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Original study

# Dose-Escalation Study of Three-Dimensional Conformal Thoracic Radiotherapy With Concurrent S-1 and Cisplatin for Inoperable Stage III Non–Small-Cell Lung Cancer

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## Abstract

**We conducted a radiation dose-escalation study with concurrent S-1 and cisplatin for stage III non–small-cell lung cancer. In the 74 Gy dose level, only 1 among 12 patients experienced dose-limiting toxicity and late toxicity was mild. These findings define the recommended phase II dose for further prospective trials.**

**Purpose:** To determine the recommended dose (RD) in concurrent conformal radiotherapy with S-1 and cisplatin chemotherapy for inoperable stage III non–small-cell lung cancer. **Patients and Methods:** Eligible patients with inoperable stage III non–small-cell lung cancer, age ≥ 20 years, performance status 0-1 received 4 cycles of intravenous cisplatin (60 mg/m$^2$, day 1) and oral S-1 (80, 100, or 120 mg based on body surface area, days 1-14) repeated every 4 weeks. Radiation doses were 66, 70, and 74 Gy for arms 1, 2, and 3, respectively. **Results:** A total of 24 patients were enrolled in our study, including 6 in arm 1, 6 in arm 2, and 12 in arm 3. The patients consisted of 14 men and 10 women, with a median age of 63 years (range, 44-73 years). The median follow-up was 27.3 months (range, 8.5-42.6 months) for all patients and 33.9 months (range, 15.2-42.6 months) for those still alive. Grade 3 febrile neutropenia, lung toxicities, and heart toxicities occurred in 2, 2, and 2 patients, respectively. Dose-limiting toxicity occurred in 2, none, and 1 patient in arms 1, 2, and 3, respectively. The median survival was not reached, and the 2-year survival rate was 70% (95% CI, 51%-89%). Two-year local relapse-free survival and distant metastasis–free survival were 74% (95% CI, 56%-92%) and 45% (95% CI, 25%-65%), respectively. **Conclusions:** High-dose radiotherapy with S-1 and cisplatin is feasible, and 74 Gy was determined as the recommended dose.

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**Keywords:** Chemotherapy, Dose escalation, Non–small-cell lung cancer, Radiotherapy

## Introduction

Treatment of locally advanced non–small cell lung cancer (NSCLC) is based on local and systemic control of the disease. The standard treatment for stage III NSCLC is a combination of thoracic radiotherapy (RT) and chemotherapy.[1,2] In previous studies that used thoracic RT and older second-generation chemotherapeutic regimens, the survival period was reported to be significantly prolonged by concurrent chemoradiotherapy.[3-5] Over the past decade, newer agents and platinum combinations, such as paclitaxel, gemcitabine, vinorelbine, and docetaxel, so-called third-generation regimens, have been shown to be more effective than second-generation regimens, as demonstrated by the increased survival in patients with metastatic NSCLC.[6,7] However, concurrent chemoradiotherapy by using third-generation chemotherapeutic agents can hardly be used at systemic doses,[8] and a phase III study to compare concurrent chemoradiotherapy by using second- or third-generation regimes indicated no significant differences in overall survival (OS).[9] Thus,

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there is still a need for new treatment regimens to prolong survival in patients with locally advanced NSCLC. Recent phase I or II trials have shown that novel agents such as pemetrexed-based regimens[10-12] or S-1-based regimens[13-15] can be used concurrently with thoracic RT at systemic dose.

S-1 is a new oral fluoropyrimidine agent that consists of tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate in a molar ratio of 1:0.4:1. For metastatic NSCLC, the combination of S-1 and cisplatin is effective as a first-line chemotherapy regimen.[16] We previously performed a phase II study of S-1 and cisplatin with concurrent RT (60 Gy) for locally advanced NSCLC; the median progression-free survival (PFS) period was 12.0 months, and the median OS period was 33.1 months.[14] Another group reported similar results as ours.[15] Toxicities were mild, and this was considered as an encouraging systemic chemotherapeutic regimen combined with concurrent RT. In our previous study, however, analysis of the initial sites of failure indicated that local failure still occurred in half of the patients with recurrences. Therefore, it is necessary to further improve local control to cure patients with inoperable NSCLC.

To enhance both local and systemic control, high-dose radiation concurrent with systemic chemotherapy is a reasonable strategy. Furthermore, use of new techniques, such as positron emission tomography and real-time endobronchial ultrasonography–guided transbronchial needle aspiration, provides more accurate tumor volumes, 3-dimensional (3D) conformal RT, and omission of elective nodal irradiation resulted in improvement of radiation-associated toxicity without worsening the local tumor control rate.[17] At the time that this trial started, there were prospective data from several groups, which showed that 74 Gy is tolerable in the setting of concurrent chemotherapy.[18,19] In these studies, however, RT with concurrent administration of carboplatin and paclitaxel as reduced doses weekly was adopted. Therefore, there is room for testing new chemotherapy regimens and high-dose RT. In this article, we report a radiation dose escalating study concurrent with S-1 and cisplatin to determine its feasibility and efficacy.

## Materials and Methods

### *Study Design*

This was an open-label, multicenter, single-arm, dose-escalating phase I study. The protocol and consent form were approved by the review board of each participating center. The dose escalation was decided based on consultation with the independent efficacy and safety evaluation committee. We planned to treat 6 patients at a given dose level and follow up for at least 90 days and then escalate to the next level if dose-limiting toxicities (DLT) occurred in ≤2 patients. If 3 patients developed a DLT, then up to 3 additional patients were to be treated at the same dose. If 4 or more DLTs among 9 patients occurred at a given dose level, then escalation was stopped, and a maximum tolerated dose and recommended dose (RD) was determined at the previous dose level. If 4 of 6 or 6 of 9 patients at a 74-Gy dose level did not experience DLTs, then maximum tolerated dose was not determined and 74 Gy was determined as the RD. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. The DLT was defined as a grade 3 nonhematologic toxicity, excluding nausea, vomiting, and esophagitis, and as grade 4 toxicity, excluding neutropenia, within 7 days for 90 days from the start of RT. Once an RD was decided, additional patients were enrolled to make a total of 12 patients at the RD level.

### *Patient Eligibility and Pretreatment Evaluation*

Eligible patients were required to have histologically or cytologically proven inoperable (multistation N2 disease, insufficient lung function for lobectomy, or pneumonectomy) stage IIIA or IIIB NSCLC defined by TNM Classification of Malignant Tumors (6th edition), no previous chemotherapy or RT, a performance status of 0-1 on the Eastern Cooperative Oncology Group scale, adequate bone marrow reserve (leukocyte count ≥4000/mm$^3$, neutrophil count ≥2000/mm$^3$, platelet count ≥100,000/mm$^3$), normal liver function (total serum bilirubin level 1.5 times the upper limit of normal or less), normal renal function (normal serum creatinine level or creatinine clearance ≥60 mL/min and pulmonary function [partial pressure of oxygen ≥ 70 Torr in room air]). Patients were excluded if they had malignant pleural or pericardial effusion; an active second cancer; concomitant serious illness, such as uncontrolled angina pectoris or myocardial infarction in the previous 3 months; heart failure; uncontrolled diabetes mellitus; interstitial pneumonia or lung disease; infection; or other diseases that contraindicated chemotherapy or RT. All the patients gave their written informed consent. For staging, all the patients underwent a computed tomography (CT) of the thorax, including the upper abdomen, and either a brain CT or brain magnetic resonance imaging. A positron emission tomography was also performed in all patients.

### *Treatment Overview*

*Chemotherapy.* Treatment in eligible patients began with the administration of 2 cycles of concurrent chemoradiotherapy and 2 cycles of consolidation chemotherapy that consisted of oral administration of S-1 twice daily for days 1 to 14, along with a 60-minute intravenous infusion of cisplatin (60 mg/m$^2$) on day 1 and then at 4-week intervals. The patients received 1 of 3 different fixed oral doses of S-1 based on the body surface area. The 3 doses administered were 40 mg (body surface area <1.25 m$^2$), 50 mg (1.25 ≤ body surface area < 1.50 m$^2$) and 60 mg (body surface area ≥1.50 m$^2$). Supportive care, which included adequate hydration and antiemetics, was provided. The use of granulocyte colony–stimulating factor during RT was not permitted. If changes in the laboratory variables after the start of treatment occurred so that a leukocyte count of ≥3000 $\mu L^{-1}$ or the neutrophil count of ≥1500 $\mu L^{-1}$ or any of the other entry eligibility criteria for the study were not met, then subsequent courses of treatment were withheld until the noted abnormality had resolved. The doses of S-1 were reduced in the event of any of the following toxicities during the previous treatment cycle: grade 4 hematologic toxicity or grade 3 or more nonhematologic toxicity. For the subsequent courses, S-1 was reduced from 60, 50, or 40 mg twice daily to 50, 40, or 25 mg twice daily, respectively.

*RT.* A volumetric treatment planning CT study was required to define gross tumor volume, clinical target volume, and planning target volume (PTV) (scan thickness ≤5 mm). Each patient was positioned in an immobilization device in the treatment position on a flat table. X-rays at 6 to 10 MV were to be used. Multileaf collimation was used to protect normal tissues outside of the target volume.

**Table 1 Patient Characteristics**

| | |
|---|---|
| **Sex, No. (%)** | |
| Men | 14 (58) |
| Women | 10 (42) |
| **Age, Median (range), y** | 63 (44-73) |
| **Performance Status, No. (%)** | |
| 0 | 20 (83) |
| 1 | 4 (17) |
| **Body Weight Loss, No. (%)** | |
| ≤5.0% | 14 (58) |
| >5.0% | 2 (8) |
| Unknown % | 8 (33) |
| **Histology, No. (%)** | |
| Adenocarcinoma | 13 (54) |
| Squamous cell carcinoma | 5 (21) |
| Large-cell carcinoma | 4 (17) |
| Pleomorphic carcinoma | 2 (8) |
| **Stage, No. (%)** | |
| IIIA | 20 (83) |
| IIIB | 4 (17) |
| **Smoking History, No. (%)** | |
| Never | 2 (8) |
| Ever | 21 (88) |
| Unknown | 1 (4) |

**Table 2 Acute Toxicities**

| | Arm 1, 66 Gy (N = 6) | | Arm 2, 70 Gy (N = 6) | | Arm 3, 74 Gy (N = 12) | |
|---|---|---|---|---|---|---|
| | Grade ≥3 | % | Grade ≥3 | % | Grade ≥3 | % |
| **Leukopenia** | 4 | 67 | 2 | 33 | 1 | 8 |
| **Neutropenia** | 5 | 83 | 2 | 33 | 0 | 0 |
| **Anemia** | 1 | 17 | 0 | 0 | 1 | 8 |
| **Thrombocytopenia** | 1 | 17 | 0 | 0 | 0 | 0 |
| **Febrile Neutropenia** | 2 | 33 | 0 | 0 | 1 | 8 |
| **Infection** | 1 | 17 | 0 | 0 | 1 | 8 |
| **Esophagitis** | 1 | 17 | 1 | 17 | 0 | 0 |
| **Anorexia** | 1 | 17 | 1 | 17 | 1 | 8 |
| **Nausea/Vomiting** | 0 | 0 | 0 | 0 | 1 | 8 |
| **Mucositis** | 1 | 17 | 0 | 0 | 0 | 0 |
| **Diarrhea** | 1 | 17 | 0 | 0 | 0 | 0 |
| **Cardiovascular** | 0 | 0 | 0 | 0 | 1 | 8 |

The primary tumor and clinically positive lymph nodes seen either on the planning CT (>1-cm short-axis diameter) or pretreatment positron emission tomography were constitute the gross tumor volume. Clinical target volume was equal to gross tumor volume in this study. The total PTV included the clinical target volume plus a total margin of at least 1.0 cm. Elective nodal irradiation was not conducted in this study. The normal anatomy to be outlined on each CT image included the lungs, heart, esophagus, and spinal cord. Field arrangements was determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The PTV was to be treated with any combination of coplanar or noncoplanar 3D conformal fields. The treatment plan used for each patient was based on an analysis of the volumetric dose, including dose-volume histogram analyses of the PTV and critical normal structures. Each field was to be treated daily. Intensity-modulated RT was not allowed in this study. Normalization of the treatment plan covered 95% of the PTV with the prescription dose. All radiation doses were calculated with inhomogeneity corrections (superposition-convolution dose calculation algorithms or an analytical anisotropic algorithm). RT started on day 1 of the first cycle of chemotherapy and was delivered once daily for 5 days per week. The total dose was 66 Gy in 33 fractions in arm 1, 70 Gy in 35 fractions in arm 2, and 74 Gy in 37 fractions in arm 3. The spinal cord dose should not exceed 48 Gy. The volume of both lungs that received ≥20 Gy (V20) should not exceed 30% of the total. Brachial plexus doses should be kept below 66 Gy. The mean dose to the esophagus was optimally kept below 34 Gy. The mean dose to the heart was optimally kept below 40 Gy. As a RT quality assurance program, individual case review was performed after obtaining treatment planning data for all cases enrolled in this study.

### *Response Evaluation and Survival*

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.0. OS was defined as the time from the date of registration to the date of death or the date of last contact. PFS was defined as the time between the date of registration to disease progression or death (whichever occurred first) or the date of last contact. Local relapse-free survival and distant metastasis–free survival were estimated by using the Kaplan-Meier product limit method.

## Results

### *Patient Characteristics*

Six, 6, and 12 patients were enrolled in arm 1 (66 Gy), arm 2 (70 Gy), and arm 3 (74 Gy), respectively. All patients were eligible for the analysis in this trial. The pretreatment characteristics of patients are shown in Table 1. The median age was 63 years (range, 44-73 years), and 58% of 24 patients were men. The median follow-up time was 27.3 months (range, 8.5-42.6 months) for all patients and was 33.9 months (range, 15.2-42.6 months) for those still alive. RT plans for 17 (71%) patients and 7 (29%) patients were per protocol and acceptable deviation, respectively. None had unacceptable deviations.

### *Dose Delivered and Toxicity*

Six patients were started in arm 1 (66 Gy). At this dose level, 2 of 6 patients developed DLTs; 1 patient developed grade 3 febrile neutropenia, grade 3 mucositis in the oral cavity, and grade 3 diarrhea, and 1 patient developed grade 3 febrile neutropenia. Next, the dose was escalated to arm 2 (70 Gy) and 6 patients were registered. No

**Table 3 Late Toxicities**

| | Grade, Arm 1, 66 Gy (N = 6) | | | | Grade, Arm 2, 70 Gy (N = 6) | | | | Grade, Arm 3, 74 Gy (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 3-4 (%) | 2 | 3 | 4 | 3-4 (%) | 2 | 3 | 4 | 3-4 (%) |
| Esophagitis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lung Toxicity | 1 | 1 | 0 | 17 | 2 | 1 | 0 | 17 | 1 | 0 | 0 | 0 |
| Cardiovascular | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 8 |

**Table 4 RT Summary Based on RT Planning Data**

| Arm | Normal Tissue Dose | | |
|---|---|---|---|
| | Lung V20 (median, range) (%) | Mean Lung Dose (median, range), Gy | Mean Esophageal Dose (median, range), Gy |
| 1 | 25 (20-27) | 18.1 (14.6-21.5) | 21.4 (11.3-28.5) |
| 2 | 23 (17-28) | 14.2 (12.9-19.2) | 19.4 (8.1-28.8) |
| 3 | 27 (18-32) | 16.5 (10.6-21.5) | 22.8 (14.6-38.6) |

Abbreviations: RT = radiotherapy; V20 = percentage of normal lung volume received ≥ 20 Gy.

**Table 5 PTV Dose**

| Arm | Median (range), Gy |
|---|---|
| 1 | 69.4 (68.2-70.1) |
| 2 | 74.6 (73.3-75.0) |
| 3 | 78.2 (76.3-79.2) |

Abbreviation: PTV = planning target volume.

DLT was observed in arm 2. Finally, the dose was escalated to arm 3 (74 Gy), and 6 patients were registered into arm 3. No DLT was observed among these patients, and 74 Gy was determined to be the RD. An additional 6 patients were added to arm 3 to check the safety at the RD level. Among these patients, 1 case of DLT (grade 3 vasospastic angina pectoris) was observed. Acute and late toxicity are summarized in Tables 2 and 3, respectively. Esophagitis was uncommon in this study. Hematologic toxicity was also mild in this regimen. Grade 4 neutropenia occurred in 2 patients and in none during concurrent chemoradiotherapy and consolidation chemotherapy, respectively. There were 3 cases of grade 3 late toxicity. One of 6 patients in arm 1 developed grade 3 pneumonitis, 1 of 6 in arm 2 developed grade 3 pneumothorax, and 1 of 12 in arm 3 developed grade 3 constrictive pericarditis. No treatment-related death was reported.

All the patients completed RT as planned. All the patients except one in arm 1 completed the concurrent chemotherapy. The dose intensity of S-1 and cisplatin was 73.6% and 83.3% in arm 1, 89.3% and 100% in arm 2, and 92.3% and 100% in arm 3, respectively. Twenty-three patients initiated consolidation chemotherapy, and 22 patients completed 4 cycles of treatment as planned.

### *Dose Volume Values*

The dose-volume RT values for all patients are shown in Tables 4 and 5. Lung (V20 and mean lung dose), esophagus (mean esophagus dose), and PTV (mean PTV dose) for plans with doses corrected for tissue heterogeneity. For the 6 patients who developed grade ≥2 pneumonitis, the mean V20 or mean lung dose values were similar to the values of patients who did not develop these toxicities.

### *Efficacy*

All 24 eligible patients were assessable for treatment response. Seventeen (71%) patients showed a partial or complete response.

### *Survival*

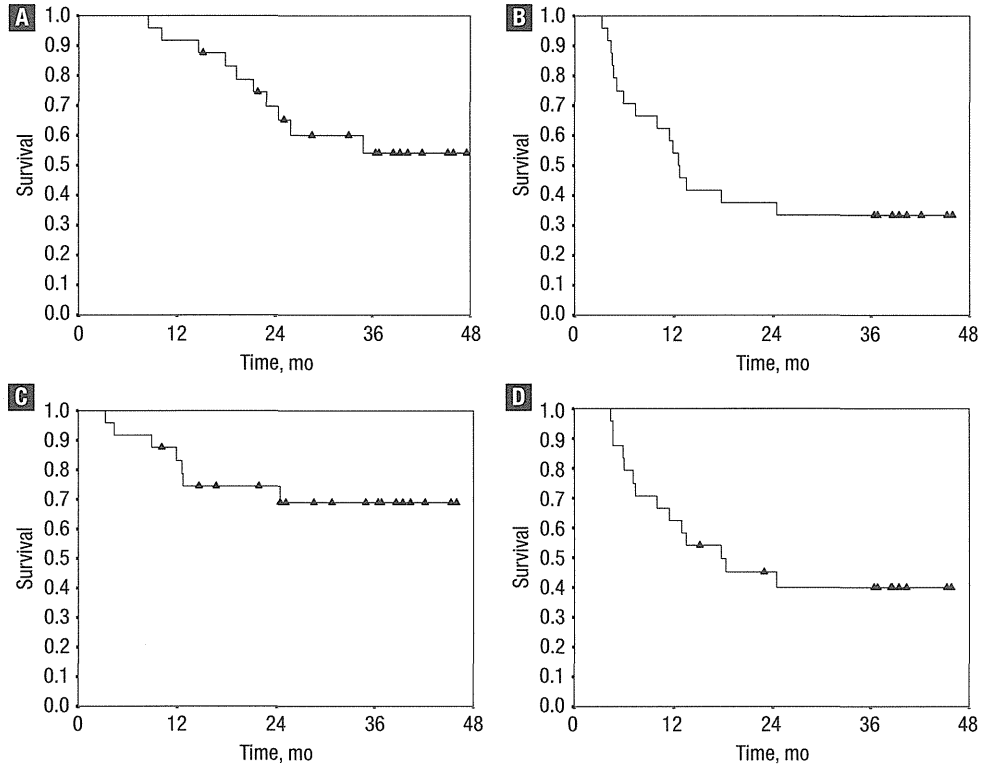
Among the 24 eligible patients, 22 survived for at least 12 months. The median OS was not reached. The survival curve by Kaplan-Meier estimation is shown in Figure 1. The survival rates at 12 and 24 months were 92% (95% CI, 81%-100%) and 65% (95% CI, 51%-89%), respectively. The PFS at 12 months was 54% (95% CI, 34%-74%), and the median PFS time was 12.6 months (95% CI, 10.2-15.0 months). Two-year local relapse-free survival and distant metastasis–free survival were 74% (95% CI, 56%-92%) and 45% (95% CI, 25%-65%), respectively.

## Discussion

The combination of high-dose thoracic RT (74 Gy) with S-1 and cisplatin has been shown to have long-term feasibility and to yield encouraging OS and PFS. We were concerned about late radiation toxicities, such as hemoptysis and lung, esophagus, and heart injury due to prescribing doses other than the conventional doses. Fortunately, both acute and late toxicity were mild with 33.9-month follow-up in surviving patients. The toxicities observed in this trial were comparable with those in our previous study. We set several dose limits, and radiation quality assurance was mandatory for all patients. We consider these to have been major reasons for the lack of severe toxicities.

Curing patients with inoperable NSCLC is not possible without local disease control. However, an isolated local failure rate in our previous study when using the same chemotherapy agents and conventional dose (60 Gy) was approximately 40%. We hypothesized that high-dose RT will kill more cancer cells, which will result in better local control and survival. The 2-year local relapse-free survival was 74% in this study. Thus, primary and metastatic lymph nodes were controlled in almost three-fourths of patients treated with high-dose thoracic RT. However, 2-year distant metastasis–free survival was 45%, and disseminative recurrence occurred in more than half of the patients. Therefore, there is room for investigating new agents to eradicate potentially disseminating cancer cells for patients with stage III NSCLC.

**Figure 1** Kaplan-Meier Estimates of Overall Survival (A), Progression Free Survival (B), Local Relapse-Free Survival (C), and Distant Metastasis-Free Survival (D)




There were several limitations in this study. First, the feasibility of high-dose RT and promising survival rates in our study must be assessed with caution because of the small number of cases; and late toxicities should be evaluated over a longer period. Second, we set several dose limits to prescribe high-dose RT and they were the same for each arm, some patients with stage III NSCLC could not be enrolled in this study with an increase in radiation dose. Therefore, the promising survival outcome in this study may have been due to patient selection bias. Third, the contribution of S-1 remains uncertain in Western patients,[20] although Japanese studies[16,21,22] have shown promising efficacy for metastatic NSCLC. There could be some pharmacogenomics difference in Asian-Japanese patients and/or the tumors within these patients.

## Conclusion

In summary, high-dose RT and concurrent S-1 and cisplatin were shown to be feasible, with encouraging survival results. Recently, preliminary findings in the Radiation Therapy Oncology Group 0617 that tested high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III NSCLC reported that a dose of 74 Gy was not associated with improved survival when compared with 60 Gy for treating inoperable stage III NSCLC with concurrent weekly paclitaxel and carboplatin with or without cetuximab. The reason why survival with 74 Gy was inferior is still unclear. If this could be explained by the toxicity, then we believe that 74 Gy with S-1 and cisplatin, as in the present study, would be sufficiently encouraging to warrant further study, because our results indicted the feasibility and encouraging survival results with this regimen. If this could be explained by distal failures, then it is necessary to further improve systemic control because this was low in this study, whereas local control was high. Moreover, if the toxicity was comparable in each arm and recurrence occurred early with 74 Gy, then we would conclude that high-dose RT will not result in better survival.

### *Clinical Practice Points*

- The standard treatment for patients with inoperable stage III NSCLC is chemotherapy given concurrently with RT.
- To enhance both local and systemic control, high-dose radiation concurrent with systemic chemotherapy is a reasonable strategy. It is fairly well established that 74 Gy plus platinum-doublets is feasible of 3D chemoradiotherapy for stage III NSCLC. However, third-generation agents cannot be combined with platinum agents and thoracic RT at the same dosing level administered in metastatic disease because of toxicities.
- This study showed that S-1 and cisplatin can be administered at a systemic full dose with 74 Gy thoracic RT. We were concerned about late radiation toxicities, but both acute and late toxicities were mild.

- Two-year OS and PFS were encouraging.
- These findings define the recommended phase II dose for further prospective trials.

## Disclosure

The authors have stated that they have no conflicts of interest.

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ORIGINAL ARTICLE

# Efficacy of bevacizumab-containing chemotherapy for non-squamous non-small cell lung cancer with bone metastases

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**Abstract**
*Purpose* Skeletal-related events (SREs) negatively affect the quality of life of patients with cancer. Vascular endothelial growth factor receptor (VEGFR)-targeted therapy is effective against bone metastasis in animal models, but the clinical efficacy of anti-VEGFR inhibitors against bone metastases remains unclear. Therefore, we aimed to investigate the efficacy of chemotherapy with bevacizumab, an anti-VEGF antibody, against bone metastases.
*Methods* We retrospectively reviewed consecutive patients with non-squamous non-small cell lung cancer who received first-line platinum-based chemotherapy with zoledronic acid at Shizuoka Cancer Center between 2007 and 2011.
*Results* Of 25 patients, 13 received bevacizumab-based chemotherapy (BEV group) and 12 received chemotherapy without bevacizumab (non-BEV group). The overall response (54 vs. 8 %, $p = 0.01$) and disease control (100 vs. 50 %, $p = 0.01$) rates were higher in the BEV group than in the non-BEV group. The bone-specific response (23 vs. 0 %, $p = 0.038$) and disease control (100 vs. 67 %, $p = 0.01$) rates were also higher in the BEV group. The median time to progression (TTP) for bone metastases was higher in the BEV group (13.7 vs. 4.3 months, $p = 0.06$), whereas that for overall disease was similar between the groups (5.7 vs. 2.6 months, $p = 0.17$). The proportions of patients with SREs were 23 and 50 % in the BEV and non-BEV groups, respectively ($p = 0.16$).
*Conclusion* Bevacizumab might potentiate the antitumor activity of chemotherapy against systemic disease and bone metastases, prolonging bone-specific TTP and reducing the incidence of SRE.

**Keywords** Bone metastases · Skeletal-related event · Bevacizumab · Chemotherapy

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## Introduction

The incidence of bone metastases in patients with lung cancer is approximately 30–40 %, and the median survival time of patients with such metastases is 7 months [1]. A more recent retrospective review of 435 patients with non-small cell lung cancer (NSCLC) indicated an incidence of 24 % for skeletal metastases. In this review, most instances of skeletal metastases (66 %) were detected at the time of initial staging [2].

Patients with metastatic bone disease frequently experience osteoclast-mediated bone destruction, resulting in clinically important complications such as a fracture, the need for bone radiation or surgical therapy, spinal cord compression, or hypercalcemia [3, 4]. These complications, collectively known as skeletal-related events (SREs) [5–7], lead to pain and decreased quality of life [8]. Thus, SREs have a negative impact on the quality of life, performance status, and functioning of patients with cancer. In a Japanese retrospective review of 259 patients with NSCLC [9], 30 % of patients were found to have skeletal metastases during their clinical course, and 50 % of these patients had SREs. Among 135 stage IV patients, 41 % had

skeletal metastases at the initial staging, and 45 % had SREs.

Zoledronic acid has been used in patients with bone metastases because the drug can reduce the incidence of SREs and delay time to the first SRE [10]. Recently, the non-inferiority of denosumab to zoledronic acid in delaying the time to the first SRE was demonstrated [11]. However, we believe that the efficacy of these drugs cannot be insufficient. The efficacy of chemotherapy against bone lesions in patients with lung cancer has not been reported previously.

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, provides a clinical benefit when combined with platinum-based chemotherapy in first-line therapy against advanced non-squamous (non-Sq) NSCLC [12–14]. In particular, the response rate and progression-free survival (PFS) compared with those of non-bevacizumab-containing chemotherapy are improved by the addition of bevacizumab. Antitumor activity may be induced by the effects of bevacizumab on tumor vasculature, interstitial pressure, and blood vessel permeability, resulting in enhanced delivery of chemotherapy agents to tumor cells [15]. Nagengast et al. [16] demonstrated that bevacizumab distribution to the bone was similar as that to other organs in an ex vivo biodistribution model. Bäuerle et al. [17] reported that bevacizumab significantly inhibited osteolysis, surrounding soft tissue tumor growth, and angiogenesis in an experimental model of breast cancer bone metastasis as visualized on volumetric computed tomography (CT) and magnetic resonance imaging (MRI). Furthermore, the blocking of VEGF–VEGF receptor (VEGFR)-2 signaling inhibited bone metastasis in animal models of lung cancer [18]. Therefore, VEGF was suggested as a therapeutic target for bone metastasis [19]. Thus, we hypothesized that bevacizumab-containing chemotherapy could have some clinical benefit in patients with non-Sq NSCLC and bone metastases. We retrospectively investigated the efficacy of bevacizumab-containing chemotherapy and compared it to that of chemotherapy without bevacizumab in this study.

## Patients and methods

### Patients

We reviewed electronic medical records of consecutive patients who visited the Shizuoka Cancer Center between January 2007 and December 2011. In addition, electronically stored images were evaluated by a diagnostic radiologist. Eligible patients were pathologically diagnosed with non-Sq NSCLC, received platinum-based first-line chemotherapy, had bone metastases at the time of receiving chemotherapy, had at least 1 evaluable bone lesion according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [20], and received zoledronic acid continuously. We permitted the inclusion of patients who received EGFR tyrosine kinase inhibitors before platinum-based chemotherapy. We selected carboplatin plus paclitaxel and carboplatin plus pemetrexed as the non-bevacizumab-containing chemotherapy regimens because we used only these regimens in combination with bevacizumab in our institution. The patients who received bevacizumab-containing chemotherapy comprised the "BEV group" and those who received chemotherapy without bevacizumab comprised the "non-BEV group".

### Evaluation

We evaluated the objective response rate, disease control rate, time to progression of overall disease (TTP), time to progression of bone metastases (B-TTP), overall survival (OS), and proportion of patients with SREs. The response to chemotherapy was accessed according to RECIST criteria (version 1.1). At the initial staging, we performed chest and abdominal CT, brain MRI, and positron emission tomography (PET)–CT/bone scintigraphy. To ascertain disease progression or the relapse of overall disease and bone metastases, patients were evaluated by physical examination, chest radiography, and CT of the chest and abdomen. If bone metastases were detected at the initial staging, the patient was regularly followed up with radiography and CT. If progression of bone metastases was suspected, we additionally performed PET–CT, MRI, or bone scintigraphy, as required. Generally, all patients were evaluated for lesions during and approximately 6–8 weeks after the treatment period.

Time to progression was measured from the start of first-line chemotherapy to the date of an event of documented disease progression/recurrence or the last follow-up visit. B-TTP was measured from the start of first-line chemotherapy to the date of an event of documented progression of bone metastases and/or SRE or the last follow-up visit. Cases of TTP or B-TTP were censored under the following conditions: no progression or recurrence of overall disease or bone metastases and death. The incidence of SREs accounted for all events that occurred from the start of platinum-based chemotherapy to the date of first progression of overall disease or the last follow-up visit. SREs included a pathologic fracture, spinal cord compression, and the need for bone radiation or surgical therapy. OS was measured from the start of first-line chemotherapy to the date of death or the last follow-up visit.

### Statistical analysis

All categorical variables, objective response rates, and incidences of SREs were analyzed and compared between the BEV and non-BEV groups using the $\chi^2$ test or Fisher's exact test, as appropriate. The distributions of TTP, B-TTP, and OS were estimated using the Kaplan–Meier method, and the BEV and non-BEV groups were compared using the log-rank test. All $p$ values were two-sided, and values less than 0.05 were considered statistically significant. All analyses were performed using JMP 9 software (SAS Institute, Cary, NC). This study was approved by the Institutional Review Board of Shizuoka Cancer Center.

## Results

A total of 25 patients, 13 patients in the BEV group and 12 patients in the non-BEV group, were eligible for this retrospective study. Patient characteristics are shown in Table 1. In the BEV and non-BEV groups, the median ages of patients were 63 and 67 years, respectively. In total, 11 of 13 (85 %) patients in the BEV group and 9 of 12 (75 %) patients in the non-BEV group were men. The BEV group included 11 (85 %) current or ever smokers, and the non-BEV group included 7 (58 %) current or ever smokers. The numbers of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 were 12 in the BEV group and 11 in the non-BEV group, and 1 patient in each group had an ECOG PS of 2. The EGFR status was not examined in 5 patients in the non-BEV group, but no statistically significant difference in EGFR status was found between the 2 groups ($p = 0.41$).

The administered chemotherapy regimens are shown in Table 1. In the BEV group, 6 patients were treated with carboplatin, paclitaxel, and bevacizumab, whereas 7 patients were treated with carboplatin, pemetrexed, and bevacizumab. In the non-BEV group, 11 patients received carboplatin plus paclitaxel, and 1 patient received carboplatin plus pemetrexed.

The response rates for overall disease were 54 % in the BEV group and 8 % in the non-BEV group ($p = 0.01$; Table 2). The disease control rates for overall disease were 100 % in the BEV group and 50 % in the non-BEV group ($p = 0.01$; Table 2). The response rates for bone metastases were 23 % in the BEV group and 0 % in the non-BEV group ($p = 0.038$; Table 3). The disease control rates for bone metastases were 100 % in the BEV group and 67 % in the non-BEV group ($p = 0.01$; Table 3).

The Kaplan–Meier curve for B-TTP is shown in Fig. 1. The median B-TTPs were 13.7 months in the BEV group and 4.3 months in the non-BEV group ($p = 0.06$). The Kaplan–Meier curve for TTP is shown in Fig. 2. The median TTPs were 5.7 months in the BEV group and 2.6 months in the non-BEV group ($p = 0.17$). Overall disease progression was observed in 12 of 13 patients in the BEV group and in all patients in the non-BEV group. The median OS was 6.6 months (range, 4.0–34.7 months) in the non-BEV group and this was not reached (range, 6.6 months-) in the BEV group ($p = 0.13$). In the present study, the median follow-up duration was 15.1 months.

Skeletal-related events occurred in 3 patients (23 %) in the BEV group and in 6 patients (50 %) in the non-BEV group (Table 4). The types of SREs were as follows: 3 instances of the need for bone radiation, 1 instance of spinal cord compression in the BEV group, and 5 instances of the need for bone radiation, 1 bone surgery, and 1 pathologic fracture in the non-BEV group.

## Discussion

To the best of our knowledge, the present study is the first report to evaluate the bone-specific efficacy of

**Table 1** Patients characteristics and chemotherapy regimens

| | | BEV | Non-BEV | *P* value |
|---|---|---|---|---|
| Number | | 13 | 12 | – |
| Age | Median (range) | 63 (35–75) | 67 (40–76) | 0.3255 |
| Sex | M/f | 11/2 | 9/3 | 0.5476 |
| Smoking | Yes/no | 11/2 | 7/5 | 0.1394 |
| PS | 0/1/2 | 3/9/1 | 0/11/1 | 0.9530 |
| EGFR | Mt/wt/unknown | 4/9/0 | 2/5/5 | 0.4054 |
| Regimen of chemotherapy | CBDCA + PTX | – | 11 | – |
| | CBDCA + PEM | – | 1 | |
| | CBDCA + PTX + BEV | 6 | – | |
| | CBDCA + PEM + BEV | 7 | – | |

*Mt* mutation, *Wt* wild type, *CBDCA* carboplatin, *PTX* paclitaxel, *PEM* pemetrexed, *BEV* bevacizumab

**Table 2** Response and control rates for overall disease

| Best response | BEV ($n = 13$) | Non-BEV ($n = 12$) | $P$ value |
|---|---|---|---|
| PR | 7 | 1 | |
| SD | 6 | 5 | |
| PD | 0 | 6 | |
| Response rate | 54 % | 8 % | 0.01 |
| Disease control rate | 100 % | 50 % | 0.01 |

*PR* partial response, *SD* stable disease, *PD* progressive disease

**Table 3** Response and control rates for bone metastases

| Best response | BEV ($n = 13$) | Non-BEV ($n = 12$) | $P$ value |
|---|---|---|---|
| PR | 3 | 0 | |
| SD | 10 | 8 | |
| PD | 0 | 4 | |
| Response rate | 23 % | 0 % | 0.04 |
| Disease control rate | 100 % | 67 % | 0.01 |

*PR* partial response, *SD* stable disease, *PD* progressive disease

chemotherapy in patients with bone metastases from NSCLC. In addition, it was important to evaluate the bevacizumab-mediated potentiation of chemotherapeutic efficacy against bone metastases. In the present study, in the BEV group, the response and disease control rates for bone metastases were 23 and 100 %, respectively, and the median B-TTP was 13.7 months.

Rosen et al. [10, 21] reported a Phase 3 trial of zoledronic acid. Among 254 patients who received zoledronic acid 4 mg, 124 patients (49 %) had NSCLC and 207 patients (82 %) received chemotherapy. The best bone response rate as per the original criteria was 8 %, and the disease control rate for bone metastases was 29 %. In this study, by using the RECIST guideline (version 1.1), the response rate for bone metastases was 0 % and the disease control rate for bone metastases was 67 % in the non-BEV group. In contrast, the response rate for bone metastases was 23 % and the disease control rate for bone metastases was 100 % in the BEV group. Although different bone lesion response criteria were used for the Phase 3 trial of zoledronic acid and this study, administration of bevacizumab-containing chemotherapy showed some potential for eliciting an effect on bone metastases. In the same Phase 3 trial, the median B-TTP of patients who received zoledronic acid 4 mg was 145 days, and the proportion of patients with at least 1 SRE over a period of 9 months was 38 %. In this study, the median B-TTPs were 130 days in the non-BEV group and 412 days in the BEV group. In terms of the proportion of patients with SREs, 50 % of patients in the non-BEV group and 23 % of patients in the BEV group had SREs until the first progression of overall disease or the last follow-up visit. These results suggest that bevacizumab-containing chemotherapy specifically controlled bone lesions as well as systemic lesions.

The antitumor activity of bevacizumab-containing chemotherapy is believed to be the result of enhanced chemotherapy delivery to tumor cells [15]. Bevacizumab distribution to bone was similar as that to other organs in ex vivo biodistribution analysis [16]. Inhibiting VEGF–VEGFR-2 signaling inhibited bone metastasis in animal models of lung cancer with bone metastasis [18]. Solares et al. [22] reported a patient with lung adenocarcinoma and bone metastases in whom a complete response was achieved with carboplatin, paclitaxel, and bevacizumab. Paule and Brion [23] reported that 2 patients with renal cell carcinoma (RCC) and bone metastases who were treated with the anti-VEGFR inhibitor sunitinib experienced long-term survival and stabilization of bone metastases. They concluded that VEGF-targeted agents such as sunitinib

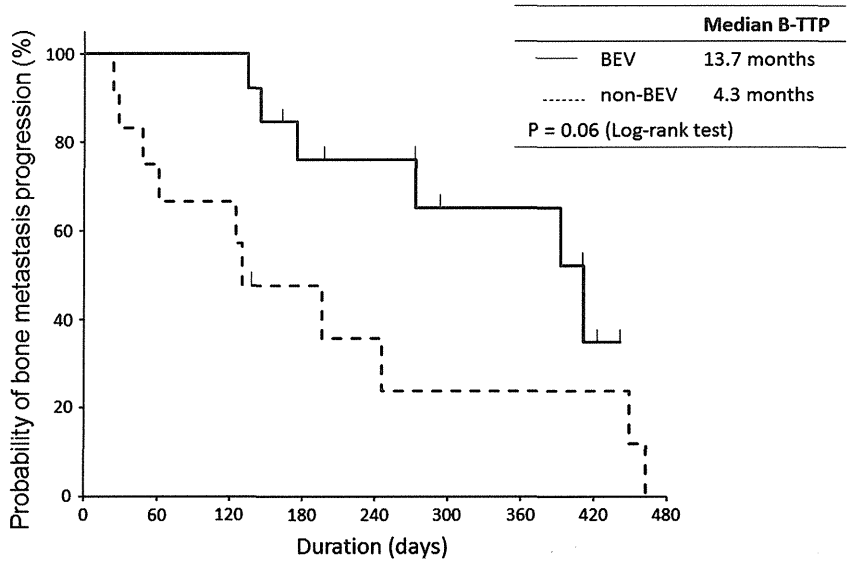


**Fig. 1** Kaplan–Meier plot of time to progression of bone metastases (B-TTP) of patients who received chemotherapy containing bevacizumab (BEV group) or lacking bevacizumab (non-BEV group). The median B-TTPs were 13.7 months in the BEV group and 4.3 months in the non-BEV group ($p = 0.06$)

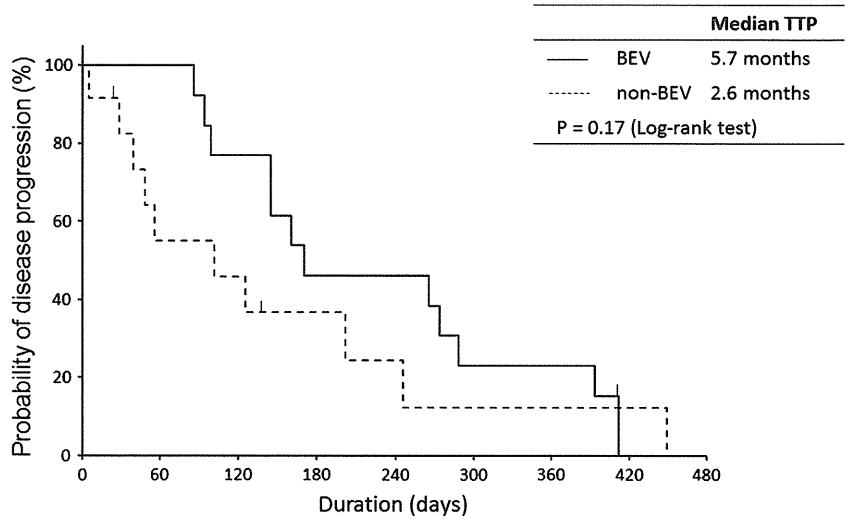


**Fig. 2** Kaplan–Meier plot of time to progression of overall disease (TTP) of patients who received chemotherapy containing bevacizumab (BEV group) or lacking bevacizumab (non-BEV group). The median TTPs were 5.7 months in the BEV group and 2.6 months in the non-BEV group ($p = 0.17$)

**Table 4** Proportion of patients with SREs until the first documented event of disease progression

| | BEV $n = 13$ | Non-BEV $n = 12$ |
|---|---|---|
| SREs* | 3 (23 %) | 6 (50 %) |
| Radiation to bone | 3 | 5 |
| Surgery to bone | 0 | 1 |
| Spinal cord compression | 1 | 0 |
| Pathologic fracture | 0 | 1 |

*SRE* skeletal-related events

* $P = 0.16$

may be effective treatments for bone metastases. Furthermore, a retrospective analysis reported that sunitinib plus bisphosphonates such as zoledronic acid and pamidronate improved the response rate, PFS, and OS in cases of RCC with bone metastases [24]. In our study, the response rates for bone metastases were 23 % in the BEV group and 0 % in the non-BEV group. These results might validate the clinical efficacy of bevacizumab-containing chemotherapy against bone metastases.

This study has several limitations. The sample size was small. This was a retrospective study with an inherent potential for bias. The collection of clinical characteristics and treatment response data was retrospective, and the follow-up interval for physical examinations was indefinite. Therefore, future studies are warranted to investigate larger sample sizes.

In conclusion, this study indicates that bevacizumab might potentiate the antitumor activity of chemotherapy against both systemic disease and bone metastases, thereby prolonging bone-specific TTP and reducing the incidence of SREs.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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# Interstitial Lung Disease Associated with Gefitinib in Japanese Patients with *EGFR*-mutated Non-small-cell Lung Cancer: Combined Analysis of Two Phase III Trials (NEJ 002 and WJTOG 3405)

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**Objective:** Interstitial lung disease associated with gefitinib is a critical adverse reaction. When geftinib was administered to *EGFR*-unknown patients, the interstitial lung disease incidence rate was approximately 3–4% in Japan, and usually occurs during the first 4 weeks of treatment. However, it has not been fully investigated in *EGFR*-mutated patients.
**Methods:** We collected clinical records of participants of two Phase III trials (WJTOG 3405 and NEJ 002), which compared gefitinib with platinum doublet chemotherapy. All patients were *EGFR* mutated, chemo-naïve and had good performance status.
**Results:** A total of 402 patients were enrolled in this study. In the gefitinib arm, 10 (5.0%) of 201 patients developed interstitial lung disease, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed interstitial lung disease (Grade 1) in the chemotherapy arm. With regard to gefitinib, smoking history was significantly associated with developing interstitial lung disease (odds ratio 0.18; 95% confidence interval: 0.05–0.74; $P = 0.01$). The cumulative incidence rate of interstitial lung disease was similar in the 0–4, 5–8 and 9–12 week time periods. However, between smokers and never-smokers, cumulative incidence rates in the first 4 weeks were significantly different (4.7% versus 0%, $P = 0.03$). Three of 10 patients developed interstitial lung disease after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively).
**Conclusions:** Among *EGFR*-mutated patients, the incidence of interstitial lung disease associated with gefitinib was not different from that in previous reports. Smoking history was associated with developing interstitial lung disease, and smokers had a higher incidence rate of interstitial lung disease in the first 4 weeks.

*Key words: epidermal growth factor receptor mutation – gefitinib – epidermal growth factor receptor-tyrosine kinase inhibitor – interstitial lung disease – Japanese*

## INTRODUCTION

The recent introduction of targeted agents has dramatically changed the treatment of non-small-cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) is a prototype of such therapy which targets NSCLC harboring the *EGFR* mutation (1,2). EGFR-TKIs have demonstrated a higher response rate and longer progression-free survival than platinum doublet chemotherapy (3–6). Common adverse events associated with EGFR-TKIs include skin rash, diarrhea and hepatotoxicity. Interstitial lung disease (ILD) is a rare but potentially fatal adverse event (7). The incidence of ILD has been reported to be higher in Japanese than in Caucasians. Two large, multi-institutional studies in Japan (8–10) reported that its incidence is 3.5–4.0%, compared with just 0.3% in the USA (11). They also suggested that male gender, history of smoking, poor performance status, pre-existing lung disorder and prior history of chemotherapy were predictive risk factors (8–10).

Today, clinical guidelines recommend that administration of EGFR-TKIs should be limited to *EGFR*-mutated patients, reflecting the high efficacy of this drug in this patient population (12). Since it is known that *EGFR* mutation is relatively rare in males or smokers, which are known risk factors of ILD, ILD incidence might be lower in patients with *EGFR* mutation. However, a detailed investigation of ILD associated with EGFR-TKIs among *EGFR*-mutated patients has not been done. Therefore, we conducted a combined analysis of two Phase III trials that compared gefitinib with platinum doublet chemotherapy in Japanese NSCLC patients with *EGFR* mutation.

## PATIENTS AND METHODS

### Patient Selection and Treatment Methods

We collected the clinical records of participants of two Phase III trials (WJTOG 3405 (3) and NEJ 002 (4)). These trials compared gefitinib with platinum doublet chemotherapy in Japanese NSCLC patients with *EGFR* mutation. *EGFR* mutation was screened by PCR-based methods as previously described (13,14). All of the participants were required to be chemo-naïve, with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 and aged between 20 and 75 years, with adequate organ function. Patients with active infectious disease or severe heart disease were excluded. All patients were confirmed not to have pulmonary fibrosis by chest computed tomography (CT) within 1 month prior to registration. Both studies were approved by the institutional review board at each participating site.

Eligible patients were randomly assigned to receive either gefitinib (250 mg daily) or standard chemotherapy. The latter consisted of paclitaxel 200 mg/m$^2$ plus carboplatin (area under the curve of six) in NEJ 002 or docetaxel 60 mg/m$^2$ plus cisplatin 80 mg/m$^2$ in WJOG 3405, every 3 weeks. All participants who had received at least one dose of a study drug were included in the safety analysis.

Baseline data were collected for each patient, including information on sex, age, history of smoking, ECOG PS, tumor histology, clinical stage and type of *EGFR* mutation.

### Evaluation of ILD and Statistical Analysis

All patients were assessed by chest CT for their response to treatment every 2 months. The diagnosis of ILD was based on clinical manifestations (worsening dry cough or dyspnea within days to weeks), accompanied by interstitial pulmonary infiltrates on a chest X-ray and a chest CT (15). Close investigation, such as blood and bacterial examination, was required in the protocols to exclude other ILDs. Bronchoalveolar lavage was also recommended, if possible. ILD was assessed according to the National Cancer Institute

**Table 1.** Baseline characteristics of the patients in the gefitinib arm

| | Total ($n = 201$) | Non-ILD ($n = 191$) | ILD ($n = 10$) | $P$ value |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean | 64 | 64 | 63 | 0.67 |
| Range | 34–75 | 34–75 | 56–75 | |
| Sex (no.) | | | | |
| Male | 71 | 65 | 6 | 0.17 |
| Female | 130 | 126 | 4 | |
| Smoking status (no.) | | | | |
| Never | 137 | 134 | 3 | 0.01 |
| Previous/current | 64 | 57 | 7 | |
| ECOG performance status (no.) | | | | 0.35 |
| 0 | 111 | 107 | 4 | (PS 0 versus 1) |
| 1 | 89 | 83 | 6 | |
| 2 | 1 | 1 | 0 | |
| Histology (no.) | | | | |
| Ad | 187 | 180 | 7 | 1.0 |
| Other | 14 | 14 | 0 | |
| Clinical stage (no.) | | | | |
| IIIB | 25 | 25 | 0 | 0.52 |
| IV | 129 | 122 | 7 | |
| Post-operative relapse | 47 | 44 | 3 | |
| Type of *EGFR* mutation | | | | |
| Exon 19 del | 108 | 104 | 4 | 0.42 |
| L858R | 85 | 80 | 5 | |
| Other | 8 | 7 | 1 | |

ILD, interstitial lung disease; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.

Common Terminology Criteria (NCI-CTC, version 3.0). All events were assessed by investigators at first; then severe cases were confirmed by independent committees based on medical, pathological and radiological findings.

Differences between covariates in patients with or without ILD were analyzed using Fisher's exact tests or Pearson's tests. The Kaplan–Meier method was used to estimate the cumulative incidence rate of ILD, and differences according to the smoking status were analyzed by the log-rank test. All the analyses were performed using JMP version 7 (SAS Institute Inc., USA).

## RESULTS

In WJOG 3405, 177 patients were randomized and 175 were included in the safety analysis. In NEJ 002, 230 patients were randomized and 227 were included in the safety analysis. In our study a total of 402 patients were enrolled, half of them in the gefitinib arm.

Baseline characteristics of the patients were well balanced between the treatment groups. As previously reported (3,4), about two-thirds of patients were female, the median age was 64 years, 65% were never-smokers, 55% had an ECOG PS of 0 and 95% had adenocarcinoma.

At the time of data cut-off, the median duration of gefitinib treatment was 165 days (WJTOG 3405) and 308 days (NEJ 002); the median number of chemotherapy cycles was four. In the gefitinib arm, 10 (5.0%) of 201 patients developed ILD, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed ILD (Grade 1) in the chemotherapy arm.

The background and clinical course of the patients in the gefitinib arm are summarized in Tables 1 and 2. The clinical background of patients who developed ILD and those who did not showed no difference other than smoking status. Univariate analysis showed that smoking history was significantly associated with developing ILD (odds ratio 0.18; 95% confidence interval (CI): 0.05–0.74; $P = 0.01$). This accounted for 10.9% (95% CI: 5.4–20.9%) of the incidence rate of ILD among smokers, versus 2.2% (95% CI: 0.8–6.3%) among never-smokers.

Figure 1 shows a Kaplan–Meier curve of the cumulative incidence rate of ILD. Among the overall population, the cumulative incidence rate in the first 4 weeks, 5th–8th weeks and 9th–12th weeks was 1.5% (95% CI: 0.5–4.3%), 1.5% (95% CI: 0.5–4.4%) and 0.5% (95% CI: 0.1–2.9%), respectively. Smoking status was associated with the timing of the onset of ILD . Between smokers and never-smokers, the cumulative incidence rate of ILD in the first 4 weeks was significantly different (4.7 versus 0%, $P = 0.03$), whereas that in the other periods (5th–8th weeks and 9th–12th weeks) was similar (Fig. 1). Three of 10 patients developed ILD after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively).

Most of the patients who developed severe ILD (Gr $\geq$ 3) were given steroid therapy. One patient was treated with an immunosuppressive agent (cyclosporine). Non-invasive positive pressure ventilation was used in one patient (No. 10) but unfortunately this patient died.

## DISCUSSION

Three large studies of ILD associated with EGFR-TKI have been conducted in Japan (Table 3). Ando et al. (8) performed a retrospective study including 1976 NSCLC patients treated with gefitinib and found an incidence rate of 3.5% and mortality rate of 1.6%. In a prospective cohort and nested-case control study by Kudoh et al. (9), cumulative incidence rates during 12 weeks of treatment were 4.0%. They also mentioned that the risk of developing ILD was higher

**Table 2.** Clinical characteristics of 10 patients who developed ILD in the gefitinib arm

| No. | Age | Sex | Smoking index (BI) | PS | Stage | Site of *EGFR* mutation | Onset day from EGFR-TKI | ILD (CTCAE grade) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 69 | M | 800 | 0 | r | Exon 19 | 48 | 1 | Improved |
| 2 | 57 | F | 0 | 1 | 4 | Exon 19 | 70 | 1 | Improved |
| 3 | 60 | M | 860 | 1 | 4 | Exon 21 | 15 | 1 | Improved |
| 4 | 56 | F | 370 | 1 | 4 | Exon 19 | 14 | 1 | Improved |
| 5 | 71 | F | 0 | 1 | 4 | Exon 21 | 171 | 2 | Improved |
| 6 | 57 | M | 740 | 0 | r | Exon 19 | 25 | 3 | Improved |
| 7 | 68 | M | 1075 | 0 | 4 | Exon 21 | 190 | 3 | Improved |
| 8 | 75 | M | 525 | 1 | 4 | Exon 21 | 53 | 3 | Improved |
| 9 | 65 | M | 1320 | 0 | r | Exon 19 | 135 | 5 | Died |
| 10 | 60 | F | 0 | 1 | 4 | Exon 21 | 32 | 5 | Died |

BI, Brinkman Index; PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, EGFR-tyrosine kinase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; M, male; F, female.

with gefitinib than with chemotherapy (the odds ratio was 3.2). With regard to erlotinib, Nakagawa et al. (10) conducted a post-marketing survey in Japan and reported that 158 of 3488 patients were confirmed to have ILD (any grade, 4.5%), with a mortality rate of 1.6%. These studies suggested that male gender, smoking history, poor PS, pre-existing lung disorder and prior history of chemotherapy were risk factors of ILD. However, none of the three studies mentioned *EGFR* mutation status.

To our knowledge, ours is the first study to describe the clinical characteristics of ILD associated with gefitinib limited to *EGFR*-mutated patients. Similar to Kudoh's report, ILD was relatively more common in the gefitinib arm than in the chemotherapy arm. The incidence rate of ILD associated with gefitinib was as high as 5% with a mortality rate of 2.5%, even though our analysis contained a high proportion of patients from low-risk groups (female, non-smokers with good PS).

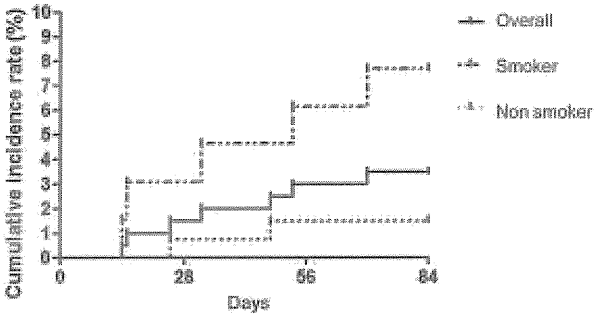


**Figure 1.** Cumulative incidence rate of interstitial lung disease associated with gefitinib. Kaplan–Meier-estimated cumulative incidence rate of interstitial lung disease in patients who were allocated to the gefitinib arm in WJTOG 3405 and NEJ 002 trial (overall population ($n = 201$), bold line; smoker ($n = 64$), dashed line; non-smoker ($n = 137$), dotted line).

Similarly to the previous studies, our analysis showed that smoking history was highly associated with developing ILD associated with gefitinib (odds ratio 0.18). Smoking induces airway epithelial damage, and lung injury could be prolonged and worsened by gefitinib in a preclinical model (16). Most of the other risk factors were excluded at the time of registration, because enrolled patients were required to be chemo-naïve, with a PS of 0–1, and confirmed not to have pulmonary fibrosis. Therefore, we should pay more attention to smoking status even if the patient has *EGFR* mutation. In terms of the timing of the onset of ILD, smoking history seemed to be an important factor. Between smokers and never-smokers, the cumulative incidence rate of ILD in the first 4 weeks was significantly different (4.7 versus 0%, $P = 0.03$). Previous studies stated that ILD occurred most commonly in the first 4 weeks (median: 23–31 days) and 60% of participants were smokers. So, despite the small subset analysis in the present study, the higher incidence rate observed in the first 4 weeks among smokers is noteworthy.

Another point is that three of 10 patients developed ILD after several months of gefitinib treatment. With erlotinib, it was reported that ILD occurred at the rate of 0.11 per 100 patient-weeks after 8 weeks of treatment. It is not clear whether the mechanism of ILD varies over time from its onset; further investigation on late-onset ILD is needed.

Our analysis has several limitations. First, this was an investigator-dependent analysis. Most of the ILD cases were diagnosed by clinical manifestations and a chest CT. Bronchoalveolar lavage was recommended in the protocols, but actually done in only one case. As acute exacerbation of ILD after bronchoscopy has been reported (15), this may be acceptable. In our analysis, all patients were assessed by chest CT every 2 months, and severe cases were confirmed by independent, multidisciplinary committees. Secondly, this analysis was done with a small sample size due to the population and rarity of incidence.

**Table 3.** ILD associated with EGFR-TKI in Japanese patients: pivotal studies and ours

| | Ando et al. (8) | Kudoh et al. (9) | Nakagawa et al. (10) | Present data |
|---|---|---|---|---|
| Study design | Retrospective | Prospective | Retrospective | Retrospective |
| No. of patients | 1976 | 1482 | 3488 | 201 |
| Type of EGFR-TKI | Gefitinib | Gefitinib | Erlotinib | Gefitinib |
| Patient selection by *EGFR* mutation status | No | No | No | Yes |
| ILD (any Grade; %) | 70 (3.5) | 59 (4.0) | 158 (4.5) | 10 (5.0) |
| ILD (Grade 5; %) | 31 (1.6) | 25 (1.7) | 55 (1.6) | 2 (1.0) |
| Risk factors of ILD | Smoking<br>Pre-existing lung disorder<br>Male | Smoking<br>Pre-existing lung disorder<br>Poor PS<br>Elderly<br>Cardiac disease | Smoking<br>Pre-existing lung disorder<br>Poor PS<br>Lung infection | Smoking |

In conclusion, the incidence of ILD associated with gefitinib among *EGFR*-mutated patients was not different from that in previous reports. Smoking history was highly associated with developing ILD. In addition, a substantial number of patients developed ILD after several months of gefitinib treatment.

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## Conflict of interest statement

A.I., K.N. and N.Y. have received honoraria from Astra Zeneca. T.M. has received honoraria from Astra Zeneca and Chugai. T.N. has received honoraria from Chugai. Y.N. has received honoraria and research grants from Chugai. All other authors declare no conflicts of interest.

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# Comparison of the Time-to-response Between Radiotherapy and Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitors for Advanced Non-small Cell Lung Cancer with *EGFR* Mutation

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**Abstract.** *Background: Patients harboring sensitive epidermal growth factor receptor (EGFR) mutations show a dramatic response to treatment with EGFR tyrosine kinase inhibitors (TKIs). However, there have been no clinical reports in lung cancer patients that compare the time-to-response between radiotherapy and EGFR-TKIs. Patients and Methods: We reviewed 17 and 32 consecutive patients with inoperable stage III/IV NSCLC who harbored sensitive EGFR mutations and who were treated with thoracic radiotherapy with or without chemotherapy and EGFR-TKIs, respectively. Results: There were statistically significant differences in time-to-partial response (PR) with regard to the treatment modalities (radiotherapy vs. EGFR-TKIs, median 57 days vs. 22 days, log-rank test, p=0.008). Conclusion: EGFR-TKIs elicit tumor shrinkage earlier than does radiotherapy in patients with a sensitive EGFR mutation, suggesting that EGFR-TKIs may be useful for early symptom improvement in these patients.*

Lung cancer is the most common cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers (1). In patients with advanced lung cancer, improvements in the quality of life and disease-related symptoms are key treatment goals. Oncological emergencies arise most commonly in patients who have advanced or metastatic disease. Many of these patients develop symptoms associated with their intrathoracic disease that are directly life threatening or can affect their quality of life.

As for the patients with advanced lung cancer, various painful symptoms often develop. These painful symptoms are often due to various causes such as superior vena cava syndrome (SVCs), venous obstruction and airway obstruction and can be relieved by reducing the size of their tumor. Prompt effects of tumor reduction often lead to palliation. Radiotherapy and chemoradiotherapy have been empirically used for reducing the size of tumor. If such treatment is ineffective, therapy directed at the underlying cause should be considered. Symptoms do not usually show rapid improvement if the tumor is unresponsive. Under these circumstances, symptom relief correlates with the magnitude of tumor response (2, 3).

Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), is an one of the options for first-line treatment for patients with NSCLC who harbor sensitive *EGFR* mutations based on the findings of previous clinical trials (4-6). Patients with sensitive *EGFR* mutations responded dramatically to gefitinib (as shown in Figure 1), demonstrating symptom improvement that correlated with radiographic tumor shrinkage in most cases. Although prompt response is important for patients with oncological emergencies, such as SVC or airway obstruction, the best treatment modality for clinical practice has not yet been established.



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*Key Words:* Epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, erlotinib, non-small cell lung cancer; radiotherapy.

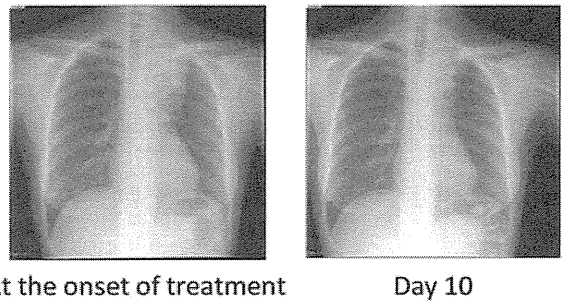


Figure 1. *Case of response to Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitor (gefitinib). A 57-year-old woman with an exon 19 deletion. Time-to-partial response, 10 days.*

Despite the correlation of symptom improvement with tumor response in patients with NSCLC receiving gefitinib (2), there have been no clinical reports comparing the time-to-response between radiotherapy and EGFR-TKIs. Therefore, this retrospective study was conducted to compare and clarify the efficacy of radiotherapy compaired to EGFR-TKIs for patients with advanced NSCLC harboring sensitive *EGFR* mutations.

## Materials and Methods

*Patients.* The eligibility criteria in this study were as follows: histologically or cytologically proven NSCLC; unresectable stage III/IV disease or recurrent disease after surgery; a tumor that harbors an *EGFR* mutation known to be associated with drug sensitivity (exon 18 G719X, exon 19 deletion, and exon 21 L858R); continuous treatment with an EGFR-TKI or radiotherapy (with or without chemotherapy); age ≥20 years; and measurable disease by chest radiography according to the response evaluation criteria in solid tumors (RECIST) ver 1.1 (7). For patients who were treated with radiotherapy and EGFR-TKIs, the first treatment employed was applicable to evaluation. Initial EGFR-TKI therapy was limited to those patients who were receiving first- or second-line chemotherapy. Based on these criteria, we reviewed 17 and 32 consecutive patients with inoperable stage III/IV NSCLC who were treated with thoracic radiotherapy, with or without chemotherapy, and who were treated with EGFR-TKIs (gefitinib or erlotinib), respectively, at Shizuoka Cancer Center between September 2002 and June 2011. The study protocol was approved by the Institutional Review Board of Shizuoka Cancer Center (#.24-J46-24-1-3).

Genomic DNA was extracted from tumor samples, and *EGFR* mutations in exons 18-21 were analyzed as described previously (8, 9).

Medical records and films were cross-reviewed by two principal investigators. To test interobserver variability, each finding was reassessed by the same investigators after completion of the first assessment. The time interval between the first and second assessments was at least four weeks. Intraobserver variability was also determined by comparing the values of the first measurements of each of the two investigators.

*Treatment methods. Radiotherapy:* Patients had disease at clinical stage III/IV and received definitive thoracic radiotherapy with or without chemotherapy. Six patients were also treated with combination chemotherapy of cisplatin plus vinorelbine, five patients with cisplatin plus S-1, two patients with carboplatin alone, and two patients with other regimens. Two patients received radiotherapy alone. The prescribed dose was over 60 Gy in 30 fractions. It was ensured that the normal lung volume receiving more than 20 Gy (V20) was equal to or less than 35% of the total lung volume. The maximal dose to the spinal cord did not exceed 45 Gy at any level. All patients were required to undergo chest computed tomography (CT) to facilitate treatment planning.

*EGFR-TKIs:* Patients received gefitinib (250 mg, orally, once daily) or erlotinib (150 mg, orally, once daily). EGFR-TKIs were continued until disease progression, the appearance of intolerable toxicity, or withdrawal of consent. All patients were EGFR-TKI-naive.

*Response evaluation:* Patients were evaluated to determine the disease stage before the start of the treatment and at the time of disease progression or relapse. Disease stage was determined according to complete medical history and a physical examination, including chest radiography, CT of the chest and abdomen, magnetic resonance imaging (MRI) of the head, and additional staging procedures such as bone scintigraphy and positron-emission tomography (PET). Radiographic tumor response was evaluated according to RECIST ver. 1.1 (7), and assessments were performed almost weekly using chest radiography from treatment initiation to the end of the first month. In the second month, chest radiography was performed almost fortnightly. After the third month, chest radiography was performed on the basis of the judgment of the physician. Tumor lesions were accurately measured in at least one dimension (longest diameter) and considered positive for a minimum size of 20 mm by chest radiography. The tumor response was evaluated and classified as follows: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of diameters of target lesions, with the baseline sum diameters as reference; progressive disease (PD), at least a 20% increase in the sum of diameters of target lesions, with the smallest sum during the study as reference (this included the baseline sum if that was the smallest during the study); and stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest sum of diameters during the study as reference. The time to PR was calculated from the date of starting radiotherapy or administration of the first dose of EGFR-TKI to the date of the occurrence of a PR as confirmed using chest radiography. Progression-free survival (PFS) was calculated from the starting date of treatment to the date of PD or the date of occurrence of death from any cause.

*Statistical analyses.* To evaluate the differences in the treatment response, the Fisher's exact test was used. A Mann-Whitney *U*-test was used to compare the mean values of the variables of the groups studied. Survival curves were plotted using the Kaplan Meier technique and a log-rank test comparison was performed. In the case of SD or PD, cases were censored at the time of confirmation using chest radiography. PFS was censored at the date of the last visit for those patients who were alive without documented PD. PFS was compared using the log-rank test according to the treatment modality (radiotherapy *vs.* EGFR-TKI). A *p*-value of 0.05 or less was considered significant for all tests. Statistical analyses were performed using the GraphPad Prism version 5.0 software program for Windows (GraphPad Software, San Diego, CA, USA).