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What phase III trials are needed to improve the treatment of advanced non-small-cell lung cancer?

Nagahiro Saijo

Platinum-based doublets are standard treatments for stage IV non-small-cell lung cancer (NSCLC). Several doublets that include new drugs improve survival, but no one regimen is clearly superior to the others, as previously discussed by Scagliotti¹ and Govindan² in *Nature Clinical Practice Oncology*.

Numerous molecular-target-based drugs have been introduced for the treatment of NSCLC, but can they replace or be used as an adjuvant to current therapy, and can they be combined with other chemotherapeutic agents, radiotherapy and/or surgery? We hypothesize that incorporation of novel molecular-target-based therapies into current treatment paradigms will improve outcomes. However, carefully designed clinical trials and translational science will be required to identify the subsets of patients likely to benefit. If these treatment strategies are to be used, we must first answer the following critical questions. First, will patients lacking the target still respond? It is still unclear why responses occur in those lacking the correct molecular target. Second, what expression levels of the target are sufficient for a response, and can we measure the target in a biologically relevant and/or technologically valid way? Third, does the agent inhibit the proposed target at the dose and schedule utilized? Fourth, is the target a critical driving force for cell growth in the tumor type in question?

Various molecular-target-based drugs for advanced NSCLC have been evaluated in randomized controlled trials, but the majority, including a matrix metalloproteinase inhibitor, a protein kinase C inhibitor, and trastuzumab, have yielded negative results.^{3,4} Gefitinib (Iressa[®]) and erlotinib (Tarceva[™]) are orally available selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) that exhibit antitumor activity in patients with previously treated advanced NSCLC. However, both drugs failed to show additive or synergistic effects when combined with platinum-based chemotherapy as a first-line treatment for NSCLC. On 17 December 2004,

Numerous molecular-target-based drugs have been introduced for the treatment of NSCLC, but what is their place in current therapy?

AstraZeneca announced the preliminary results of their ISEL (Iressa[®] Survival Evaluation in Lung Cancer) study of 1,692 patients with advanced recurrent or refractory NSCLC. Unfortunately, gefitinib failed to prolong survival significantly compared with placebo (hazard ratio 0.89, $P=0.11$) in the overall patient population or among patients with adenocarcinoma (hazard ratio 0.83, $P=0.07$). A retrospective analysis of patients treated with gefitinib showed that tumor response was associated with distinct subgroups: women, patients with no history of smoking, patients with adenocarcinoma, and Japanese patients. Survival in the gefitinib group in the ISEL study was significantly higher for non-smokers ($P<0.01$) and Asians ($P<0.01$) than in the placebo group. The survival curves of the two treatment groups were the same for non-Asians. The results of similar randomized trials of erlotinib (the BR21 study) were presented at the American Society of Clinical Oncology meeting in 2004. Erlotinib significantly prolonged survival in patients with advanced, previously treated, refractory or recurrent NSCLC. The survival of non-smokers in the erlotinib group in the BR21 study was extremely good and contributed to the improvement in overall survival. The presence of an *EGFR* mutation has been demonstrated to be a strong predictor of a favorable response to EGFR-TKI. Mutations have recently been reported to be significantly more frequent in women, in patients with adenocarcinoma, and in those who had never smoked, and these findings are consistent with the clinical predictors of tumor response in patients treated with EGFR-TKI. Mitsudomi *et al.* reported that patients with *EGFR* mutations survived longer after the initiation of gefitinib treatment than those without mutations.⁵ It can be concluded that translational studies are extremely important for the development of molecular-target-based drugs.

N Saijo is an Advisory Board member of Nature Clinical Practice Oncology.

Competing interests

The author declared he has no competing interests.

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Supplementary information, in the form of a reference list, is available on the *Nature Clinical Practice Oncology* website.

Is radiotherapy optimally combined with chemotherapy in elderly patients with limited-stage small-cell lung cancer?

GLOSSARY

ECOG PERFORMANCE STATUS (ECOG PS)

A scoring system to assess the wellbeing of cancer patients and their ability to perform ordinary tasks (0 = fully active to 5 = dead)

Original article Schild SE *et al.* (2005) Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer* 103: 2349–2354

SYNOPSIS

KEYWORDS cisplatin, combined-modality therapy, etoposide, radiotherapy, small-cell lung cancer

BACKGROUND

It is important to understand the effects of modern combined-modality therapy in elderly patients with lung carcinoma. Half of the patients who are diagnosed with lung carcinoma are ≥ 70 years of age.

OBJECTIVES

To determine the relationship between age and outcome in patients with limited-stage small-cell lung cancer (SCLC) treated with etoposide and cisplatin in addition to once-daily or twice-daily radiotherapy (QDRT or BIDRT respectively).

DESIGN AND INTERVENTION

From September 1990 to November 1996, this North Central Cancer Treatment Group phase III trial enrolled patients with limited-stage disease confirmed by pathology as SCLC, with ECOG PERFORMANCE STATUS (ECOG PS) ≤ 2 and sufficient organ function. Six 3-day cycles of etoposide and cisplatin were given, with a 28-day interval between cycles. Cisplatin (30 mg/m² given intravenously over 30–60 minutes), and etoposide (130 mg/m² given intravenously over 45 minutes) were administered on each chemotherapy day. After the first three cycles, the dose of etoposide was reduced to 100 mg/m² per cycle. Patients were randomized to receive thoracic radiotherapy (in parallel to chemotherapy cycles 4–5), either QDRT (50.4 Gy in 28 fractions) or BIDRT (48 Gy in 32 fractions).

OUTCOME MEASURES

Toxicity, disease control and survival.

RESULTS

Of 263 evaluable patients (median age 63 years, range 37–81 years), followed for a median of 8.1 years (range 4.6–11.9 years), 209 were younger than 70 years old and 54 were 70 years old or older. Baseline ECOG PS and weight loss were worse in the older group. Tumor progression rates, survival, local control, and overall, hematologic and nonhematologic toxicities did not differ according to patient age. The 2-year and 5-year survival rates were 48% and 22% respectively, in patients aged < 70 years, versus 33% and 17% in older patients ($P = 0.14$). Hematologic toxicities \geq grade 3 or \geq grade 4 did not occur more frequently in elderly patients. Grade 3 toxicity or worse occurred in 91% of patients aged < 70 years compared with 94% of elderly patients ($P = 0.58$). Toxicities of grade 4 or more occurred in 46% of patients aged < 70 years compared with 50% of older patients ($P = 0.65$). Grade ≥ 3 nonhematologic toxicity occurred in 46% of those aged < 70 years compared with 52% of older patients ($P = 0.45$). Grade ≥ 4 nonhematologic toxicity occurred in 12% of patients aged < 70 years compared with 11% of elderly patients ($P = 1.0$). Of the nonhematologic toxicities, only grade ≥ 4 pneumonitis occurred more frequently in elderly patients. Grade ≥ 3 esophagitis occurred in similar numbers of patients in the two age groups. Treatment-related toxicity caused death in 4 of 263 patients (2%)—3 in the elderly group (pneumonitis) and 1 in the younger group (infection).

CONCLUSION

Elderly patients should be encouraged to receive combined-modality therapy, especially within clinical trials.

COMMENTARY

Nagahiro Saijo

Cisplatin plus etoposide with concurrent thoracic radiotherapy is the standard treatment for limited-disease small-cell lung carcinoma (LD-SCLC) in the elderly.^{1,2} In Intergroup study 0096, Turrisi *et al.* found that, when combined with etoposide plus cisplatin chemotherapy, a total radiation dose of 45 Gy administered as a twice-daily therapy (1.5 Gy twice daily) produced superior survival to the same total dose administered as a once-daily therapy (1.8 Gy once daily).¹ The Japan Clinical Oncology Group also obtained excellent survival data (median survival time 27 months) using concurrent chemotherapy and twice-daily irradiation (Japan Clinical Oncology Group 9104).² In 2004, Schild *et al.* reported that equivalent survival benefit was achieved with twice-daily and once-daily irradiation with etoposide plus cisplatin chemotherapy.³ Once-daily radiotherapy was administered continuously, and twice-daily radiotherapy was administered with a 2.5-week intermission after 24 Gy. The treatment schedule of the Intergroup study differed from that of the present study in that concurrent radiotherapy was given from the start of chemotherapy, and radiotherapy was given without a break. The dose intensity of the combination of chemotherapy and radiotherapy in the Intergroup study was higher in the twice-daily group. Efficacy improved with increased intensity of combined-modality therapy, as did adverse events. Elderly patients usually experience more toxicity than younger patients, and cannot tolerate intensive treatment. Few studies have specifically targeted elderly populations.

The elderly patients in the present analysis (aged ≥ 70 years) experienced significantly greater weight loss and poorer performance status than the younger patients (aged < 70 years). The 2-year and 5-year survival rates were 48% and 22% for younger patients, compared with 33% and 17% for elderly patients. The incidence of grade 4 pneumonitis was higher in the elderly patients. Grade 5 toxicity occurred in 1 of 209 younger patients versus 3 of 54 older patients. Schild *et al.* concluded that LD-SCLC patients over 70 years of age are candidates for clinical

trials of aggressive treatment if they do not have severe comorbidity. Yuen *et al.* reviewed the elderly subset results from the Intergroup 0096 study.⁴ Quon *et al.* also studied the influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined-modality treatment of limited stage small-cell lung cancer.⁵ In both analyses it was suggested that an elderly subset seems to be at risk of toxicity, but that those patients completing therapy do as well as their younger counterparts. It is extremely difficult, however, to distinguish those patients who are at risk of toxicity before toxicity occurs.

LD-SCLC is curable by chemotherapy and radiotherapy without surgery. Since the average age of LD-SCLC patients will increase year by year, fit elderly patients with LD-SCLC should be encouraged to undergo combined-modality therapy. An initial cycle of chemotherapy before concurrent treatment might unveil the vulnerable subset. The role of sequential chemotherapy should be evaluated in elderly patients considered marginal, to help us to distinguish those patients that are able to tolerate aggressive therapy from those that are too easily tipped over into a less-fit category. In conclusion, it is extremely important to establish a safe and effective standard treatment for the elderly patient population.

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PRACTICE POINT

Further study of combined-modality therapy within clinical trials is needed to establish a safe and effective standard treatment for elderly patients with lung carcinoma

CLINICAL INVESTIGATION

Lung

A PHASE II STUDY OF HYPERFRACTIONATED ACCELERATED
RADIOTHERAPY (HART) AFTER INDUCTION CISPLATIN (CDDP) AND
VINORELBINE (VNR) FOR STAGE III NON-SMALL-CELL LUNG CANCER
(NSCLC)

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Purpose: The purpose was to assess the feasibility and efficacy of hyperfractionated accelerated radiotherapy (HART) after induction chemotherapy for Stage III non-small-cell lung cancer.

Methods and Materials: Treatment consisted of 2 cycles of cisplatin 80 mg/m² on Day 1 and vinorelbine 25 mg/m² on Days 1 and 8 every 3 weeks followed by HART, 3 times a day (1.5, 1.8, 1.5 Gy, 4-h interval) for a total dose of 57.6 Gy.

Results: Thirty patients were eligible. Their median age was 64 years (range, 46–73 years), 24 were male, 6 were female, 8 had performance status (PS) 0, 22 had PS 1, 9 had Stage IIIA, and 21 had Stage IIIB. All but 1 patient completed the treatment. Common grade ≥ 3 toxicities during the treatment included neutropenia, 25; infection, 5; esophagitis, 5; and radiation pneumonitis, 3. The overall response rate was 83%. The median survival was 24 months (95% confidence interval [CI], 13–34 months), and the 2-year overall survival was 50% (95% CI, 32–68%). The median progression-free survival was 10 months (95% CI, 8–20 months).

Conclusion: Hyperfractionated accelerated radiotherapy after induction of cisplatin and vinorelbine was feasible and promising. Future investigation employing dose-intensified radiotherapy in combination with chemotherapy is needed. © 2005 Elsevier Inc.

Non-small-cell lung cancer, Hyperfractionated accelerated radiation therapy, Chemoradiotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death for men and the second for women in Japan. During 2001, approximately 55,000 patients died of lung and bronchus cancer (1). Surgery is the standard of care for patients with Stage I–II non-small-cell lung cancer (NSCLC), but a combination of chemotherapy and thoracic radiotherapy with or without surgery is indicated for the majority of patients with Stage III disease. Cisplatin (CDDP) based chemotherapy with conventional radiotherapy improved survival compared to conventional radiotherapy alone (2–6) and was the standard of care in the 1990s. Recently, concurrent chemoradiotherapy has been revealed to be superior to sequential chemoradiotherapy (7, 8), but it is difficult to give full-dose chemotherapy using newer cytotoxic agents concurrently with radiotherapy, and the optimal combination has not yet been clarified. In the meantime, continuous hyperfractionated accelerated radiotherapy (CHART) with 3 daily fractions to intensify the local effect of

radiotherapy has been found to be superior to conventional radiotherapy (9). The survival benefit of CHART was encouraging, but the protocol including treatments on weekends and 6-h intervals between fractions had some difficulties in practicality. Mehta *et al.* introduced hyperfractionated accelerated radiotherapy (HART) (modified CHART) with 3 daily fractions and 4-h interfraction intervals with weekend breaks and also showed promising results similar to those using sequential chemoradiotherapy (10). After these results, we started a Phase II trial to evaluate the feasibility and efficacy of induction chemotherapy with HART for patients with Stage III NSCLC.

METHODS AND MATERIALS

Eligibility criteria

Eligibility criteria included previously untreated patients with pathologically proven NSCLC with clinical tumor-node-metastasis system Stage III, and pathologic N2 was also required for Stage

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IIIA; age, 20 to 74 years; performance status (PS) (based on Eastern Cooperative Oncology Group [ECOG] scale) 0 to 1; measurable disease; adequate hematologic (WBC count $\geq 4,000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, and hemoglobin $\geq 9.5 \text{ g/dL}$), hepatic (AST and ALT level ≤ 2 times the upper limit of normal and total bilirubin level \leq the upper limit of normal), and renal (creatinine $\leq 1.2 \text{ mg/dL}$ and creatinine clearance $\geq 60 \text{ mL/min}$) functions; $\text{PaO}_2 \geq 70 \text{ torr}$; no pleural and pericardial effusion; radiation field encompassed one-half or less of the ipsilateral lung; and no serious comorbidity. All patients signed written informed consent in accordance with our institutional review board.

Pretreatment evaluation included history and physical examination; serum chemistries (lactate dehydrogenase, alkaline phosphatase, AST, ALT, bilirubin, albumin, creatinine, and calcium); chest radiograph; CT scan of the chest; ultrasound of the abdomen; MRI or CT scan of the brain; and bone scintigraphy.

Treatment details

The treatment consisted of 2 cycles of CDDP 80 mg/m^2 on Day 1 and vinorelbine (VNR) 25 mg/m^2 on Days 1 and 8 every 3 weeks followed by HART; 3 times a day with minimal interval of 4 hours for a total dose of 57.6 Gy in 36 fractions over 2.5 weeks.

Radiation therapy was started after the patient recovered from the toxicity of chemotherapy and was delivered with megavoltage equipment. Lung heterogeneity corrections were not used. The first and third fraction of each day consisted of anterior-posterior opposed fields that encompassed the primary tumor, the metastatic lymph nodes, and the regional lymph nodes with a 1.5 to 2-cm margin. The fraction size was 1.5 Gy. Regional nodes excluding the contralateral hilar and supraclavicular nodes were included in these fractions. However, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The second fraction of each day consisted of bilateral oblique fields that encompassed the primary tumor and the metastatic lymph nodes with a 1.5 to 2-cm margin; the fraction size was 1.8 Gy. Attempts were made to design the field of the second fraction to minimize the irradiated volume of the esophagus without compromising the margin around the tumor or spinal cord.

Toxicity assessment

Patients were observed weekly during treatment to monitor toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity was graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

Follow-up evaluation

The following evaluations were performed until disease progression every 2 months for the first year, every 3 months for the second year, and every 6 months thereafter: physical examination, toxicity assessment, and chest radiograph. CT scan of the chest was performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. Restaging at 6 months after the treatment was also performed with ultrasound of the abdomen, MRI or CT scan of the brain, and bone scintigraphy.

Response assessment

Complete response (CR) was defined as complete disappearance of all measurable and assessable lesions for ≥ 4 weeks, partial

response (PR) was defined as a decrease of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions for ≥ 4 weeks, and progressive disease (PD) was defined as an increase of 25% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions or the appearance of any new lesion. Stable disease was defined as the remainder of evaluable patients without CR, PR, or PD.

Pattern of failure

Patterns of failure were defined as first site of failure. Local/regional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Statistics

A Simon's two-stage optimal design was used for this study with the assumption that a protocol compliance rate of less than 60% would not be feasible, and protocol compliance rate of 80% or greater with α error of 0.10 and β error of 0.10 would warrant further investigation of this regimen. In the first stage, 11 assessable patients were entered. If fewer than 7 patients completed the treatment, accrual would be stopped with the conclusion that the regimen was not feasible for further investigation. If 7 or more patients completed the treatment, an additional 27 patients would be accrued in the second study. According to this design, this study would be determined to be feasible and be proceeded to a multicenter Phase II study if 27 patients completed the treatment. The actuarial median survival time and 2-year survival were estimated by the Kaplan-Meier method (11).

RESULTS

Patient population

Between July 1999 and March 2001, 30 patients were enrolled in the study. The accrual was stopped, because 29 of 30 patients completed the treatment, and conclusions could be drawn at that time. The patients' median age was 64 years (range, 46–73 years), 24 were male, and 6 were female. The patient and tumor characteristics are summarized in Table 1.

Treatment compliance and toxicity

All patients completed 2 cycles of induction chemotherapy. Six of 30 patients required dose modification, and 13 patients had treatment delay. The median time to start of HART from start of chemotherapy was 49 days (range, 41–62 days). Twenty-nine of 30 patients completed HART, and the median overall treatment time of HART was 17 days (range, 16–22 days). In total, 29 of 30 patients (97%; 95% confidence interval [CI], 83–100%) completed this combined treatment.

The toxicity profile of the treatment is shown in Tables 2 and 3. Common Grade 3 or greater acute toxicities were neutropenia, 25 (83%); infection, 5 (17%); esophagitis, 5 (17%); and radiation pneumonitis, 3 (19%). There were 2 cases of treatment-related death due to radiation pneumonitis. As of the date of this analysis, 2 cases with Grade

Table 1. Patient and tumor characteristics

Number of patients	30
Age	
Median	64
Range	46–73
Gender	
Male	24
Female	6
Performance status	
0	8
1	22
Weight loss	
<5%	25
≥5%	5
Tumor and lymph nodes	
T1N2	3
T1N3	1
T2N2	5
T2N3	5
T3N2	1
T4N0	1
T4N1	4
T4N2	9
T4N3	1
Stage	
IIIA	9
IIIB	21
Histology	
Squamous	13
Nonsquamous	17

3 s.c. tissue fibrosis and 1 case with spontaneous rib fracture were observed as late toxicities.

Response and survival

Of 30 patients, 2 achieved CR, and 23 achieved PR with a response rate of 83% (95% CI, 65–94%). Five patients remained in a stable disease state, and there were no PD patients. With a median follow-up period of 40 months for surviving patients, the median survival and the 2-year and 3-year survivals (Fig. 1) were 24 months (95% CI, 13–34 months), 50% (95% CI, 32–68%), and 32% (95% CI, 15–49%), respectively. The median progression-free survival and the 1-year progression-free survival (Fig. 2) were 10 months (95% CI, 8–20 months) and 47% (95% CI, 29–65%), respectively.

Pattern of failure

At the time of this analysis, 22 of 30 patients (73%) showed tumor progression, 2 patients (7%) had died as a result of treatment, and 6 patients (20%) were alive without disease progression. The patterns of first failure were as follows: local/regional only, 13 (43%); local/regional and distant, 4 (13%); distant only, 5 (17%).

DISCUSSION

In the 1970s, treatment of locally advanced NSCLC was by conventional radiotherapy alone. In the 1980s, sequential chemotherapy and conventional radiotherapy

Table 2. Hematologic toxicities (*n* = 30)*

	Grade					≥Grade 3 (%)
	0	1	2	3	4	
Leukopenia	1	3	8	16	2	18 (60)
Neutropenia	3	0	2	6	19	25 (83)
Thrombocytopenia	20	7	1	2	0	2 (7)
Anemia	1	10	16	3	0	3 (10)

* National Cancer Institute–Common Toxicity Criteria version 2.

were revealed to be superior to conventional radiotherapy alone. In the 1990s, optimal sequences of chemoradiotherapy and radiation fractionation were investigated. The West Japan Lung Cancer Group compared sequential vs. concurrent radiotherapy with induction CDDP, vindesine, and mitomycin (7). In an RTOG 9410 trial, induction CDDP and vinblastine plus sequential standard radiotherapy, CDDP and vinblastine plus concurrent standard radiotherapy, and CDDP and etoposide plus concurrent twice-daily hyperfractionated radiotherapy were compared (8). Both trials showed similar results; concurrent chemoradiotherapy was superior to the sequential approach and achieved 5-year survivals for concurrent and sequential approach of approximately 20% and 10%, respectively. However, twice-daily hyperfractionated radiotherapy, which seemed to be promising in a preceding RTOG 9015 trial (12), failed to show a survival advantage over standard once-daily radiotherapy, and concurrent chemotherapy and once-daily radiotherapy is the standard of care today. Recently, a Czech randomized Phase II trial (13) suggested a similar advantage of the concurrent approach using CDDP and VNR, a newer cytotoxic agent. However, there remains some argument that newer cytotoxic agents cannot be delivered as full-dose chemotherapy with concurrent radiotherapy, and the survival advantage of newer cytotoxic agents over old ones has not yet been demonstrated in Stage III NSCLC patients. The optimal schedule and fractionation of thoracic radiotherapy in combination with chemotherapy also remains to be determined.

Another promising regimen was altered fractionation of radiotherapy such as CHART or HART, 3 times a day with a fraction interval of 4 to 6 hours over 2.5 weeks or less. CHART was developed at Mount Vernon Hospital, United Kingdom, in the 1980s. It was designed to combine both a shortening of the overall treatment time of radiotherapy, which is analogous to the concept of dose intensification of cytotoxic chemotherapy, and a reduction in dose per fraction. The rationale was to overcome accelerated repopulation of the tumor during the course of radiotherapy, which may lead to local failure, and to reduce normal tissue toxicities that depend on the dose per fraction. After the results of a randomized trial that showed survival benefits of CHART over conventional

Table 3. Nonhematologic toxicities (n = 30)*

	Grade						≥Grade 3 (%)
	0	1	2	3	4	5	
Acute toxicity							
Nausea	7	16	4	3	0	0	3 (10)
Vomiting	23	3	4	0	0	0	0
Infection	20	3	2	5	0	0	5 (17)
Esophagitis	1	11	13	4	1	0	5 (17)
Pneumonitis	18	4	5	1	0	2	3 (10)
Late radiation morbidity [†]							
Esophagus	26	1	0	0	0	0	0
Heart	26	0	1	0	0	0	0
Lung	9	13	5	0	0	0	0
Subcutaneous tissue	17	6	2	2	0	0	2 (7)
Bone	26	0	0	0	1	0	1 (3)

* National Cancer Institute–Common Toxicity Criteria version 2.

[†] Three patients died within 90 days of the beginning of radiotherapy.

radiotherapy (9), the Department of Health in the United Kingdom recommended CHART as the radiotherapy schedule of choice in inoperable NSCLC, and a CHART implementation group was formed to facilitate its introduction throughout the United Kingdom (14). There were difficulties in changing departmental working hours and a lack of sufficient financial support in UK hospitals to introduce CHART into routine practice (15), although it was suggested that CHART gave more benefit than any sequential combination of conventional radiotherapy and chemotherapy with minimally increased toxicity. To make the accelerated regimen more widely applicable, Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less (CHARTWEL) and HART were introduced and were found to be as effective as CHART. Both CHARTWEL and HART showed improved survival over conventional radiotherapy, but the local tumor control was still unsatisfactory. Radiation dose escalation and

use of chemotherapy combined with CHARTWEL/HART were also investigated to improve the local control and survival. Saunders *et al.* (16) reported on CHARTWEL combined with induction chemotherapy (17). In that study, 113 patients were enrolled, and dose escalation from 54 Gy to 60 Gy with or without chemotherapy was successfully achieved. Locoregional control at 2 years was 37% and 55% for CHARTWEL 54 Gy and 60 Gy alone, respectively, compared with 72% in those treated with 60 Gy and induction chemotherapy. These results suggested that chemotherapy improved locoregional control, but unfortunately they failed to show a statistically significant survival advantage, because of the relatively small number of patients and imbalanced tumor characteristics enrolled in each arm. The advantage of dose-escalated CHARTWEL against conventional radiotherapy is currently being investigated in a German Phase

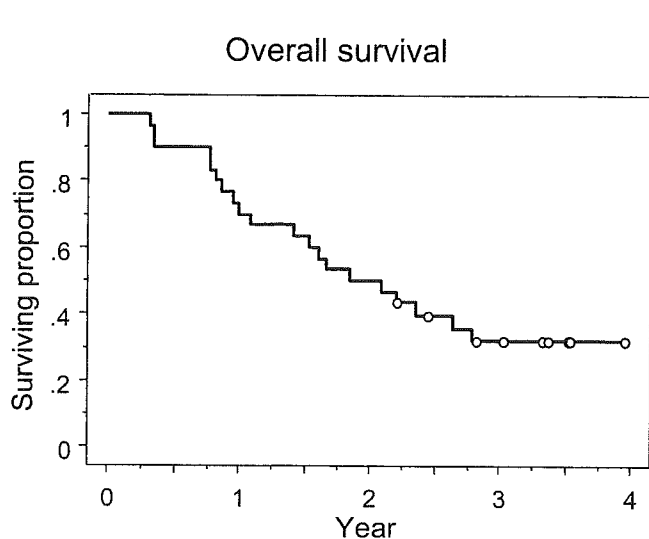


Fig. 1. Overall survival for all patients enrolled in this study.

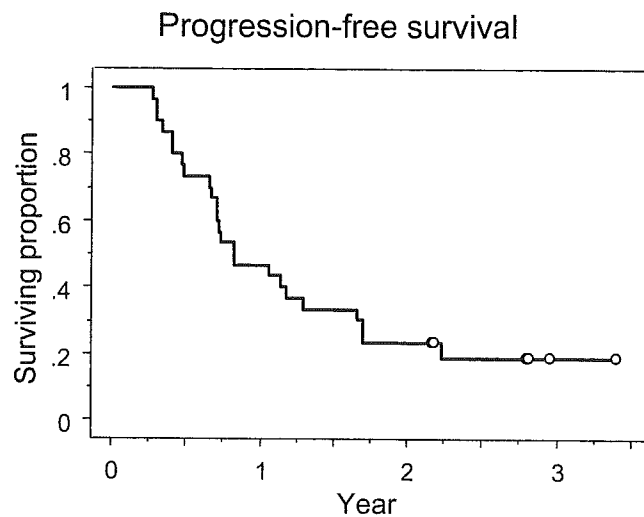


Fig. 2. Progression-free survival for all patients enrolled in this study.

III trial (18). Belani *et al.* reported the results of a randomized Phase III trial (19) that compared conventional radiotherapy with HART after induction chemotherapy (ECOG 2597). This study randomized 119 patients and unfortunately was closed because of slow accrual, but the results were provocative: The median survival time and the 2-year survivals for conventional radiotherapy and HART were 13.7 months and 33% vs. 22.2 months and 48%, respectively. These results seemed to be reliable despite the modest number of patients, because the median survival time of 13.7 months for the conventional radiotherapy arm was similar to that of a sequential chemoradiotherapy trial (2). The optimum chemotherapy regimen in combination with radiotherapy has not yet been determined, and we used a CDDP/VNR regimen instead of the carboplatin/paclitaxel regimen used in the ECOG 2597 trial. Both regimens are standards for advanced-stage NSCLC (20, 21). The compliance and toxicity profiles of chemotherapy in our study were acceptable, the incidence of esophagitis after HART was less than we expected, and the survival figure was nearly identical to that of the ECOG 2597 trial. This suggests that HART after induction CDDP/VNR or carboplatin/paclitaxel can achieve reproducible and promising results.

The pattern of failure in our study showed that local

failure was still high (17 of 30, 57%) compared with distant metastasis (9 of 30, 30%), and further improvement of local control is needed. Future directions may include further dose intensification of radiotherapy and introduction of molecular-targeted agents. Recent innovation of information technology has made it possible to use sophisticated three-dimensional conformal radiotherapy (3DCRT). This can deliver intensified radiation doses to the tumor while minimizing the doses to the normal tissues that prevented further dose escalation using conventional two-dimensional radiotherapy. There have been several reports evaluating dose-intensified 3DCRT (22–25), and the technique is now under investigation in combination with cytotoxic chemotherapy in the Radiation Therapy Oncology Group trial (RTOG L-0117). Currently, molecular-targeted agents are being investigated most enthusiastically in Phase II and Phase III trials (26–29). It will be determined in the near future whether or not the combination of these agents has a survival impact. However, the optimal combination of these agents, newer cytotoxic agents, radiation fractionation, and 3DCRT will still need to be determined. Further investigation employing dose-intensified radiotherapy will be necessary to make a great leap in the treatment of locally advanced NSCLC.

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Pilot Study of Concurrent Etoposide and Cisplatin Plus Accelerated Hyperfractionated Thoracic Radiotherapy Followed by Irinotecan and Cisplatin for Limited-Stage Small Cell Lung Cancer: Japan Clinical Oncology Group 9903

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Abstract Purpose: Irinotecan and cisplatin (IP) significantly improved survival compared with etoposide and cisplatin (EP), in patients with extensive-stage small cell lung cancer (SCLC) in a previous Japan Clinical Oncology Group (JCOG) randomized trial. JCOG9903 was conducted to evaluate the safety of sequentially given IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for the treatment of limited-stage SCLC (LSCLC).

Experimental Design: Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Thirty patients were assessable for toxicity, response, and survival. Treatment consisted of etoposide 100 mg/m² on days 1 to 3, cisplatin 80 mg/m² on day 1, and concurrent twice-daily TRT of 45 Gy beginning on day 2. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m² on days 1, 8, and 15 and cisplatin 60 mg/m² on day 1, with three 28-day cycles.

Results: There were no treatment-related deaths. The response rate was 97% (complete response, 37%; partial response, 60%). Median overall survival was 20.2 months; 1-, 2-, and 3-year survival rates were 76%, 41%, and 38%, respectively. Of the 24 patients who started the IP regimen, 22 received two or more cycles. Hematologic toxicities of grade 3 or 4 included neutropenia (67%), anemia (50%), and thrombocytopenia (4%). Nonhematologic toxicities of grade 3 or 4 included diarrhea (8%), vomiting (8%), and febrile neutropenia (8%). Of the 20 patients with recurrence, none had local recurrence alone and only two had both local and distant metastasis as the initial sites of disease progression.

Conclusions: IP following concurrent EP plus twice-daily TRT is safe with acceptable toxicities. A randomized phase III trial comparing EP with IP following EP plus concurrent TRT for LSCLC is ongoing (JCOG0202).

Despite efforts to curb smoking, lung cancer remains the leading cause of cancer deaths in many industrialized countries. Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer histology. Whereas combination

chemotherapy is the cornerstone of SCLC treatment, meta-analyses showed that adding thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC (LSCLC; i.e., disease confined to the hemithorax; refs. 1, 2). Several randomized trials have shown that early use of concurrent thoracic radiotherapy is superior to sequential or late use when etoposide and platinum are employed as combination chemotherapy (3-5). An intergroup phase III study showed accelerated hyperfractionated radiotherapy with etoposide and cisplatin (EP) to be superior to standard fractionation, with 5-year survival rates of 26% and 16%, respectively (6). Although substantial progress has been made during the past two decades, many LSCLC patients experience tumor recurrence and succumb to the disease, indicating the need for improved LSCLC therapy.

The Japan Clinical Oncology Group (JCOG) previously conducted a randomized phase III trial comparing irinotecan and cisplatin (IP) with EP in patients with extensive-stage SCLC. The response rate and overall median survival were significantly better for IP (i.e., 84.4% and 12.8 months with IP versus 67.5% and 9.4 months with EP, respectively). The 2-year

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Note: Portions of this study were presented at the 39th Annual Meeting of the American Society of Clinical Oncology, May 31 to June 3, 2003, Chicago, Illinois.

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survival rates were 19.5% for IP and 5.2% for EP (7). These encouraging results prompted us to explore the use of IP in LSCLC. We therefore undertook a pilot study to evaluate the safety of IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for LSCLC.

Experimental design

Eligibility criteria. Patients with histologically or cytologically documented LSCLC, defined as disease confined to one hemithorax including bilateral supraclavicular nodes, were enrolled in this study. Additional eligibility criteria consisted of measurable or assessable disease, age <75 years, Eastern Cooperative Oncology Group performance status of 0 to 2, no previous treatment, leukocyte count $\geq 4,000/\text{mm}^3$, platelet count $\geq 10^5/\text{mm}^3$, hemoglobin ≥ 9.5 g/d, serum creatinine ≤ 1.5 mg/d, creatinine clearance ≥ 60 mL/min, serum bilirubin ≤ 1.5 mg/d, serum transaminase $\leq 2 \times \text{ULN}$, and $\text{PaO}_2 \geq 70$ mm Hg. Exclusion criteria included active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 3 months, interstitial pneumonia/active lung fibrosis on chest X-ray, peripheral neuropathy, malignant pleural or pericardial effusion, diarrhea, intestinal obstruction or paralysis, and active concomitant malignancy. The TRT portal should be no more than half of the hemithorax. No prior chemotherapy or radiotherapy was permitted. Pregnant or lactating women were excluded. Before enrollment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest X-ray, electrocardiogram, chest computed tomographic scan, and whole-brain computed tomographic or magnetic resonance imaging, abdominal ultrasound and/or computed tomographic, and isotope bone scans. Blood cell counts, differential white counts, and other laboratory data were obtained weekly during each course of chemotherapy. All patients were reassessed at the end of treatment in the same manner as at the time of enrollment.

Treatment plan. Induction chemotherapy consisted of cisplatin $80 \text{ mg}/\text{m}^2$ on day 1 and etoposide $100 \text{ mg}/\text{m}^2$ on days 1 to 3. TRT was begun on day 2 of the induction chemotherapy and given twice daily (1.5 Gy per fraction, with ≥ 6 hours between fractions) and directed to the primary tumor for a total dose of 45 Gy in 3 weeks. The initial field included the primary disease site with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was nodal tumor involvement). TRT was done with linear accelerators and the energy was 6 to 10 MV photons. After the administration of 30 to 36 Gy, the radiation field was reduced around the primary tumor and involved lymph nodes using parallel opposed oblique fields to limit the dose to the spinal cord and protect the uninvolved lung field. Following chemoradiotherapy, patients were treated with three cycles of IP. The IP regimen started on day 29 and consisted of irinotecan $60 \text{ mg}/\text{m}^2$ on days 1, 8, and 15 and cisplatin $60 \text{ mg}/\text{m}^2$ on day 1, with three 28-day cycles. If the leukocyte count decreased to $< 3,000/\text{mm}^3$ or the platelet count fell below $100,000/\text{mm}^3$ on the first day of IP, chemotherapy was withheld until the counts recovered to $\geq 3,000/\text{mm}^3$ and $\geq 100,000/\text{mm}^3$, respectively. Administration of irinotecan was skipped on day 8 and/or 15 if the leukocyte count was $\leq 2,000/\text{mm}^3$, the platelet count was $\leq 50,000/\text{mm}^3$,

or there was any diarrhea regardless of grade, or a fever of $\geq 37.5^\circ\text{C}$. The dose of irinotecan in subsequent cycles was reduced by $10 \text{ mg}/\text{m}^2$ from the planned dose if grade 4 hematologic toxic effects or grade 2 or 3 diarrhea developed. Administration of granulocyte colony-stimulating factor was prohibited on the days of chemotherapy or radiotherapy. Primary prophylactic granulocyte colony-stimulating factor was not given. For patients who had developed grade 4 neutropenia during the previous cycles of chemotherapy, secondary prophylactic granulocyte colony-stimulating factor administration was allowed. Prophylactic antibiotics were not given.

Treatment was discontinued in patients with grade 4 nonhematologic toxicity. Prophylactic cranial irradiation (25 Gy in 10 fractions) was conducted for patients showing a complete response or near complete response defined as a reduction of $>90\%$ in the sum of the products of the greatest perpendicular dimensions of bidimensional lesions. Tumor responses were assessed radiographically. Standard WHO response criteria (8) were used, and all responses were confirmed ≥ 28 days after initial documentation of the response. JCOG criteria were used to assess toxicity (9). JCOG criteria are similar to those of the National Cancer Institute Common Toxicity Criteria (10). Esophageal toxicity was graded as follows: grade 3, moderate to severe ulceration and edema, cannot eat, requires narcotic drugs; grade 4, serious ulceration and edema, resulting in complete obstruction or perforation.

Statistical consideration. The primary objective of this study was to evaluate the safety and feasibility of sequential administration of IP following EP plus concurrent twice-daily TRT. Simon's optimal two-stage design was used to determine the sample size and decision criteria (11). The regimen would be considered feasible if two cycles or more of IP were completed without grade 4 nonhematologic toxicity or treatment related death in at least 90% of patients and not feasible if the completion rate was $\leq 70\%$. The required number of patients was estimated to be 27, with $\alpha = 0.05$ and $\beta = 0.80$. We determined the planned sample size for the study to be 30 patients accrued over 12 months, with 36 months of additional follow-up.

Time-to-progression was calculated from the date of entry into study until the date of documented progression or death (in the absence of progression). Survival was calculated from the protocol treatment start date until the date of death. Both intervals were determined by the Kaplan-Meier method.

The protocol was approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of the participating institutions. All patients provided written informed consent.

Results

Patient characteristics. Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Patient characteristics are detailed in Table 1. Although eligible, no patients with a performance status of 2 were actually enrolled in this trial. Thirty-one patients ultimately participated. One patient did not receive the protocol treatment because of a problem with the radiation equipment in the institution providing treatment. Thus, this patient was not evaluable.

Adherence to treatment plan. All patients completed concurrent chemoradiotherapy. Six patients did not receive the IP regimen, because of disease progression, septic shock

Table 1. Patient characteristics

Patient registered	31
Assessable	30
Not assessable (not treated)	1
Median age (range)	64 (43-74)
Gender	
Male	27
Female	4
Performance status 0/1	8/23

during chemoradiotherapy, renal dysfunction, or leukocytopenia, and two refused IP. Of the 24 patients given the IP regimen, 22 received two cycles or more of IP. The reasons for terminating IP before the second treatment cycle were grade 4 diarrhea in one patient and refusal, not significant toxicity, in one patient. Of the 22 patients who received two cycles or more of IP, nine received the original planned dose. In five patients, dose reductions in the second cycle of IP were necessary, 11 patients skipped day 8 and/or 15 irinotecan, and one patient had a minor protocol violation. Fifteen patients required that the second cycle of IP be delayed for 1 to 14 days. Of 17 patients (58%) who received the entire treatment, the median time delay from the planned protocol was 4 days (range, 0-21 days). Six patients were able to start the third cycle of IP without delay, relative to the first cycle of IP.

Toxicity. Toxicities associated with concurrent chemoradiotherapy are summarized in Table 2. The major toxicity was neutropenia. One patient had febrile neutropenia and septic shock. The same patient experienced grade 3 fatigue and anterior chest pain. IP was well tolerated (Table 3), despite diarrhea, vomiting, and hematologic toxicities. One patient, who had grade 2 nausea/vomiting, refused further treatment after the first cycle of IP. Another patient, who refused days 8 and 15 irinotecan during the second cycle, had grade 2 diarrhea and nausea/vomiting. No grade 3 or 4 pulmonary toxicity was observed. There were no treatment-related deaths.

Table 2. Major toxicities concurrent EP/TRT (n = 30)

Toxicity	Grade 3, no. patients (%)	Grade 4, no. patients (%)
Hematologic		
Anemia	0	0
Leucopenia	13 (43)	15 (50)
Neutropenia	9 (30)	19 (63)
Thrombocytopenia	2 (7)	1 (3)
Nonhematologic		
Esophagitis	2 (7)	0
Infection	1 (3)	0
Hypotension*	0	1 (3)
Fatigue*	1 (3)	0
Anterior chest pain*	1 (3)	0
Febrile neutropenia	2 (7)	

*These events occurred in the same patient.

Table 3. Major toxicities irinotecan and cisplatin (IP), (n = 24)

Toxicity	Grade 2, no. patients (%)	Grade 3, no. patients (%)	Grade 4, no. patients (%)
Hematologic			
Anemia	6 (25)	12 (50)	0
Leucopenia	6 (25)	12 (50)	5 (21)
Neutropenia	5 (21)	12 (50)	5 (21)
Thrombocytopenia	5 (21)	1 (4)	0
Nonhematologic			
Diarrhea	4 (17)	1 (4)	1 (4)
Vomiting	3 (13)	2 (8)	0
Febrile neutropenia	—	2 (8)	0
Fever	2 (8)	0	0
Infection	4 (17)	0	0

Neither grade 2, or more severe, late radiation toxicities nor radiation recall reactions were reported.

Response and survival. The overall response rate was 97% (complete response, 37%; partial response, 60%). Overall and progression-free survivals are depicted in Figs. 1 and 2. The median follow-up time of all patients was 20 months and that for surviving patients 40 months. The median progression-free survival was 9 months, and the median overall survival was 20 months. The 24- and 36-month overall survivals were 41% and 38%, the 24- and 36-month progression-free survivals 30% and 26%, respectively.

Pattern of relapse. First sites of disease progression are presented in Table 4. Of the 18 patients who have died to date, all died of progressive disease. Surprisingly, no patient showed relapse solely at the local-regional site (within TRT field). Only two patients had both local and distant involvement. There were 11 patients whose initial site of relapse was the brain. Of these, six had relapses solely in the brain. Whereas two patients had complete response and received prophylactic cranial irradiation, four had partial remission and did not receive prophylactic cranial irradiation.

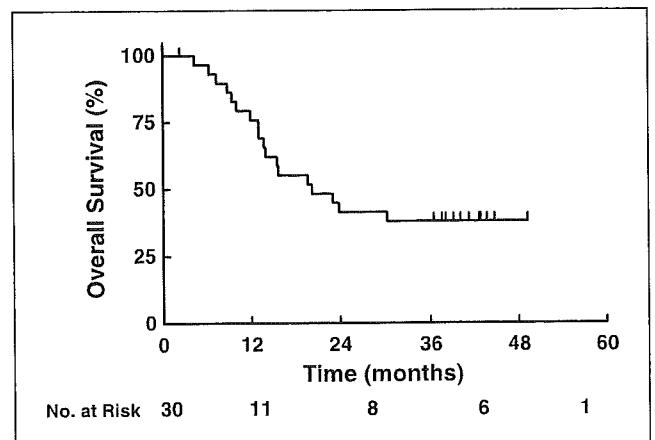


Fig. 1. Overall survival.

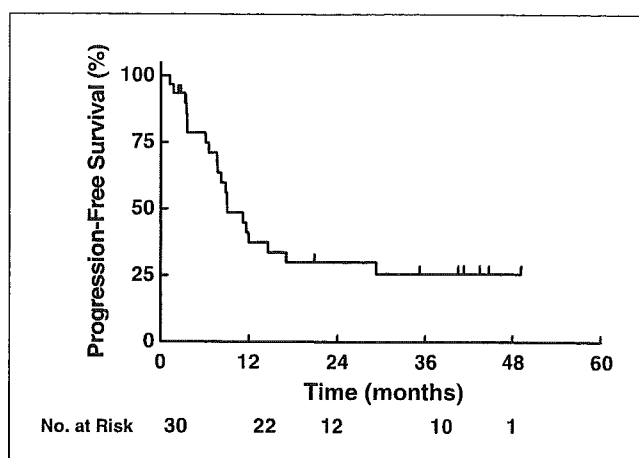


Fig. 2. Progression-free survival.

Other relapse sites included the liver in four patients, bone in three, pleural effusion in three, and supraclavicular lymph nodes in two.

Discussion

Irinotecan is one of the most active agents against SCLC (12). A phase II study of irinotecan and cisplatin yielded a response rate of 86% and median survival of 13.2 months in patients with extensive SCLC (13). A phase III study confirmed excellent results and showed IP to be more effective than etoposide and cisplatin in extensive SCLC (7). Three confirmatory trials, comparing IP with EP for extensive SCLC are ongoing in Europe and the United States. Although dose-finding studies to explore integrating irinotecan into the early concurrent phase of chemoradiation for LSCLC are also currently being conducted by the Radiation Therapy Oncology Group and other U.S. groups. The dose-finding JCOG study of concurrent use of IP with TRT in stage III non-small cell lung cancer showed that the full dose of irinotecan could not be given due to neutropenia, diarrhea, and pulmonary toxicity (14). Thus, we employed IP as a sequential treatment following EP plus concurrent TRT.

The present trial showed IP following concurrent EP plus twice-daily TRT to be safe, with acceptable toxicities. Hematologic toxicities and diarrhea, while on the IP regimen following concurrent chemoradiotherapy, are similar to those of a previous phase III trial conducted by JCOG (JCOG9503; ref. 7). Neither grade 3 or 4 pulmonary toxicity nor treatment related deaths were observed. The West Japan Thoracic Oncology Group conducted a similar phase II study of EP plus twice-daily TRT followed by IP for LSCLC (15). Promising response (88%) and 2-year survival (51%) rates were reported, with acceptable toxicities.

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Table 4. Sites of first failure ($n = 20$)

Site	No. patient (%)
Isolated local-regional failure	0 (0)
Local-regional and distant	2 (10)
Distant	18 (90)
Brain only	6 (30)
Other sites of failure*	12 (60)

*Recurrence at sites other than the primary tumor or brain only.

Local failure is an important problem in the treatment of LSCLC. Turrisi et al. showed the rate of local failure to be reduced in the twice-daily TRT plus EP group as compared with the once-daily TRT plus EP group: the rate was 52% in the group receiving once-daily therapy and 36% in that receiving twice-daily therapy (6). Eighteen percent of patients who received EP plus concurrent twice-daily TRT had first progression within the thorax in the previous JCOG phase III trial (5). It is noteworthy that no patient relapsed solely at the local-regional site and only two patients had both local and distant involvement in the present trial. There may be an interaction between TRT and IP even given sequentially. Another possibility relates to recent improvements in radiotherapeutic techniques with better imaging of the target volume by chest computed tomographic. This possibility should be assessed in a future randomized trial.

It is important to integrate new active anticancer agents to the combined modality treatments for LSCLC. Irinotecan has been clearly shown to have clinical activity in a randomized trial, against extensive-stage SCLC. Several other new agents including targeted therapies have failed to show clinical activity against SCLC. Based on these considerations, we conducted a randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC (JCOG0202). In the JCOG0202, eligible patients were randomized after the completion of induction chemoradiotherapy. Although feasibility may be a limitation of the present study, improvements are anticipated with appropriate use of granulocyte colony-stimulating factor, antibiotics, and patient education.

In summary, irinotecan and cisplatin following EP plus concurrent twice-daily TRT is a safe and active regimen for LSCLC. The observed low rate of local recurrence is encouraging. A randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC is currently under way.

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First-Line Single Agent Treatment With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer: A Phase II Study

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A B S T R A C T

Purpose

We conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced non-small-cell lung cancer (NSCLC) to assess its efficacy and toxicity.

Patients and Methods

Patients received 250 mg doses of gefitinib daily. Administration of gefitinib was terminated if partial response (PR) was not achieved within 8 weeks or if tumor reduction was not observed within 4 weeks. In these cases, platinum-based doublet chemotherapy was given as a salvage treatment. We evaluated mutation status of the epidermal growth factor receptor (EGFR) gene in cases with available tumor samples.

Results

Forty-two patients were enrolled between March and November 2003, with 40 of these patients being eligible. The response rate was 30% (95% CI, 17% to 47%). The most common toxicity included grade 1 or 2 acne-like rash (50%) and grade 1 diarrhea (18%). Grade 2 or 3 hepatic toxicity was observed in 8% of patients. Four patients developed grade 5 interstitial lung disease (ILD). Thirty patients received second-line chemotherapy. Median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%. Tumor samples were available in 13 patients, including four cases of PR, six cases of stable disease, and three cases of progressive disease. *EGFR* mutations (deletions in exon 19 or point mutations [L858R or E746V]) were detected in four tumor tissues. All four patients with *EGFR* mutation achieved PR with gefitinib treatment.

Conclusion

Single agent treatment with gefitinib is active in chemotherapy-naïve patients with advanced NSCLC, but produces unacceptably frequent ILD in the Japanese population.

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Previous meta-analysis demonstrated that cisplatin-based chemotherapy yielded a modest but significant survival benefit over best supportive care in advanced non-small-cell lung cancer (NSCLC).¹⁻⁴ In the 1990s, new agents, including vinorelbine, gemcitabine, paclitaxel, docetaxel, and irinotecan became available for the treatment of NSCLC. Several phase III trials comparing doublet platinum-based chemotherapies demonstrated no significant difference with respect to response rate, survival, or quality of life.^{5,6} Nonplatinum or triplet platinum-based combination chemotherapies have been investigated, but none of these produced longer survival than standard doublet platinum-based chemotherapy.⁷⁻⁹

Recently, molecular-targeted agents have been introduced for the treatment of NSCLC. Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, which displays activity against recurrent NSCLC after platinum-based chemotherapy. Two international, randomized phase II trials in patients with advanced or metastatic NSCLC after platinum-based chemotherapy demonstrated response rates of 12% to 18% (28% in the Japanese population).^{10,11} Two international, randomized, double-blinded, placebo-controlled phase III trials investigated the role of gefitinib combined with platinum-based chemotherapy regimens, including carboplatin and paclitaxel, or cisplatin and gemcitabine in chemotherapy-naïve patients with advanced NSCLC.^{12,13} Surprisingly, there were no improvements in overall survival,

time to progression, or response rate. There are no data available regarding first-line treatment with single agent gefitinib against NSCLC in the Japanese population. Here, we conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced NSCLC. If a failure with gefitinib treatment was perceived, standard platinum-based doublet chemotherapy was performed as salvage. The primary end point of this phase II trial was response rate, and the secondary end points were toxicity, survival, and response rate of salvage chemotherapy.

Patient Population

Patients were required to have histologically or cytologically confirmed stage IIIB (malignant pleural or pericardial effusion and/or metastasis in the same lobe) or stage IV NSCLC. Recurrences after surgical resection were permitted. Other criteria included: (1) age 20 years or older, but younger than 75 years; (2) Eastern Cooperative Oncology Group performance status (PS) 0 or 1; (3) measurable disease; (4) PaO₂ ≥ 60 mmHg; (5) adequate organ function (ie, total bilirubin ≤ 2.0, AST and ALT ≤ 100 U/L, serum creatinine ≤ 1.5 mg/dL, leukocyte count 4,000 to 12,000/mm³, neutrophil count ≥ 2,000/mm³, hemoglobin ≥ 9.5 g/dL, and platelets ≥ 100,000/mm³); (6) no prior chemotherapy or thoracic radiotherapy; (7) no interstitial pneumonia or pulmonary fibrosis, as determined by chest x-ray; (8) no paralytic ileus or vomiting; (9) no symptomatic brain metastases; (10) no active infection; (11) no active concomitant malignancy; (12) no pregnancy or breast-feeding; (13) no severe allergy to drugs. Patients with PaO₂ less than 60 mmHg were excluded, because those patients might have pulmonary fibrosis, which is a risk factor of interstitial lung disease (ILD).¹⁴ All patients were required to provide written informed consent and the institutional review board at the National Cancer Center approved the protocol.

Treatment Plan

Treatment was started within a week after enrollment in the study. Patients received 250 mg of gefitinib orally daily. In the event of grade 3 or more and/or unacceptable toxicities, gefitinib was postponed until these toxicities were improved to grade 2 or less. Dose reduction was not performed. If treatment was postponed four times or more, the treatment was terminated. Therapy was continued unless the patient experienced unacceptable toxicity or progressive disease, partial response (PR) was not achieved within 8 weeks, or the sum of the longest diameters of the target lesions decreased less than 10% within 4 weeks. If the gefitinib treatment failed according to these criteria, platinum-based doublet chemotherapy was performed as a salvage regimen.

Previous trials of gefitinib for pretreated patients with NSCLC reported that most responding patients showed rapid tumor regression within 4 or 8 weeks.¹¹ Furthermore, most responses by gefitinib were extreme shrinkage of the tumor. Minor response, as frequently seen by the treatment with cytotoxic agents, was seldom experienced. Stable disease with gefitinib corresponded to no tumor reduction or slight progression. If patients with stable disease continued the treatment with gefitinib until progressive disease became obvious, those patients might not be able to receive platinum-based salvage chemotherapy because of poor PS due to progressive disease. Platinum-based combination chemotherapy is the standard care for patients with advanced NSCLC and good PS. Platinum-based chemotherapy was thought to be essential for patients with no response from the first-line single agent treatment with gefitinib. Therefore, we implemented these early stopping criteria for treatment with gefitinib.

Study Evaluations

Pretreatment evaluations consisted of a complete medical history, determination of performance status, physical examination, hematologic and biochemical profiles, arterial blood gas examination, ECG, chest x-ray, bone scan, and computed tomography (CT) scan of the chest, ultrasound or CT scan of the abdomen, and magnetic resonance imaging or CT scan of the whole brain.

Evaluations performed included a weekly chest x-ray for 4 weeks, and once every 2 weeks for biochemistry, complete blood cell, platelet, leukocyte differential counts, physical examination, determination of performance status, and toxicity assessment. Imaging studies were scheduled to assess objective response every month.

Response and Toxicity Criteria

Response evaluation criteria in solid tumors (RECIST) guidelines were used for evaluation of antitumor activity.¹⁵ The target lesions were defined as ≥ 2 cm in the longest diameter on CT scans. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A PR was defined as an at least 30% decrease in the sum of the longest diameters of the target lesions for more than 4 weeks with no new area of malignant disease. Progressive disease (PD) indicated at least a 20% increase in the sum of the longest diameter of the target lesions or a new malignant lesion. Stable disease was defined as insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Mutation Analysis of the EGFR Gene

Tumor specimens were obtained during diagnostic or surgical procedures. Biopsied or surgically resected specimens were fixed with formalin or 100% methanol, respectively. Tumor genomic DNA was prepared from paraffin-embedded sections using laser capture microdissection in biopsied specimens or macrodissection in surgically resected specimens at Mitsubishi Chemical Safety Institute LTD. Exons 18, 19, and 21 of the *EGFR* gene were amplified and sequenced as previously described.¹⁶

Statistical Analysis

In accordance with the minimax two-stage phase II study design by Simon,¹⁷ the treatment program was designed to refuse response rates of 10% (P_0) and to provide a significance level of .05 with a statistical power of 80% in assessing the activity of the regimen as a 25% response rate (P_1). The upper limit for first-stage drug rejection was two responses in the 22 assessable patients; the upper limit of second-stage rejection was seven responses within the cohort of 40 assessable patients. Overall survival was defined as the interval between enrollment in this study and death or the final follow-up visit. Median overall survival was estimated by the Kaplan-Meier analysis method.¹⁸ Fisher's exact test was used in a contingency table.

Patient Population

A total of 42 patients were enrolled in this study between March and November, 2003, with 40 of these patients being eligible. One patient was found ineligible due to anemia, the other because spinal magnetic resonance imaging could not confirm a positive bone scan. Patient characteristics are listed in Table 1. Sixty percent of patients were male; median age was 61 years. The most common histologic subtype was adenocarcinoma (75%). Most patients (93%) had stage IV disease or recurrence after surgical resection. Eighty percent of patients were current or former smokers.

Efficacy

One patient (3%) has been receiving gefitinib after 22 months. Four patients suspended gefitinib for 11, 14, 27, or 29 days, because of liver dysfunction ($n = 3$) and fever due to urinary tract infection ($n = 1$). Thirty-nine patients terminated gefitinib because of progressive disease ($n = 20$), no tumor reduction within 4 weeks ($n = 12$), not achieving PR within 8 weeks ($n = 1$), toxicities including pulmonary ($n = 3$), nausea and vomiting ($n = 1$), rash ($n = 1$), or hepatic dysfunction ($n = 1$).

There were 12 PRs in 40 eligible patients, and the objective response rate was 30% (95% CI, 17% to 47%; Table 2). All but one

Table 1. Patient Characteristics

Characteristic	No. of Patients
Patients enrolled	42
Patients eligible	40
Sex	
Male	24
Female	16
Age, years	
Median	61
Range	44-74
Performance status	
0	14
1	26
Stage	
IIIB	3
IV	34
Recurrence after surgery	3
Histologic type	
Adenocarcinoma	30
Squamous cell carcinoma	3
Large cell carcinoma	7
Smoking history	
Current	27
Former	5
Never	8

patient from this subgroup achieved PR within 4 weeks, with the remaining patient achieving PR within 8 weeks. The background of the 12 responding patients was as follows: nine females, three males; 11 adenocarcinomas, one large-cell carcinoma; six individuals who never smoked, five current smokers, and one former smoker. Response rates based on patient characteristics were as follows: three of 24 (13%) males, nine of 16 (56%) females ($P = .0050$); 11 of 30 (37%) individuals with adenocarcinoma, one of 10 (10%) individuals with squamous or large-cell carcinoma ($P = .0048$); six of 32 (19%) current or former smokers, and six of eight (75%) individuals who never smoked ($P = .0048$).

The median follow-up time was 23 months, and nine patients were still alive at the most recent follow-up. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55% (Fig 1).

Safety and Toxicity

Toxicity was evaluated in all eligible patients. The most common toxicity was rash (Table 3). Thirty-eight percent and 13% of patients

Table 2. Efficacy of Single Agent Treatment With Gefitinib in Patients With Stage IIIB or IV Non-Small-Cell Lung Cancer

Type of Response	No. of Patients	% of Patients
Complete	0	0
Partial	12	30
CR + PR	12	30
95% CI		17 to 47
Stable disease	16	40
Progression	12	30

Abbreviations: CR, complete response; PR, partial response.

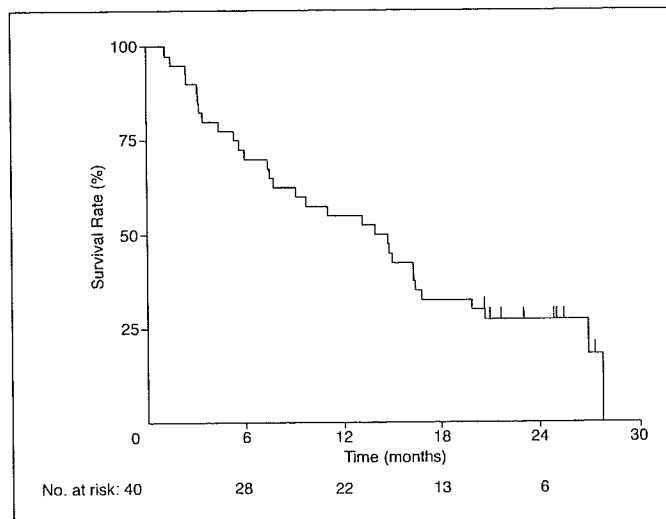


Fig 1. Overall survival of all eligible patients ($n = 40$) was calculated according to the Kaplan-Meier method. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%.

experienced grade 1 or 2 rash, respectively. One patient experienced grade 3 nausea and vomiting, leading to gefitinib treatment being terminated. Grade 3 hepatic toxicity was observed in one patient, also causing termination of gefitinib treatment.

The most problematic toxicity was ILD. We reviewed the medical records, chest x-rays, and CT films of all the cases, which were suspected as ILD by the physician in charge. ILD was diagnosed on the basis of standard or high-resolution CT findings of the chest (diffuse ground-glass opacity, consolidation, or infiltrate) and no response to antibiotics. We diagnosed that four patients experienced grade 5 ILD during or after first-line treatment with gefitinib. The first patient was a 61-year-old man. He developed dyspnea and fever elevation (38.1°C) on day 23 of the treatment with gefitinib and administration of gefitinib was terminated. Chest CT demonstrated bilateral diffuse ground-glass opacity, and PaO_2 was 43.7 mmHg in the room air. KL-6 antigen, a serum marker of interstitial pneumonia, was not elevated

Table 3. Maximum Toxicity Grades Associated With Single Agent Treatment With Gefitinib in 40 Patients With Non-Small-Cell Lung Cancer

Toxicity	Toxicity Grade									
	1		2		3		4		5	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Rash	15	38	5	13	0	0	0	0	0	0
Dry skin	4	10	0	0	0	0	0	0	0	0
Diarrhea	7	18	0	0	0	0	0	0	0	0
Nausea	3	8	0	0	1	3	0	0	0	0
Mucositis	6	15	0	0	0	0	0	0	0	0
Alopecia	4	10	0	0	0	0	0	0	0	0
Hyponatremia	24	60	0	0	3	8	0	0	0	0
Hypokalemia	12	30	0	0	0	0	0	0	0	0
Hepatic	11	28	2	5	1	3	0	0	0	0
Renal	4	10	1	3	0	0	0	0	0	0
ILD	0	0	0	0	0	0	0	0	4	10

Abbreviation: ILD; interstitial lung disease.

(351 U/mL) on day 24, but elevated on day 31 (1,400 U/mL). Beta-D-glucan, a serum marker of fungal infection and *Pneumocystis carinii* pneumonia, was also negative. Methylprednisolone and antibiotics were administered, with temporal improvement of ILD. However, subsequently, pulmonary function gradually deteriorated, leading to death. Autopsy revealed alveolar damage with organization around the bronchus and vessels in both neoplastic and non-neoplastic lesions, compatible with drug-induced ILD. The second patient was a 64-year-old man. Chest CT on day 27 showed stable disease, but administration of gefitinib was continued (protocol violation). Periodic chest x-ray film on day 45 showed abnormal shadow in the left lung field. High-resolution CT of the chest on the same day revealed reticular shadow on bilateral upper lobe. The treatment with gefitinib was terminated on day 45. KL-6 antigen was not elevated on day 49 (276 U/mL). Methylprednisolone and antibiotics were administered, but were not effective, leading to death. The third patient was a 67-year-old man. Chest CT on day 30 demonstrated enlargement of primary lesion and bilateral reticular shadow in subpleural lesions. Gefitinib was terminated on day 30. The patient developed dyspnea without fever elevation on day 37. Pao₂ in the room air fell to 61.0 mmHg from 82.4 mmHg at pretreatment. Chest x-ray showed that the bilateral diffuse reticular shadow deteriorated. Methylprednisolone and antibiotics were administered, but were not effective, leading to death. Autopsy revealed severe fibrotic thickness of alveolar septum, compatible with severe interstitial pneumonia. There was no pathological evidence of carcinomatous lymphangiosis. The fourth patient was a 59-year-old woman. Chest x-ray showed consolidation in the left lung on day 21. Slight fever (37.9°C) developed on day 22. Blood culture was negative. Antibiotics were administered, but consolidation deteriorated and spread to both lungs on day 25. Gefitinib was terminated on day 25. KL-6 antigen was elevated to 3,590 U/mL. Methylprednisolone was administered, but was not effective, leading to death (Table 4). Four other patients experienced ILD after second-line or third-line chemotherapy. Two patients received second-line treatment with cisplatin plus vinorelbine (one and four courses), one patient received treatment with cisplatin plus gemcitabine (one course), and one patient received third-line treatment with docetaxel (four courses). Three of four patients received steroids, with temporal

improvement of ILD being observed in two patients. However, ILD deteriorated during tapering of steroid treatment, with three patients subsequently dying. One patient stopped the third-line treatment with docetaxel, with the associated ILD showing improvement in this case without steroid treatment (Table 4).

We retrospectively reviewed the pretreatment chest x-rays and CT films of all patients. Interstitial shadow was not detected on pretreatment chest x-ray films in any patients. However, six patients showed evidence of interstitial shadow on pretreatment chest CT films. Three of the six patients with interstitial shadow, as determined by pretreatment chest CT, experienced ILD either during or following administration of gefitinib or second-line chemotherapy. None of the six patients responded to gefitinib treatment. On the other hand, four of 34 patients who showed no interstitial shadow on pretreatment chest CT films experienced ILD. Interstitial shadow as determined by pretreatment chest CT was not a statistically significant risk factor of ILD ($P = .0819$; Table 5).

Second-Line Chemotherapy

A total of 30 patients received second-line chemotherapy. Twenty-seven patients received platinum-based chemotherapy (cisplatin plus vinorelbine; $n = 17$), carboplatin plus paclitaxel ($n = 5$), cisplatin plus gemcitabine ($n = 3$), cisplatin plus docetaxel ($n = 1$), and cisplatin plus irinotecan ($n = 1$). The remaining three patients received vinorelbine plus gemcitabine or vinorelbine alone. Nine of 30 patients achieved PR with these second-line chemotherapies. The objective response rate of second-line chemotherapy was 30% (95% CI, 15% to 50%).

Mutation Status of the EGFR Gene

Out of 42 enrolled patients, 16 patients were diagnosed pathologically, 22 were diagnosed cytologically, and four patients recurred after surgical resection. Biopsied specimens were available in nine patients. Therefore, tissue samples were available in a total of 13 patients. These 13 patients included four PRs, six with stable disease, and three PDs. EGFR mutations were detected in four tumor tissues, including the in-frame nucleotide deletions in exon 19 ($n = 3$) and an L858R mutation in exon 21 ($n = 1$). One tumor had an in-frame deletion and

Table 4. Four Patients Developed Interstitial Lung Disease During First-Line Chemotherapy With Gefitinib, With Another Four Patients Showing ILD During Either Second- or Third-Line Chemotherapy

Age (years)	Sex	Smoking Index	Pathology	Onset of ILD	Response to Gefitinib	Death From Chemotherapy
61	M	1,520	AD	Day 23*	PD	Day 74
64	M	880	AD	Day 45*	SD	Day 51
67	M	1,880	SQ	Day 37†	PD	Day 45
59	F	0	AD	Day 21*	PD	Day 35
61	M	820	AD	Day 131‡	SD	Day 154
68	M	2,000	LA	Day 37‡	PD	Day 106
68	M	705	AD	Day 22§	PR	Day 87
59	M	1,170	AD	Day 108	SD	Alive

Abbreviations: ILD, interstitial lung disease; M, male; F, female; AD, adenocarcinoma; SQ, squamous cell carcinoma; LA, large-cell carcinoma; PD, progressive disease; SD, stable disease; PR, partial response.

*During gefitinib administration.

†One week after discontinuation of gefitinib.

‡After 2nd-line chemotherapy of cisplatin and vinorelbine.

§ After 2nd-line chemotherapy of cisplatin and gemcitabine.

|| After 3rd-line chemotherapy of docetaxel.

Table 5. Interstitial Shadow on Pretreatment Chest Computed Tomography Films and ILD

Interstitial Shadow on Pretreatment Chest Computed Tomography Scans	No ILD	ILD
No existence	29	5
Existence	3	3

NOTE. $P = .0819$.

Abbreviation: ILD interstitial lung disease.

an E746V mutation in exon 19. All four PR patients had *EGFR* mutations (Table 6).

DISCUSSION

This phase II study was designed to evaluate the efficacy and safety of first-line single agent treatment with gefitinib in patients with advanced NSCLC. There is no other paper that evaluates single agent treatment with gefitinib prospectively in patients with advanced NSCLC. The observed response rate of 30% (95% CI, 17% to 47%), median survival of 13.9 months and 1-year survival of 55% are promising. However, grade 5 ILD occurred in 10% (95% CI, 3% to 24%) of patients. This high rate of ILD was not acceptable. The incidence of ILD was seen to be less than 1% in two randomized controlled studies comparing gefitinib with placebo in combination with gemcitabine and cisplatin or paclitaxel and carboplatin.^{12,13} The reason for the high incidence of ILD observed in our study is unknown. The West Japan Thoracic Oncology Group analyzed 1,976 patients receiving gefitinib retrospectively. In this case, the incidence of ILD was 3.2% (95% CI, 2.5% to 4.6%) and the death rate due to ILD was 1.3% (95% CI, 0.8% to 1.9%). Multivariate analyses found that risk factors in-

cluded being male, individuals who smoked, and complication of interstitial pneumonia.¹⁴ Our retrospective analyses revealed that three of six patients with interstitial shadow on pretreatment chest CT films, but not detected on chest x-ray films developed ILD; on the other hand, five of 34 patients without interstitial shadow developed ILD. Interstitial shadow on pretreatment chest CT was a marginally significant risk factor of ILD ($P = .0819$). It might be suggested that patients with interstitial shadow on pretreatment chest CT films be excluded from administration of gefitinib; however, our analyses were biased because we analyzed retrospectively and did not blind patient clinical information. Prospective analysis is needed to evaluate interstitial shadow by chest CT before treatment with gefitinib.

The Southwest Oncology Group conducted a phase II trial to evaluate gefitinib in patients with advanced bronchioloalveolar carcinoma (SWOG 0126). Previously untreated ($n = 102$) and treated ($n = 36$) patients were entered and eligible in SWOG 0126. The response rate was 19% and the median survival time was 12 months in the untreated population.¹⁹ These subset analyses were comparable to our results.

Recently, mutations in the tyrosine kinase domain of *EGFR* were found to be associated with gefitinib sensitivity in patients with NSCLC.^{16,20,21} Our retrospective analyses demonstrated that *EGFR* mutations were detected in four of 13 patients, and those four patients achieved PR in the single agent treatment of gefitinib. These results were compatible with previous reports.^{16,20,21}

Thirty patients received second-line chemotherapy, including platinum-based ($n = 27$) and nonplatinum-based ($n = 3$) regimens; the response rate was 30%. Pretreatment with gefitinib does not seem to adversely affect the response of second-line chemotherapy. However, our small-scale study does not suggest the best second-line regimen. Platinum combined with any third-generation agents including paclitaxel, docetaxel, vinorelbine,

Table 6. Mutation Status of the *EGFR* Gene

Sex	Age (years)	Pathologic Type	Smoking Status	Overall Survival (months)	<i>EGFR</i> Gene	Effect of Mutation	Response to Gefitinib	Response to Second Line Chemotherapy
M	68	AD	Current	14.9	Deletion of 15 nucleotides (2236-2250)	In-frame deletion (E746-A750)	PR	PD
F	67	AD	Current	16.2	Deletion of 15 nucleotides (2236-2250)	In-frame deletion (E746-A750)	PR	PD
F	54	AD	Current	5.6	Deletion of 18 nucleotides (2238-2255) and substitution of T for A at nucleotides 2237	In-frame deletion (L747-S752) and amino acid substitution (F746V)	PR	NR
F	57	AD	Never	25.4	Substitution of G for T at nucleotide 2573	Amino acid substitution (L858R)	PR	SD
M	61	AD	Current	7.5	Wild	—	SD	SD
M	54	AD	Current	9.7	Wild	—	SD	SD
M	45	AD	Current	16.2	Wild	—	SD	PR
M	59	AD	Current	14.7	Wild	—	SD	PR
M	67	SQ	Current	2.4	Wild	—	SD	NR
M	59	AD	Current	24.9	Wild	—	SD	PR
M	61	AD	Current	2.4	Wild	—	PD	NR
F	61	SQ	Current	3.4	Wild	—	PD	PD
F	61	AD	Current	16.3	Wild	—	PD	PR

Abbreviations: *EGFR*, epidermal growth factor receptor; M, male; F, female; AD, adenocarcinoma; SQ, squamous cell carcinoma; PR, partial response; SD, stable disease; PD, progressive disease; NR, not received.