocardiogram, and pulmonary function tests. Staging work-up examination consisted of chest radiograph, computerized tomography (CT) of the chest and abdomen, magnetic resonance imaging of the brain, radionucleotide bone scan, and fiberoptic bronchoscopy. On laboratory examination, patients were required to have adequate organ function, as evidenced by a leukocyte count between 4000 and 12,000/μl, a neutrophil count of 2000/μl, a hemoglobin level of 9.5 g/dl, a platelet count of 100,000/μl, a total bilirubin level of 1.5 mg/dl, AST and ALT levels 2.5 times the upper limit of the normal range, a serum creatinine level not more than the upper limit of the normal range, and a $PaO_2$ of 65 mmHg. Patients with active infection, interstitial pneumonia, peripheral edema, or pleural or pericardial effusion that required drainage (patients with pleural effusion who had been successfully treated with agents other than anticancer drugs were eligible), a history of severe hypersensitivity, symptomatic brain metastasis, or active concomitant malignancy were excluded. Patients who were for other reasons considered not suited for study entry by the treating physician were also excluded. In addition, concomitant use of ketoconazole, miconazole, erythromycin, or clarithromycin was not permitted in this study, because it is possible that docetaxel metabolism is inhibited by these agents via liver cytochrome P450 isozyme CYP3A [7].

Written informed consent was obtained from all patients. Three institutions participated in this study, and each of their Institutional Review Boards approved this study. The registration office (National Shikoku Cancer Center) entered the patients after verification of eligibility. Patients who were considered ineligible for this study were also registered in order to assess the reasons for ineligibility and estimate the proportion of eligible patients among the entire elderly population with advanced NSCLC.

### Chemotherapy

Eligible patients received at least two cycles of docetaxel monotherapy. Docetaxel was given at a dose of 60 mg/m$^2$ on day 1 and repeated every 3 weeks. It was diluted in 500 ml 5% glucose or 0.9% saline solution, and was infused over a 1-h period. Antiemetic treatment was left to the treating physician. Prophylactic administration of dexamethasone was used to prevent fluid retention or hypersensitivity reaction, as well as for the prevention of emesis. Administration of granulocyte-colony stimulating factor (G-CSF) was allowed when grade 4 neutropenia or grade 3 neutropenic fever occurred. This administration was continued until the neutrophil count recovered to 5000/μl. The dose of docetaxel was reduced to 50 mg/m$^2$ in the presence of grade 4 hematologic toxicities lasting 3 days or when grade 3 non-hematologic toxicities had developed in the prior cycle of chemotherapy. Chemotherapy was withdrawn when similar toxicities were observed at this reduced dose level. In addition, docetaxel administration was postponed for up to 2 weeks (a maximum 6 weeks between administrations) when leukocyte, neutrophil, and platelet counts were less than 4000,

2000, and 100,000/μl, respectively. Chemotherapy was discontinued when delay of hematologic recovery continued for over 2 weeks. Other criteria for early interruption of this protocol treatment included progression of disease, emergence of intolerable toxicities, and withdrawal of consent. In addition, chemotherapy was discontinued for patients who were assessed as having stable disease after completion of two cycles of chemotherapy. Responders were allowed to continue this treatment until disease progression or the emergence of intolerable toxicities.

### Toxicity and response evaluation

For evaluation of response and toxicity, all patients underwent as inpatients a series of examinations consisting of complete blood cell counts with differential, routine chemistry profiles, and chest radiograph on at least a weekly basis during the treatment period and then on a monthly basis. In addition, the patients' clinical characteristics such as symptoms, body temperature, and weight were periodically recorded. Evaluation of target lesions was performed after each cycle of chemotherapy, and the same examinations as for the staging work-up study were performed after completion of treatment.

Responses were assessed using the World Health Organization criteria [8]. The response to treatment, including eligibility and assessability, was determined for each patient by extramural reviewers. Complete response was defined as the disappearance of all measurable lesions for at least 4 weeks. Partial response (PR) was defined as a 50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. Progressive disease (PD) was defined as a 25% increase in the sum of the products of the perpendicular diameters of all measurable disease or the appearance of new lesions. If no response or progression of disease occurred during therapy, treatment outcome was considered to be no change (NC). Toxicities were assessed and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0 (the Japan Clinical Oncology Group version) [10]. The worst degree of toxicity experienced throughout the treatment was computed for each patient.

### Symptom control assessment

A quality-of-life (QOL) questionnaire for cancer patients treated with anticancer drugs (QOL-ACD) has been developed in Japan [5]. It is a 22-item questionnaire that covers four domains consisting of functional, physical, mental, and psychosocial well-being. In addition, global QOL is assessed using a face scale. In this study, assessment of symptoms during chemotherapy was performed using a questionnaire that consisted of four items selected from the QOL-ACD questionnaire (feeling, appetite, vomiting, and sleep) and an additional item concerning respiratory condition (cough and sputum). Assessment of global QOL using the face scale was also performed. Each patient was asked to fill in this questionnaire at the time of study entry (baseline symptom score) and immediately before each cycle of chemotherapy. Severity of each symptom during chemotherapy was scored using a visual analogue scale and was assessed compared with the baseline value.

### Pharmacokinetic evaluation

The pharmacokinetics of docetaxel were studied in the first cycle of chemotherapy. Samples were taken at the following time points: predose, midinfusion, end of infusion, and 30 min and 2, 3, 5, 7, 23, 47 and 71 h after infusion. All blood samples were immediately centrifuged and the heparinized plasma was stored at −20°C until analysis. Subsequent assays and pharmacokinetic analysis were performed based on a previously described method [13]. Briefly, docetaxel concentrations in plasma were determined by high-performance liquid chromatography with UV detection. Docetaxel and internal standard were determined by a UV detector adjusted to 225 nm, and peak heights were used for quantification. Pharmacokinetic parameters were calculated using WinNonlin computer software (Pharsight, Mountain View, Calif.). The maximum plasma concentration ($C_{max}$) was obtained from the actual value. The terminal rate constant (k) was determined by log-linear regression analysis of the terminal phase of the plasma concentration vs time curve. The terminal half-life time ($t_{1/2}$) was calculated by the equation $t_{1/2} = 0.693/k$. The area under the concentration vs time curve (AUC) was calculated by the linear trapezoidal rule up to the last measurable data points with extrapolation to infinity. The clearance (CL) was calculated by dividing the dose received by the AUC.

### Statistical considerations

The sample size of this study was determined with the assumption of an expected response rate of 20%, with a 95% confidence interval (CI) of ± 10%. Accrual of 61 patients was therefore required for this study. Statistical analyses were performed using the SPSS Base System and Advanced Statistics programs (SPSS, Chicago, Ill.). The significances of differences between baseline and during-treatment or post-treatment symptom scores were determined using Student's paired *t*-test. The global QOL score was similarly analyzed. Survival time was defined as the period from initiation of treatment to death or last follow-up evaluation. In addition, time to progression was defined as the period from initiation of treatment to PD. Patients who received additional thoracic radiotherapy were censored at the start of

irradiation. Survival curves were calculated using the method of Kaplan and Meier.

## Results

### Patient characteristics

Between November 1999 and December 2001, 35 elderly patients with advanced NSCLC were accrued to this study. Of these, 15 (43%) met the study eligibility criteria. Although the sample size of this study was designed to be 61 patients on an eligible patient basis, the study was terminated early due mainly to the slow rate of accrual of patients.

The characteristics of the entire group of patients and eligible patients are listed in Table 1. The median ages and age ranges were similar for the two groups. However, the proportions of patients with a poor PS, adenocarcinoma, or metastatic disease were higher in the entire group than in the eligible group. The proportion of patients with weight loss was not determined in the entire group, since assessment of weight loss was not required for registration of patients ineligible for this study. The reasons for ineligibility for study entry were poor PS ($n=6$), poor bone marrow function ($n=6$), hypoxemia ($n=6$), life expectancy less than 3 months ($n=4$), physician's discretion ($n=4$), symptomatic brain metastasis ($n=2$), double cancer ($n=2$), poor renal function ($n=1$), infection ($n=1$), and interstitial lung disease ($n=1$). More than one reason was noted in seven patients. In addition, two patients refused chemotherapy. Among ineligible patients, two received chemotherapy; one with anemia received docetaxel at a dose of 60 mg/m$^2$, and the other with anemia and hypoxemia received vinorelbine monotherapy. The serum albumin values (means ± SD) were 3.6 ± 0.30 g/dl in 15 eligible patients and 3.9 ± 0.39 g/dl in 20 ineligible patients. In addition, the value of plasma alpha-1 acid glycoprotein (AAG), which was measured in ten eligible patients, was 1.22 ± 0.39 g/l.

**Table 1** Patient characteristics (*NE* not evaluated)

| | All patients ($n=35$) | Eligible patients ($n=15$) |
|---|---|---|
| Age (years) | | |
| Median | 78 | 78 |
| Range | 76–87 | 76–87 |
| Sex | | |
| Male | 27 | 12 |
| Female | 8 | 3 |
| ECOG performance status | | |
| 0 | 4 | 3 |
| 1 | 19 | 10 |
| 2 | 6 | 2 |
| 3 | 3 | 0 |
| 4 | 3 | 0 |
| Histology | | |
| Adenocarcinoma | 18 | 7 |
| Squamous cell | 14 | 6 |
| Adenosquamous cell | 2 | 1 |
| Not otherwise specified | 1 | 1 |
| Stage | | |
| IIIA | 8 | 3 |
| IIIB | 8 | 6 |
| IV | 19 | 6 |
| Weight loss | | |
| < 5% | NE | 12 |
| ≥5% | NE | 3 |

### Chemotherapy outcome

A total of 49 cycles of chemotherapy were administered to 15 eligible patients. The median number of chemotherapy cycles was two (1 cycle in two patients, 2 cycles in six, 3 cycles in four, 5 cycles in one, 6 cycles in one, and 12 cycles in one). Two patients who had disease progression or developed docetaxel-related interstitial lung toxicity received only one cycle of chemotherapy. Four patients underwent reduction of dose of docetaxel because of grade 4 neutropenia lasting for 3 days ($n=3$), grade 3 neutropenic fever ($n=1$), or grade 3 nausea ($n=1$). One patient developed both grade 4 neutropenia and grade 3 nausea. In addition, the median interval between each cycle of chemotherapy was 22 days (range 19–30 days).

Of the 15 patients, 6 achieved PR, 6 NC, and 2 PD. Response was not evaluated for one patient who developed docetaxel-related interstitial pneumonia. The overall response rate was 40%, with a 95% CI of 15–65%. Four patients with stage IIIA ($n=3$) or IIIB disease ($n=1$) received additional thoracic radiotherapy. The plasma AAG levels of two patients with PD were 1.85 and 1.79 g/l, respectively, which were the highest and the second highest values in this study. With a median follow-up period of 27.9 months (range 16.2–42.5 months), median progression-free survival time was 6.1 months (95% CI 5.6–6.6 months). At the time of analysis, 11 patients had died and four were still alive. The cause of death was directly related to NSCLC in ten patients and unrelated in one (interstitial pneumonia). This complication of interstitial pneumonia, occurring in another patient who developed docetaxel-related lung toxicity, was observed more than 12 months after completion of chemotherapy. The median survival time was 15.6 months (95% CI 11.4–19.8 months), with 1-year and 2-year survival rates of 73.3% and 37.3%, respectively.

The toxicities observed in the 15 patients during treatment and the follow-up period are listed in Table 2. The major toxicity was myelosuppression, with grade 3 or higher leukopenia and neutropenia observed in 9 patients (60%) and 13 patients (87%), respectively. Grade 3 neutropenic fever occurred in five patients (33%). G-CSF was administered to 13 patients (87%) over a median duration of 4 days (range 2–6 days). Grade 3 nonhematologic toxicities observed in this study included fatigue (33%), dyspnea (13%), electrolyte dis-

Table 2 Maximum NCI-CTC toxicities by number of patients

| | NCI-CTC grade | | | | Grade 3/4 toxicity (% of patients) |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Leukocytes | 1 | 5 | 8 | 1 | 60 |
| Neutrophils | 0 | 2 | 1 | 12 | 87 |
| Platelets | 1 | 1 | 0 | 0 | 0 |
| Hemoglobin | 10 | 4 | 1 | 0 | 7 |
| Nausea | 7 | 1 | 2 | – | 13 |
| Vomiting | 1 | 0 | 1 | 0 | 7 |
| Dyspnea | – | 2 | 2 | 0 | 13 |
| Neutropenic fever | – | – | 5 | 0 | 33 |
| Fatigue | 2 | 3 | 3 | 0 | 20 |
| Liver | 7 | 1 | 0 | 0 | 0 |
| Electrolytes | 1 | 0 | 2 | 0 | 13 |
| Worst hematologic toxicity | 0 | 1 | 2 | 12 | 93 |
| Worst non-hematologic toxicity | 5 | 2 | 8 | 0 | 53 |

turbance (13%), nausea (13%), and vomiting (7%). Grade 3 dyspnea observed in two patients was associated with bacterial pneumonia and docetaxel-related interstitial lung toxicity. No patients experienced hypersensitivity reactions or peripheral edema. Overall, grade 3 or higher hematologic and nonhematologic toxicities were observed in 14 patients (93%) and 8 patients (53%), respectively. No treatment-related death occurred.

### Changes in symptom scores during chemotherapy

A total of 39 questionnaires were collected throughout the study. The overall collection rate was 61% (39/64), with rates after the first, second, and third cycle of chemotherapy of 87% (13/15), 38% (5/13), and 43% (3/7), respectively. Changes in symptom and global QOL (face scale) scores up to the third assessment are shown in Fig. 1, where individual scores are presented as relative values as compared with the baseline value. At each assessment, patients exhibited improvement in feeling, appetite, and global QOL; whereas slight deterioration was found in vomiting, cough and sputum. However, there were no significant differences in the changes in these scores during the treatment period. In addition, no relationship was found between relative symptom score and response to treatment.

### Pharmacokinetic results

Blood sampling for pharmacokinetic analysis was not performed in three patients because of patient refusal. The $C_{max}$ ($1.35 \pm 0.32$ μg/ml, mean ± SD), $AUC_{0 \rightarrow inf}$ ($1.79 \pm 0.52$ μg h/ml), and $t_{1/2}$ ($4.1 \pm 2.3$ h) in the 12 elderly patients were somewhat lower than those ($C_{max}$, $1.61 \pm 0.59$ μg/ml; $AUC_{0 \rightarrow inf}$, $2.44 \pm 0.83$ μg·h/ml; $t_{1/2}$, $7.5 \pm 6.3$ h; $n = 6$) in non-elderly patients in a phase I study in Japan (docetaxel dose 60 mg/m$^2$; infusion time 60–160 min) [15]. Conversely, the CL ($38.5 \pm 8.5$ l/h/m$^2$) in this study was somewhat higher than that ($27.8 \pm 11.6$ l/h/m$^2$) in the phase I study. The non-elderly pharmacokinetic participants were required to have an Eastern Cooperative Oncology Group PS of two or less, to be aged between 15 and 75 years old, and to have a leukocyte count ≥4000/μl, a neutrophil count ≥1500/μl, a hemoglobin level ≥9.5 g/dl, a total bilirubin level ≤ 1.5 mg/dl, AST and ALT levels not more than two times the upper limit of the normal range, and a serum creatinine level not more than the upper limit of the normal range [15].

## Discussion

This is, to our knowledge, the first study of an every 3-weeks schedule of docetaxel in chemotherapy-naive elderly patients with advanced NSCLC. The percentage

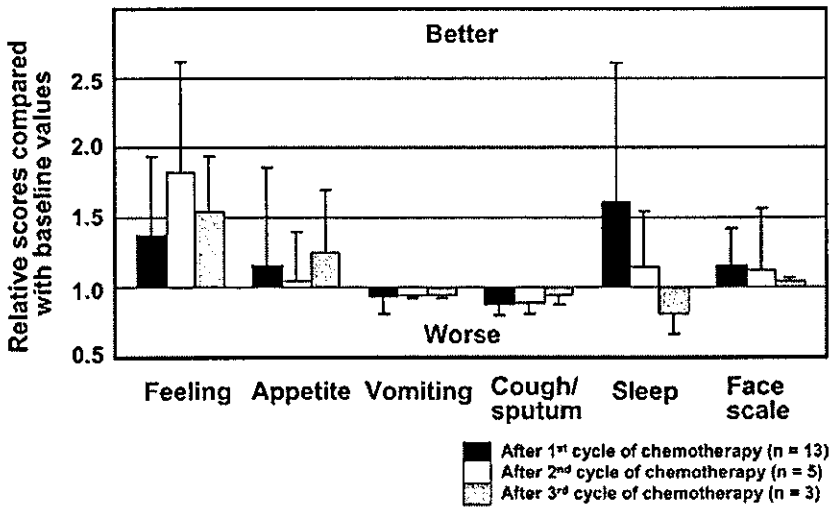


Fig. 1 Changes in relative symptom scores during the treatment period. The histograms represent mean and standard deviation

of patients who are reluctant to receive chemotherapy or who should not be treated with chemotherapy due to poor PS or comorbidity appears to be much higher among elderly patients than among younger patients [3]. In this study, we attempted to estimate the proportion of patients eligible for docetaxel among all elderly patients with advanced NSCLC who visited our hospitals. In a previous study by Oshita et al., 10 of 34 elderly (aged at least 75 years) patients (29%) with lung cancer were eligible for cisplatin-based chemotherapy [12]. In addition, in our retrospective series, 37% of elderly patients with advanced NSCLC underwent either cisplatin-based or non-platinum combination chemotherapy [16]. The results of these studies as well as that (proportion of eligible patients, 43%) of our own suggest that chemotherapy can be administered to approximately 30–40% of elderly patients with advanced NSCLC. However, these findings should be cautiously interpreted because the figures might include a considerable degree of physician discretion with regard to chemotherapy drug and dosing in the elderly.

The initial estimated sample size was 61 patients, which was determined with the efficacy endpoint (one of four primary endpoints) of this study. However, this study was terminated early due to the slow rate of patient accrual. Although the sample size was extremely small, the response rate (40%, 95% CI 15–65%) can be considered at least comparable to that (19%, 95% CI 11–29%) in a phase II study of docetaxel, which was conducted for the application for approval of docetaxel in Japan [4]. In that study, advanced NSCLC patients with a median age of 67 years (range 40–80 years) received docetaxel at a dose of 60 mg/m$^2$. In addition, the median survival time (15.6 months) in the present study is superior to that in the previous phase II study (9.8 months) [4], although four of nine patients with stage III disease underwent additional thoracic radiotherapy.

The major toxicity in our study was myelosuppression, with grade 3 or higher leukopenia and neutropenia, and grade 3 neutropenic fever observed in 60%, 87%, and 33% of patients, respectively. The incidence and severity of myelosuppression in our study were similar to those (49%, 87%, and 11%, respectively) in the Japanese phase II study [4]. However, hematologic toxicity was easily manageable, and did not lead to treatment-related death. Concerning non-hematologic toxicities, grade 3 or higher fatigue was more frequently observed in our study (20%) than in the phase II study (4%). However, there were no differences in the incidences of other non-hematologic toxicities between the two studies. In this study, relative symptom and global QOL scores did not decline during the treatment period. However, particularly after the second cycle of chemotherapy, only a small number of patients answered the questionnaire, adding limited information to this assessment.

It is believed that the pharmacokinetic profiles of docetaxel are not affected by patient age [6]. Compared with the result of a Japanese phase I study of docetaxel conducted in non-elderly patients [15], the values of $C_{max}$, $AUC_{0 \rightarrow inf}$, and $t_{1/2}$ were slightly lower in our study, with a slight increase in CL. We cannot explain why docetaxel was cleared more rapidly in this study population. In addition, we have no clear explanation for the relationship between relatively increased total body clearance of docetaxel and high incidence of severe neutropenia. It seems difficult to compare the pharmacokinetic profiles of docetaxel between these studies, since docetaxel in the phase I study was infused at a dose of 60 mg/m$^2$ over 60–160 min.

In conclusion, 43% of elderly patients with advanced NSCLC received single-agent docetaxel without a reduction in their symptoms in our study, although careful attention should be paid to the physiologic changes associated with ageing to ensure safe administration of anticancer drugs to the elderly. Based on the result of the "ELVIS" study, vinorelbine monotherapy has been considered the treatment of choice for elderly patients with advanced NSCLC [17]. Docetaxel monotherapy also appears to be useful for the treatment of elderly patients with advanced NSCLC, although the validity of the results is limited due to the small sample size. In future studies the endpoint should be limited and the age range should be reconsidered (e.g., 70 years or more). In addition, comorbidity, number of medications, and functional and cognitive status should be evaluated to ascertain the "physiologic age" of the elderly.

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ORIGINAL REPORT

# Meta-Analysis of Randomized Clinical Trials Comparing Cisplatin to Carboplatin in Patients With Advanced Non–Small-Cell Lung Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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## ABSTRACT

**Purpose**
It remains undetermined whether cisplatin and carboplatin are equally effective for advanced non–small-cell lung cancer (NSCLC). We therefore did a meta-analysis of trials that compared cisplatin-based chemotherapy with carboplatin-based chemotherapy.

**Methods**
We performed a literature search to identify trials that had investigated the substitution of carboplatin for cisplatin in the treatment of advanced NSCLC. We evaluated these trials for inclusion, rated methodologic quality, and abstracted relevant data.

**Results**
Of 1,191 reports, eight trials (2,948 patients) were identified, five of which investigated drug regimens containing platinum plus a new agent. Cisplatin-based chemotherapy produced a higher response rate, but the survival advantage was not significant (hazard ratio = 1.050; 95% CI, 0.907 to 1.216; $P = .515$). Subgroup analysis revealed that combination chemotherapy consisting of cisplatin plus a new agent yields 11% longer survival than carboplatin plus the same new agent (hazard ratio = 1.106; 95% CI, 1.005 to 1.218; $P = .039$). Patients on cisplatin-based chemotherapy frequently developed nausea and vomiting; thrombocytopenia was more frequent during carboplatin-based chemotherapy. No significant difference in treatment-related mortality was observed.

**Conclusion**
We found that combination chemotherapy consisting of cisplatin plus a new agent yields a substantial survival advantage compared with carboplatin plus a new agent in patients with advanced NSCLC, although we failed to find any survival difference in an analysis that included both new and old agents. The strength of our conclusion is limited because we used abstracted data, and careful interpretation is thus required. Nevertheless, our results raise a critical point that needs to be evaluated in future studies.

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## INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in many countries. Approximately one third of patients with non–small-cell lung cancer (NSCLC) have metastatic disease at the time of diagnosis.[1] Cisplatin-based chemotherapy is currently considered to be the standard treatment in advanced NSCLC, with a 10% absolute improvement in the 1-year survival rate compared to supportive care alone.[2] However, many medical oncologists remain skeptical about these data and have not routinely used cisplatin-based chemotherapy to treat patients with advanced NSCLC.[3] This reluctance may be partly explained by the severe toxicity that is associated with cisplatin-based chemotherapy.

In an attempt to circumvent cisplatin-induced toxicities, carboplatin, an analog of cisplatin, was introduced into clinical trials in 1981.[4] Indeed, cisplatin has already been replaced by carboplatin for the chemotherapy of a few other malignancies, such as ovarian cancer.[5] In patients with advanced NSCLC, carboplatin-based chemotherapy has also been extensively investigated.[6-14] A two-drug combination consisting of carboplatin plus paclitaxel has been frequently used in clinical practice as well as in clinical trials, especially in the United States.[14] However, it is still unclear whether carboplatin has efficacy equivalent to that of cisplatin or not. Go et al[15] reviewed reports directly comparing the effectiveness of cisplatin with that of carboplatin. In their report, carboplatin was shown to possess inferior activity to that of cisplatin in germ cell, head and neck, and esophageal cancers. Furthermore, comparisons between cisplatin and carboplatin in NSCLC have been based on limited data. Accordingly, we performed a meta-analysis to compare the effect of carboplatin-based chemotherapy with that of cisplatin-based chemotherapy on overall survival, response rate, and toxicity in patients with advanced NSCLC.

## Methods

### Search for Trials

We searched for trials that had completed recruitment by December 31, 2001. To avoid publication bias, both published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from the past 13 conferences of the American Society of Clinical Oncology (ASCO). We searched using the following terms: "lung cancer," "chemotherapy," and "randomized controlled trial." Only references published in English were included. We also examined reference lists of original articles, review articles, and relevant books, and the Physician Data Query registry of clinical trials.

### Selection of Trials

Trials were eligible if they investigated the substitution of carboplatin for cisplatin in combination chemotherapy for patients with advanced NSCLC. Whatever drug was combined with cisplatin or carboplatin had to be the same cytotoxic agents in both treatment arms. Patients with pathologically confirmed NSCLC who had not previously received chemotherapy were enrolled in these trials.

### Validity Assessment

We performed an open assessment of the trials and used the instrument reported by Jadad et al.[16]

### Data Abstraction

To avoid bias in the data abstraction process, two observers (K.H. and H.U.) independently abstracted the data from the trials and compared results. The following information was obtained from each source article: year of publication, study period, number of patients, sex, clinical stage, performance status, chemotherapy regimen, objective response rate, overall survival, and specific toxicity data. New chemotherapy agents were defined as docetaxel, paclitaxel, vinorelbine, gemcitabine, and irinotecan.[17]

All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. All principal investigators of the trials were contacted to confirm or update the published data. For response assessment, we used only trials that included patients with measurable or assessable disease, and that were analyzed with well-accepted criteria. Toxicity profiles were reported according to the WHO's criteria or the cooperative groups' criteria.

### Quantitative Data Synthesis

We calculated odds ratios (ORs) to assess objective response rate and toxic events. We constructed $2 \times 2$ tables from abstracted data for response and for each toxic event. ORs and their variances for the subjects who received cisplatin-based chemotherapy relative to those receiving carboplatin-based chemotherapy were calculated from the tables. An OR above unity indicates that the cisplatin-based chemotherapy achieved worse results than the carboplatin-based chemotherapy. For OR calculations we excluded ineligible subjects from each evaluation.

A hazard ratio (HR) was calculated to assess the survival advantage of the carboplatin-based chemotherapy as compared with the cisplatin-based chemotherapy. The crude log HR value and its variance in each trial were calculated using the abstracted survival probabilities in the Kaplan-Meier curve at specific time points according to the methods proposed by Parmar et al.[18] Minimum and maximum follow-up times were used to estimate censored subjects under the assumption that censoring happens constantly throughout follow-up. If the minimum follow-up time was not available, time zero was substituted for it. As we assumed constant hazard for the two types of therapy within an individual trial, all the survival probabilities available in each trial were used to obtain a representative HR for each trial instead of limiting time points to specified times. HRs were calculated to show how many times higher the probability of death from any cause was in patients receiving a carboplatin-based chemotherapy as compared with those receiving a cisplatin-based chemotherapy. Therefore, an HR greater than unity indicates that the cisplatin-based chemotherapy is better than the carboplatin-based chemotherapy.

A general variance-based method was used to estimate the summary HR, ORs, and their 95% CIs. We looked for heterogeneity among the trials based on standard methods.[19] We also calculated the between-study variation ($\tau^2$) from the Q statistic according to the method described by DerSimonian and Laird.[20] Based on the statistical significance of the Q test, we applied a random effect model which allows meta-analyses to take into consideration between-study-variation. We also used Begg's funnel plots[21] and Egger's test[22] to detect possible publication bias. Meta-regression analysis was applied to detect the source of heterogeneity in the analysis for survival. The factors examined in meta-regression analysis were study quality score,[16] starting year of trial, proportion of patients with performance status 0-1, proportion of stage IV patients, proportion of male patients, inclusion of new agents, number of stratifications in the random allocation, and median age of patients. Cumulative meta-analysis was applied in the event that heterogeneity was probable in an ordinal variable with statistical significance ($P < .15$).

All statistical analyses were conducted with STATA version 8 software (College Station, TX). We defined a statistical test with a $P$ value less than .05 as significant.

## RESULTS

### Trial Flow

The flow chart of our study is shown in Figure 1. One of the nine trials retrieved for more detailed evaluation compared cisplatin plus tirapazamine with carboplatin plus tirapazamine.[23] Since tirapazamine is not a cytotoxic agent and the effectiveness of tirapazamine for advanced NSCLC has not been determined,[24] we excluded this trial from our analysis. Thus, eight trials involving 2,948 patients with advanced NSCLC were ultimately analyzed.[6-13]

### Characteristics of the Eight Trials

Baseline characteristics of the eight trials are listed in Table 1. In total, 2,948 patients were randomly assigned to cisplatin-based chemotherapy (1,478 patients) or carboplatin-based chemotherapy (1,470 patients). Patients were stratified by four variables in four trials, by three in one, and by two in three. Clinical stage was used for stratification in all trials.

Of the eight trials, seven were randomized phase III trials,[6-11,13] and the remaining one was a randomized phase II trial.[12] There was no placebo-controlled double-blind

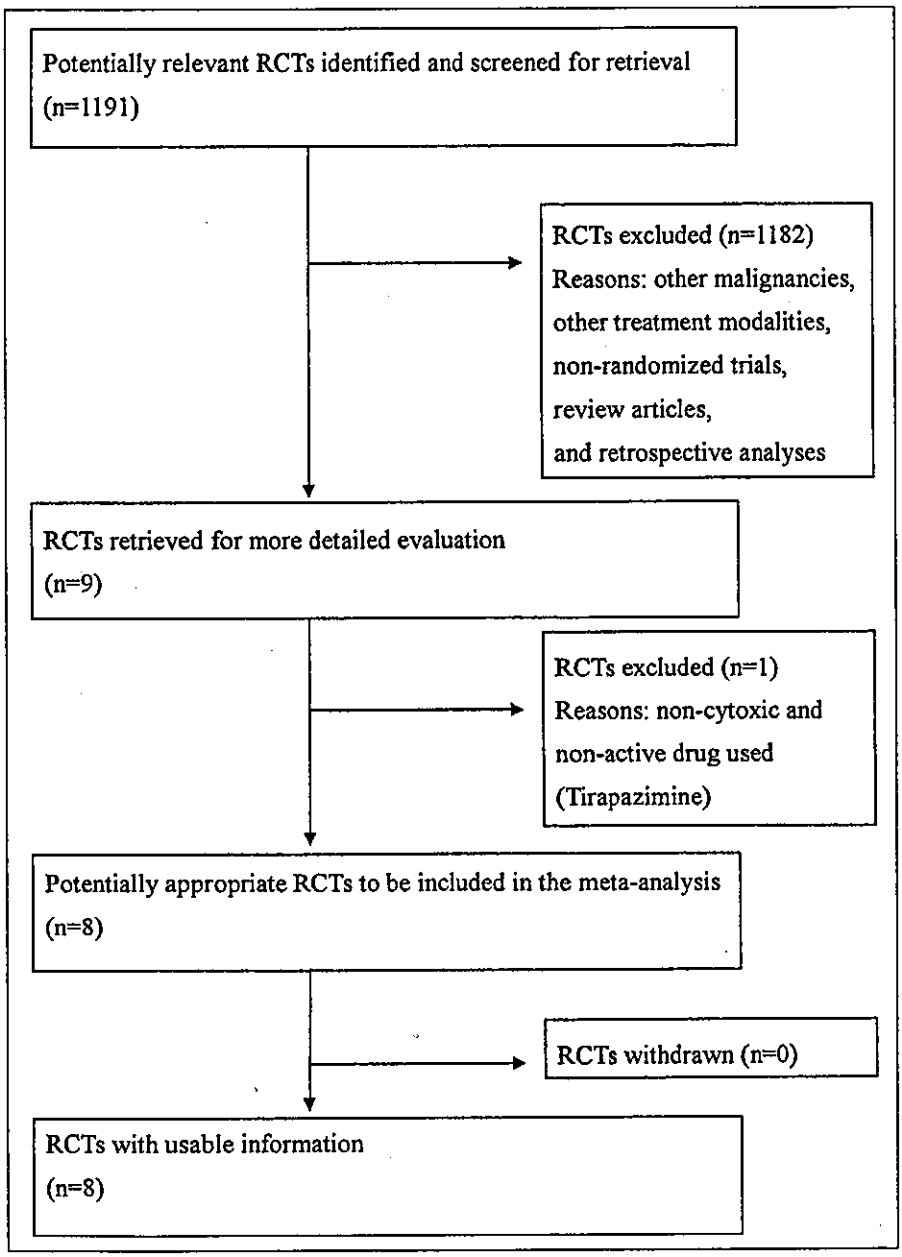


**Fig 1.** A flow chart showing the progress of trials through the review. RCT, randomized controlled trials.