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clinical

Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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(Received April 28, 2004/Revised June 23, 2004/Accepted June 25, 2004)

To determine the recommended phase II dose of vinorelbine in combination with cisplatin and thoracic radiotherapy (TRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), 18 patients received cisplatin (80 mg/m^2) on day 1 and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) on days 1 and 8 every 4 weeks for 4 cycles. TRT consisted of a single dose of 2 Gy once daily for 3 weeks followed by a rest of 4 days, and then the same TRT for 3 weeks to a total dose of 60 Gy. Fifteen (83%) patients received 60 Gy of TRT and 14 (78%) patients received 4 cycles of chemotherapy. Ten (77%) of 13 patients at level 1 and all 5 patients at level 2 developed grade 3–4 neutropenia. Four (31%) patients at level 1 and 3 (60%) patients at level 2 developed grade 3–4 infection. None developed ≥grade 3 esophagitis or lung toxicity. Dose-limiting toxicity was noted in 33% of the patients in level 1 and in 60% of the patients in level 2. The overall response rate (95% confidence interval) was 83% (59–96%) with 15 partial responses. The median survival time was 30.4 months, and the 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively. In conclusion, the recommended dose is the level 1 dose, and this regimen is feasible and promising in patients with stage III NSCLC. (Cancer Sci 2004; 95: 691–695)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases.[1] Successful treatment of this disease rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases, and therefore a combination of systemic chemotherapy and thoracic radiotherapy is indicated in many patients with good performance status and no pleural effusion.[2] Concurrent chemoradiotherapy is superior to the sequential approach, as shown by recent phase III trials in unresectable stage III NSCLC, in which the median survival time was 15.0 to 17.0 months in the concurrent arm and 13.3 to 14.6 months in the sequential arm, although acute esophagitis was more severe in the concurrent arm.[3–5] Chemotherapy regimens combined with simultaneous thoracic radiotherapy have consisted of cisplatin plus etoposide and cisplatin plus vinca alkaloids,[3,4] and a combination of cisplatin plus vindesine, with or without mitomycin, has been widely used in Japan.[5–8]

Vinorelbine, a new semisynthetic vinca alkaloid with a substitution in the catharanthine ring, interacts with tubulin and microtubule-associated proteins in a manner different from the older vinca alkaloids, and it more selectively depolymerizes microtubules in mitotic spindles.[9] Several randomized trials have shown vinorelbine to be more active against advanced or metastatic NSCLC than vindesine as a single agent or in combination with cisplatin.[10–13] Thus, incorporation of vinorelbine into concurrent chemoradiotherapy instead of vindesine is an important strategy for the treatment of locally advanced NSCLC. The objective of this study was to determine the maximum tolerated dose (MTD) and recommended dose of vinorelbine for phase II studies in combination with cisplatin, with or without mitomycin, and thoracic radiotherapy for patients with unresectable stage III NSCLC. We planned to start with the cisplatin and vinorelbine combination and then add mitomycin.

Patients and Methods

Patient selection. The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14]; adequate bone marrow function (12.0×10^9/liter ≥white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min); and a PaO_2 of 70 Torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment evaluation. The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment schedule. The dose levels and doses of each anticancer agent are shown in Table 1. Cisplatin and vinorelbine were administered at dose levels 1 and 2. It was planned to give cisplatin, vinorelbine, and mitomycin at dose levels 3–5, but because the MTD was determined to be dose level 2, dose levels 3–5 were not used. Cisplatin was administered on day 1 by intravenous infusion over 60 min together with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 40 ml of normal saline was administered by bolus intravenous injection on days 1 and 8. All patients received prophylactic antiemetic ther-

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apy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 4 weeks for 4 cycles.

Thoracic radiotherapy with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV at a single dose of 2 Gy once daily given 15 times over 3 weeks was begun on day 2 of the first cycle of cisplatin and vinorelbine chemotherapy, and followed by a short rest period of 4 days. The same radiotherapy was begun on day 1 of the second cycle of chemotherapy to a total dose of 60 Gy. The clinical target volume (CTV) was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes whose short diameter was 1 cm or larger (CTV2), and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3 with the superior and inferior field margins extended to 1 to 2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The boost PTV included only CTV1–2 based on the second CT scans with the same margins. The spinal cord dose was limited to 40 Gy by using oblique parallel opposed fields.

Toxicity assessment and treatment modification. Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria version 2.0 issued in 1998, and late toxicity associated with thoracic radiotherapy was graded according to the RTOG Late Radiation Morbidity Scoring Schema.[15] Vinorelbine administration on day 8 was omitted if any of the following toxicities was noted: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. The doses of cisplatin and vinorelbine were reduced by 25% in all subsequent cycles if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, or grade 3 or severer non-hematological toxicity, except for nausea and vomiting. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, esophagitis ≥grade 3, fever ≥38°C, performance status ≥3, or PaO_2 <70 Torr. Thoracic radiotherapy was terminated if this toxicity persisted for more than 2 weeks. Granulocyte colony-stimulating factor support was used if the neutrophil count was $<0.5\times10^9$/liter for more than 4 days, the WBC count was $<1.0\times10^9$/liter, or febrile neutropenia ≥grade 3 was noted.

Dose-limiting toxicity, MTD, and recommended dose for phase II studies. The dose-limiting toxicity (DLT) was defined as a neutrophil count $<0.5\times10^9$/liter lasting 4 days or longer, febrile neutropenia ≥grade 3, platelet count $<20\times10^9$/liter, grade 3 or more severe non-hematological toxicity other than nausea and vomiting, and patient's refusal to receive subsequent treatment. Doses were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If one or none of them experienced DLT, the next cohort of patients was treated at the next higher dose level. If 2 of the 6 patients experienced DLT, then 6 additional patients were enrolled at the same dose level to make a total of 12 patients. If 4 or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. If 3 of the initial 6 patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response evaluation. Objective tumor response was evaluated according to the WHO criteria issued in 1979.[16] A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) was defined as an at least 50% decrease in total tumor size for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions.

Study design, data management, and statistical considerations. This study was designed as a phase I study at two institutions, the National Cancer Center Hospital and Kanagawa Cancer Center. The protocol and consent form were approved by the Institutional Review Board of each institution. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 18 months were planned. Overall survival time and progression-free survival time were estimated by the Kaplan-Meier method.[17] Survival time was measured from the date of registration to the date of death due to any cause. Progression-free survival time was measured from the date of registration to the date of disease progression or death. Patients who were lost to follow-up without event were censored at the date of their last known follow-up.

Table 1. Dose level and the dose of each anticancer agent

Dose level	Cisplatin (mg/m²)	Vinorelbine (mg/m²)	Mitomycin (mg/m²)
−1	80	15	—
1	80	20	—
2	80	25	—
3	80	15	8
4	80	20	8
5	80	25	8

Results

Registration and characteristics of the patients. From October 1999 to August 2000, 13 patients were registered at dose level 1 and 5 patients at dose level 2. The detailed demographic characteristics of the patients are listed in Table 2. All patients had unresectable IIIA-N2 or IIIB disease. One of the 6 patients enrolled at dose level 1 developed bacterial meningitis during the second cycle of chemotherapy, and that case is described in detail elsewhere.[18] We did not include it in the assessment of DLT, because the bacterial meningitis was not specifically related to treatment. We registered another patient at the same dose level, and 2 cases of DLT were noted among the initial 6 patients evaluable for DLT. We added another 6 patients, and DLT was noted in 4 of the 12 patients registered at the dose level 1. Of the 5 patients registered at level 2, 3 patients developed DLT. This dose level was determined to be the MTD, and patient accrual to this study was terminated.

Treatment delivery. Treatment delivery was generally well maintained, and it did not differ between the two dose levels (Table 3). Full dose (60 Gy) thoracic radiotherapy was completed in 77% and 100% of the patients at dose levels 1 and 2,

Table 2. Patients' characteristics

		Median (range)	N (%)
Number of patients			18
Gender	male		16 (89)
	female		2 (11)
Age	median (range)	59 (48–69)	
PS	0		4 (22)
	1		14 (78)
Body weight loss	<5%		12 (67)
	5–9%		4 (22)
	≥10%		2 (11)
T-factor	1		1 (6)
	2		6 (33)
	3		7 (39)
	4		4 (22)
N-factor	2		11 (61)
	3		7 (39)
Clinical stage	IIIA		9 (50)
	IIIB		9 (50)
Histology	adenocarcinoma		14 (78)
	squamous cell carcinoma		3 (17)
	adenosquamous carcinoma		1 (6)

Table 3. Treatment delivery

	Dose level 1 (N=13)	Dose level 2 (N=5)
	N (%)	N (%)
Initial irradiation field (cm^2) median (range)	171 (128–529)	182 (128–248)
Total dose of radiotherapy (Gy)		
60	10 (77)	5 (100)
50–59	1 (8)	0
<50	2 (15)	0
Delay of radiotherapy (days)[1]		
<5	6 (60)	3 (60)
5≤	4 (40)	2 (40)
Number of chemotherapy cycles		
4	10 (77)	4 (80)
3	0	1 (20)
2	2 (15)	0
1	1 (8)	0
Omission of vinorelbine administration on day 8		
0	9 (69)	2 (40)
1	4 (31)	2 (40)
3	0	1 (20)

1) Evaluated in patients who received 60 Gy radiotherapy (N=15).

respectively. Delays in radiotherapy evaluated in patients who completed the full course of radiotherapy amounted to less than 5 days in 60% of the patients at both levels. Full cycles (4 cycles) of chemotherapy were administered to 77% and 80% of the patients at dose levels 1 and 2, respectively, but vinorelbine administration on day 8 was more frequently omitted at dose level 2 (Table 3).

Toxicity, MTD, and the recommended dose for phase II trials. Acute severe toxicity was mainly hematological (Table 4). Grade 3–4 leukopenia and neutropenia were noted in 77% and 100% of the patients at dose levels 1 and 2, respectively. Grade 3 anemia was observed in 23% and 20% of the patients at dose levels 1 and 2, respectively, but no blood transfusions were required. Thrombocytopenia was mild. Grade 4 transaminase elevation was observed in 1 patient during the first cycle of chemotherapy, but no subjective manifestations associated with liver dysfunction were noted. Chemotherapy was discontinued and the transaminases quickly decreased to within their normal ranges. Transient asymptomatic grade 3 hyponatremia was noted in 1 patient. Grade 3–4 infection was noted in 7 patients. Bacterial meningitis unassociated with neutropenia developed on day 6 of the second cycle of chemotherapy in 1 patient.[18] The other grade 3–4 infections were all associated with neutropenia. Esophagitis was mild in this study, and no grade 3–4 esophagitis was noted. No deaths occurred during or within 30 days of therapy.

DLT was noted in 4 of the 12 (33%) evaluable patients at dose level 1, and in 3 of the 5 (60%) at dose level 2. Six of these 7 DLTs were grade 3–4 infection associated with neutropenia, and the other 1 was grade 4 transaminase elevation. Thus, we determined that dose level 2 was the MTD, and dose level 1 was recommended as the dose for phase II trials.

Table 4. Acute toxicity

Toxicity	Dose level 1 (*N*=13), Grade					Dose level 2 (*N*=5), Grade				
	1	2	3	4	3–4 (%)	1	2	3	4	3–4 (%)
Hematological										
Leukopenia	0	2	9	1	(77)	0	0	4	1	(100)
Neutropenia	1	1	7	3	(77)	0	0	1	4	(100)
Anemia	4	6	3	0	(23)	2	2	1	0	(20)
Thrombocytopenia	1	2	0	0	(0)	1	0	0	0	(0)
Non-hematological										
AST	2	0	0	1	(8)	1	0	0	0	(0)
ALT	7	0	0	1	(8)	0	1	0	0	(0)
Total bilirubin	2	1	0	0	(0)	2	0	0	0	(0)
Creatinine	2	2	0	0	(0)	1	0	0	0	(0)
Hyponatremia	6	0	1	0	(8)	1	0	0	0	(0)
Infection	1	3	2	2	(31)	0	0	3	0	(60)
Nausea	4	1	0	0	(0)	3	0	0	0	(0)
Diarrhea	0	1	0	0	(0)	0	0	0	0	(0)
Stomatitis	2	0	0	0	(0)	0	2	0	0	(0)
Esophagitis	6	1	0	0	(0)	4	0	0	0	(0)
Sensory neuropathy	2	0	0	0	(0)	0	0	0	0	(0)

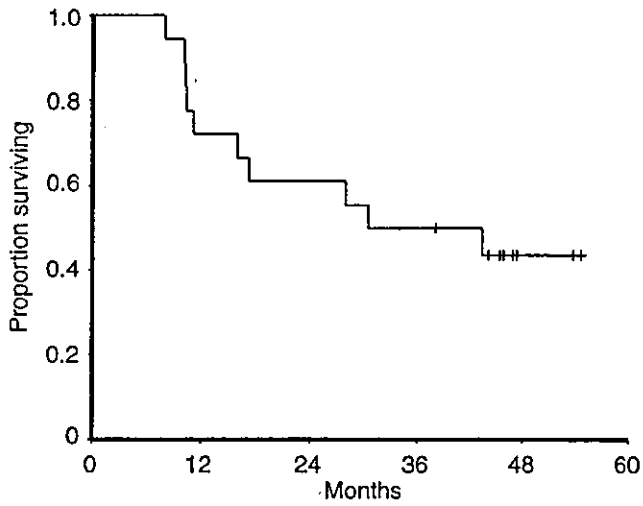

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

Late lung toxicity associated with thoracic radiotherapy was grade 3 in 1 (6%) patient, grade 2 in 4 (22%) patients, and grade 1 in 8 (44%) patients. No late esophageal toxicity was noted.

Objective responses, relapse pattern, and survival. All patients were included in the analyses of tumor response and survival. No CR, 15 PRs, and 1 NC were noted, and the overall response rate (95% confidence interval) was 83% (59–96%). Relapse was noted in 12 (67%) of 18 patients. Initial relapse sites were locoregional alone in 5 (28%) patients, locoregional and distant in 3 (17%) patients, and distant alone in 4 (22%) patients. Brain metastasis was detected in 5 patients, and the brain was the most frequent site of distant metastasis. The median progression-free survival time was 15.6 months, and the median overall survival time was 30.4 months. The 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively (Fig. 1).

Discussion

The combination of cisplatin, vindesine, and mitomycin with concurrent thoracic radiotherapy has been shown to yield an encouraging survival outcome, a median survival time of 17–19 months, and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC.[5,7,8] A Japanese randomized trial revealed that replacement of vindesine by vinorelbine in combination with cisplatin and mitomycin yielded a promising response rate (57% versus 38%, P=0.025) and median survival time (15 months versus 11 months, P<0.01) in patients with stage IIIB or IV NSCLC.[13] Thus, the combination of cisplatin, vinorelbine, and mitomycin is a chemotherapy regimen with potential for combination with concurrent thoracic radiotherapy. The present study, however, showed that a DLT developed in 60% of patients who received cisplatin and vinorelbine 25 mg/m^2 days 1 and 8 (level 2), and since the DLTs were associated with myelosuppression, which is the major critical toxicity of mitomycin, we concluded that it would be impossible to incorporate mitomycin into this regimen.

The recommended doses of vinorelbine of 20 mg/m^2 on days 1 and 8 and cisplatin of 80 mg/m^2 on day 1 repeated every 4 weeks in this study are comparable to the doses used in the CALGB (vinorelbine 15 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 repeated every 3 weeks),[19,20] and the Czech Lung Cancer Cooperative Group (vinorelbine 12.5 mg/m^2 on days 1, 8, and 15 and cisplatin 80 mg/m^2 on day 1, repeated every 4 weeks),[21] but lower than in a Mexican study (vinorelbine at 25 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks).[22] These recommended doses are also lower than expected when compared with the recommended vinorelbine dose combined with cisplatin for metastatic NSCLC (vinorelbine 30 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1, repeated every 3 weeks),[23] and when compared with the results of vindesine, cisplatin, and mitomycin combined with thoracic radiotherapy, where the full doses can be administered concurrently.[8] Thus, vinorelbine can be safely administered with cisplatin and concurrent thoracic radiotherapy at a maximum dose of two-thirds the optimal dose without radiotherapy.

The results for response and survival in this study, however, were very encouraging. This may have been attributable to patient selection bias, but the percentage of patients who had stage IIIB disease in this study was similar to the percentage in the CALGB randomized phase II study.[20] In addition, 33% of the patients in this study had ≥5% body weight loss, whereas only 7% of the patients did in that study.[20] The median survival time was 30.4 months and exceeded the results of concurrent

chemoradiotherapy with old drug combinations that yielded a median survival time of 15–19 months.[3–8] Thus, it could be argued that the combination of cisplatin and vinorelbine is more active for locally advanced NSCLC than the older drug combinations, although there have not been any randomized trials comparing this regimen with old drug combinations in combination with thoracic radiotherapy in patients with stage III NSCLC. Our results also seem better than those of other trials using concurrent cisplatin, vinorelbine, and thoracic radiotherapy, in which the median survival time was 13 to 18 months.[20,22] Those trials used induction chemotherapy followed by chemoradiotherapy. Since the response rate to induction chemotherapy is no more than 40%, induction chemotherapy may be disadvantageous. This issue is being evaluated in an on-going CALGB phase III trial.

Severe esophagitis and pneumonitis have been DLTs in many trials of concurrent chemoradiotherapy, but neither was observed in this study. Nevertheless, since the occurrence of these non-hematological toxicities associated with thoracic radiotherapy is sporadic, the sample size in this study may have been too small to detect them. Thus, careful observation for these toxicities is needed in further phase II and phase III trials to definitely establish the safety profile of this regimen.

In conclusion, cisplatin and vinorelbine chemotherapy combined with concurrent full-dose thoracic radiotherapy is feasible, and the recommended dose of vinorelbine for phase II trials is 20 mg/m^2 on days 1 and 8 repeated every 4 weeks. This regimen was highly active in patients with stage III NSCLC.

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan, and was presented in part at the 42th Annual Meeting of the Japan Lung Cancer Society, Osaka, Japan, November 1–2, 2001. We thank Ms. Yuko Yabe for preparation of the manuscript.

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Lung Cancer (2004) 45, 93–104

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Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib

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Received 22 September 2003; received in revised form 2 January 2004; accepted 9 January 2004

KEYWORDS
Gefitinib;
Non-small cell lung cancer;
Interstitial lung diseases;
Pulmonary fibrosis;
Risk factors;
Predictive factors

Summary A high incidence of interstitial lung disease (ILD) has been reported in patients with non-small cell lung cancer (NSCLC) treated with gefitinib in Japan. We retrospectively analyzed 112 patients with advanced NSCLC who received gefitinib monotherapy. Univariate and multivariate analyses were used to identify risk factors for gefitinib-related ILD and predictive factors for tumor response to gefitinib. The incidence of ILD was 5.4%, and it was higher in the patients with pre-existing pulmonary fibrosis (33% versus 2%; $P < 0.001$). The results of a multivariate analysis showed that pulmonary fibrosis was a significant risk factor for ILD (odds ratio: 177, 95% confidence interval: 4.53–6927, $P = 0.006$). The response rate was 33% in the 98 evaluable patients and higher in women (53% versus 23%; $P = 0.003$), patients with adenocarcinoma (38% versus 6%; $P = 0.010$), never-smokers (63% versus 18%; $P < 0.001$), and the patients with no history of thoracic radiotherapy (39% versus 13%; $P = 0.015$). The results of a multivariate analysis showed that the predictors of tumor response were "no history of smoking" and "no history of thoracic radiotherapy". Never-smokers had a significantly longer survival time than smokers ($P = 0.007$). Although gefitinib therapy confers a clinical benefit on patients with advanced NSCLC, especially on women, patients with adenocarcinoma, never-smokers, and patients with no history of thoracic radiotherapy, it also poses a high risk of ILD, especially to patients with pulmonary fibrosis. The risk-benefit ratio must be carefully considered.

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doi:10.1016/j.lungcan.2004.01.010

1. Introduction

Gefitinib (Iressa®; AstraZeneca, Osaka, Japan) is an orally available, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that displays antitumor activity in patients with previously treated advanced non-small cell lung cancer (NSCLC). The safety and tolerability of gefitinib was established in four open-labeled, multicenter, phase I dose-escalation studies [1–4]. Although diarrhea, skin rash/acne, and nausea were common adverse effects, most of them were mild. Two large-scale, multicenter, randomized phase II studies (IDEAL 1 and 2; Iressa® Dose Evaluation in Advanced Lung Cancer) have demonstrated clinically significant antitumor activity of gefitinib monotherapy in patients with advanced NSCLC who had previously received platinum-based chemotherapy [5,6]. The response rate for gefitinib 250 mg per day in the IDEAL 1 and 2 trials was 18.4 and 11.8%, respectively. These studies also showed that gefitinib monotherapy significantly improved disease-related symptoms and quality of life.

Based on the results of the IDEAL trials, gefitinib was approved in Japan for the treatment of inoperable or recurrent NSCLC on 5 July 2002, and an estimated 28,300 patients had been treated with gefitinib as of April 2003. During the first few months after its approval, many patients demanded to be treated with gefitinib as a "magic bullet" cure; however, when the incidence of interstitial lung disease (ILD) came to light in October 2002, the media reported it in a sensational manner, and as a result patients have become confused by excessive expectations and fear of ILD. The Ministry of Health, Labour and Welfare of Japan reported that the number of gefitinib-related cases of ILD had reached 616 as of 22 April 2003 and that 246 of the patients had died of it. The incidence of ILD and mortality rate from it has been calculated at 2.2 and 0.87%, respectively. Some case reports also suggested a high incidence of gefitinib-related ILD in Japan [7]. In view of this situation, an evidence-based assessment of the risk-benefit of gefitinib for the treatment of NSCLC was urgently needed. However, many questions regarding gefitinib administration remained unanswered, particularly in regard to the risk factors associated with ILD complications. We therefore analyzed a series of cases treated with gefitinib at the National Cancer Center Hospital (NCCH) in Tokyo.

2. Patients and methods

Between July and December 2002, 115 NSCLC patients at the NCCH began taking gefitinib and the 112 of these patients who were followed at the NCCH were retrospectively analyzed in this study. The other three patients were excluded from the analysis because they were followed-up at other hospitals after the first prescription of gefitinib. All the 112 patients had histologically or cytologically confirmed NSCLC. Their disease was locally advanced, recurrent, and/or metastatic. They all received gefitinib monotherapy at a dose of 250 mg per day.

Two independent board-certified diagnostic radiologists (M.K. and U.T.) diagnosed pre-existing pulmonary fibrosis (PF) on the basis of the findings on chest X-rays taken within 1 week of the start of gefitinib therapy. The radiologists had no knowledge of the patients' outcome. The diagnostic criteria for PF were a diffuse linear or honey-comb pattern on chest X-rays that was predominant in the lower zone of the lung.

If a patient had measurable disease, the World Health Organization criteria were used to assess the tumor response. The response rate was calculated as the total percentage of patients with a complete or partial response. Drug-related adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria (Version 2.0). Chest X-rays were performed periodically to evaluate response and detect pulmonary toxicity, and computed tomography scans of the chest were performed as needed to confirm the response or diagnose ILD. The extent of patients' smoking history was evaluated by using pack-years, which are defined as the average number of cigarettes smoked per day multiplied by the total duration of smoking in years divided by 20. Patients who had smoked for 0, 1–39, and ≥40 pack-years were categorized as "never-smokers", "moderate smokers", and "heavy smokers", respectively.

Univariate and multivariate analyses were performed to identify risk factors for ILD and predictive factors for tumor response to gefitinib. The patient characteristics tested as potential risk factors for ILD and predictive factors for tumor response were age (<70 versus ≥70 years in the univariate analysis and as a continuous variable in the multivariate analysis), sex (female versus male), histological diagnosis (adenocarcinoma versus non-adenocarcinoma), smoking history (never-smokers versus moderate/heavy smokers), performance status (PS 0–1 versus PS 2–3), prior surgery (yes versus no), prior chemotherapy (yes versus no), prior thoracic radiotherapy (yes versus no), and PF (yes versus no). These factors were compared by using a chi-square test in the univariate analysis. Logistic regression analyses were also performed to adjust for each factor. Differences

in time to treatment failure (TTF) and overall survival (OS) among the subgroups were compared by using Kaplan–Meier curves and log-rank tests. TTF was defined as the interval between the start of gefitinib administration and discontinuation of treatment for any reason, confirmed disease progression, or death. All analyses were performed using SPSS statistical package (SPSS version 11.0 for Windows, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

The patient characteristics are listed in Table 1. All patients were Japanese. Twenty-eight patients (25%) received gefitinib as a first-line treatment; 19 were considered unfit for platinum-based chemotherapy because of poor PS (10 patients) or advanced age (9 patients), and 9 refused platinum-based chemotherapy. The diagnosis of pre-existing PF was almost the same between two radiologists. Although discordance occurred in three cases, 12 patients were finally diagnosed as PF by consensus. All of the 12 patients had computed tomography findings consistent with idiopathic pulmonary fibrosis/usual interstitial pneumonia.

3.2. Interstitial lung disease (ILD) and other toxicities

Among the 112 patients reviewed, ILD developed in 6 (5.4%) during the course of gefitinib therapy, and 4 patients (3.6%) died from ILD. The characteristics of the six patients with ILD are listed in Table 2. All of them had acute onset or exacerbation of respiratory symptoms. In five patients, chest computed tomography scanning revealed new diffuse interstitial changes in both lungs with ground-glass appearances. Because bronchoalveolar lavage or lung biopsy was not performed, we cannot completely exclude lymphangiosis carcinomatosa or other diseases, but the clinical courses and imaging appearances were consistent with drug-induced ILD. Although the other patient (patient 3) died before imaging diagnosis, the autopsy revealed diffuse alveolar damage, and we concluded she died from gefitinib-related ILD.

The results of univariate and multivariate analyses on risk factors for ILD are shown in Table 3. The incidence of ILD was 33% (4/12) among patients with PF and 2.0% (2/100) among the other patients. PF was the only significant risk factor for ILD in the univariate analysis (odds ratio [OR]: 16.7, 95% confidence interval [95% CI]: 3.40–83.3, $P < 0.001$), and this finding was supported by the results of the multivariate analysis (OR: 177, 95% CI: 4.53–6927, $P = 0.006$). Since all of the patients with ILD were smokers, pack-years were analyzed as a continuous variable in the multivariate analysis, and the results of it suggested the association between increased pack-years and a higher risk of ILD ($P = 0.062$). Since all of the ILD cases had a PS score of 1 and had never undergone thoracic radiotherapy, it was impossible to assess the association between poor PS or prior thoracic radiotherapy and ILD in the multivariate analysis.

Table 1 Patient characteristics

	Patients ($n = 112$)	
	No.	%
Age		
Median (range) (years)	63 (29–83)	
<70 years	80	71
≥70 years	32	29
Sex		
Female	35	31
Male	77	69
Histological diagnosis		
Adenocarcinoma	93	83
Squamous cell carcinoma	12	11
Non-small cell carcinoma (not specified)	6	5
Large cell neuroendocrine carcinoma	1	1
Smoking history (pack-years)		
Never-smokers (0)	34	30
Moderate smokers (1–39)	30	27
Heavy smokers (≥40)	48	43
ECOG performance status		
0–1	92	82
2–3	20	18
Stage		
IIIA/IIIB	21	19
IV	58	52
Recurrence after surgery	33	29
Prior chemotherapy		
Yes	84	75
No	28	25
Prior thoracic radiotherapy		
Yes	26	23
No	86	77
Pre-existing pulmonary fibrosis		
Yes	12	11
No	100	89

Table 2 Characteristics of patients who developed interstitial lung disease

	Age (years)	Sex	Histological diagnosis	PS	PY	Stage	Prior chemotherapy		Thoracic radiotherapy	Pre-existing lung disease	Length of treatment (days)	Survival (days)
							First	Second				
1	66	M	Ad	1	44	IIIB	CDDP+VNR	DTX	No	PF	10	22[a]
2	69	M	Ad	1	28	IV	CBDCA+PTX	–	No	PF	32	67[a]
3	52	F	Ad	1	48	IV	CDDP+GEM	–	No	None	42	42[a]
4	71	M	Ad	1	51	IIIB	UFT	–	No	PF	47	123[a]
5	64	M	Sq	1	129	IV	CBDCA+PTX	DTX	No	None	18	237[b]
6	74	M	Ad	1	64	Rec	CBDCA+PTX	–	No	PF	39	400[b]

Ad: adenocarcinoma, Sq: squamous cell carcinoma, PS: performance status, PY: pack-years smoked, Rec: recurrence after surgery, CDDP: cisplatin, CBDCA: carboplatin, VNR: vinorelbine, DTX: docetaxel, PTX: paclitaxel, GEM: gemcitabine, PF: pulmonary fibrosis.

[a] Treatment-related death.

[b] Death from lung cancer.

Table 3 Risk factors for interstitial lung disease ($n = 112$)

	No. of patients	Incidence of ILD (%)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	*P*-values	Odds ratio (95% CI)	*P*-values
Total	112	5.4				
Age						
<70 years	80	5.0	0.80 (0.15–4.18)	0.791	2.05 (0.46–9.17)	0.347[a]
≥70 years	32	6.3	1			
Sex						
Female	35	2.9	0.44 (0.053–3.62)	0.428	19.1 (0.44–837)	0.126
Male	77	6.5	1		1	
Histological diagnosis						
Adenocarcinoma	93	5.4	1.02 (0.13–8.26)	0.984	0.26 (0.012–5.46)	0.383
Non-adenocarcinoma	19	5.3	1		1	
Smoking history (pack-years)						
Heavy smokers (≥40)	48	10.4	–	0.096[b]	1.50 (0.98–2.29)	0.062[c]
Moderate smokers (1–39)	30	3.3	–			
Never-smokers (0)	34	0.0	1			
PS						
2–3	20	0.0	0	0.240		
0–1	92	6.5	1			
Prior surgery						
Yes (recurrence)	33	3.0	0.48 (0.056–3.94)	0.480	2.48 (0.14–43.2)	0.534
No (advanced disease)	79	6.3	1		1	
Prior chemotherapy						
Yes	84	7.1	–	0.146		
No	28	0.0	1			
Prior thoracic radiotherapy						
Yes	26	0.0	0	0.166		
No	86	7.0	1			
Pulmonary fibrosis						
Yes	12	33	16.7 (3.40–83.3)	<0.001	177 (4.53–6927)	0.006
No	100	2.0	1		1	

CI: confidence interval.

[a] Age was analyzed as a continuous variable in the multivariate analysis. Odds ratio was calculated per 10-year decrease.

[b] Smoking history was analyzed by comparing never-smokers and moderate/heavy smokers in the univariate analysis.

[c] Smoking history (pack-years) was analyzed as a continuous variable in the multivariate analysis. Odds ratio was calculated per 10-pack-year increase.

The incidence of drug-related adverse events is listed in Table 4. Grade 1 or 2 skin rash (81%) and diarrhea (56%) were the most frequent adverse events. Grades 1–3 elevation in glutamic-oxaloacetic transaminase (GOT) and/or glutamic-pyruvic transaminase (GPT) levels was observed in 46% of the patients.

3.3. Efficacy

Of the 112 patients, 98 had measurable disease. Four patients were not evaluated due to early discontinuation. Complete response, partial response, stable disease, and progressive disease were observed in 2, 30, 29, and 33 patients,

Table 4 Toxicity

	No. of patients evaluated	Grade			
		1	2	3	4
Skin rash	109	59	29	0	0
Diarrhea	109	57	4	0	0
GOT/GPT	106	31	8	10	0
Nausea	109	21	5	0	0
Interstitial lung disease (ILD)	112	0	1	1	4[a]

[a] Treatment-related death.

respectively. The response rate was 33% (32/98). The response rates in each subgroup of patients are listed in Table 5. According to the results of the univariate analysis, female gender ($P = 0.003$), adenocarcinoma ($P = 0.010$), no history of smoking ($P < 0.001$), and no history of thoracic radiotherapy ($P = 0.015$) were significant predictors of tumor response to gefitinib. The response rate of male smokers was 14% (8/56), which was lower than both that of female smokers (40%, $P = 0.052$) and that of male never-smokers (70%, $P < 0.001$). When pack-years were analyzed as a continuous variable among the smokers, the association between

Table 5 Response rates among subgroups of patients ($n = 98$)

	No. of patients	Response rate (%)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	*P*-values	Odds ratio (95% CI)	P values
Total	98	33				
Age						
<70 years	69	36	1.50 (0.76–2.97)	0.244	1.57 (0.96–2.56)	0.071[a]
≥70 years	29	24	1			
Sex						
Female	32	53	2.34 (1.34–4.06)	0.003	1.84 (0.51–6.56)	0.349
Male	66	23	1		1	
Histological diagnosis						
Adenocarcinoma	81	38	6.51 (1.58–26.8)	0.010	4.27 (0.48–37.0)	0.191
Non-adenocarcinoma	17	6	1		1	
Smoking history (pack-years)						
Never-smokers (0)	32	63	3.44 (1.98–5.97)	<0.001[b]	3.92 (1.03–14.9)	0.045[b]
Moderate smokers (1–49)	22	23	1		1	
Heavy smokers (≥50)	44	16				
PS						
0–1	83	31	0.78 (0.38–1.62)	0.510	0.46 (0.10–2.09)	0.314
2–3	15	40	1		1	
Prior surgery						
No (advanced disease)	68	28	0.64 (0.36–1.14)	0.134	1.25 (0.35–4.41)	0.732
Yes (recurrence)	30	43	1		1	
Prior chemotherapy						
No	24	42	1.40 (0.76–2.58)	0.279	1.32 (0.35–4.95)	0.678
Yes	74	30	1		1	
Prior thoracic radiotherapy						
No	74	39	3.14 (1.24–7.90)	0.015	6.76 (1.30–35.7)	0.023
Yes	24	13	1		1	

CI: confidence interval.

[a] Age was analyzed as a continuous variable in the multivariate analysis. The odds ratio was calculated per 10-year decrease.

[b] Smoking history was analyzed by comparing never-smokers and moderate/heavy smokers.

increased pack-years and a lower response rate was also shown (OR per 10-pack-year increase: 0.74, 95% CI: 0.56–0.99, $P = 0.041$).

The results of a multivariate analysis showed that "no history of smoking" ($P = 0.045$) and "no history of thoracic radiotherapy" ($P = 0.023$) were significant predictors of response. It was also suggested that younger patients tended to obtain a higher response rate ($P = 0.071$). Although female gender and adenocarcinoma were not found to be predictive factors in the multivariate analysis, sex and histological diagnosis were significantly associated with smoking history, and these variables may have canceled each other's effect on the dependent variable. The proportion of never-smokers was 69% (22/32) among the women versus 15% (10/66) among the men (correlation coefficient [r] = 0.536, $P < 0.001$), and 67% (54/81) among the patients with adenocarcinoma versus 0% (0/17) among those with non-adenocarcinoma ($r = 0.319$, $P = 0.001$). When a multivariate analysis was performed excluding smoking history as a factor, the OR of the females and patients with adenocarcinoma was 3.81 (95% CI: 1.36–10.7, $P = 0.011$) and 6.45 (95% CI: 0.76–55.6, $P = 0.087$), respectively.

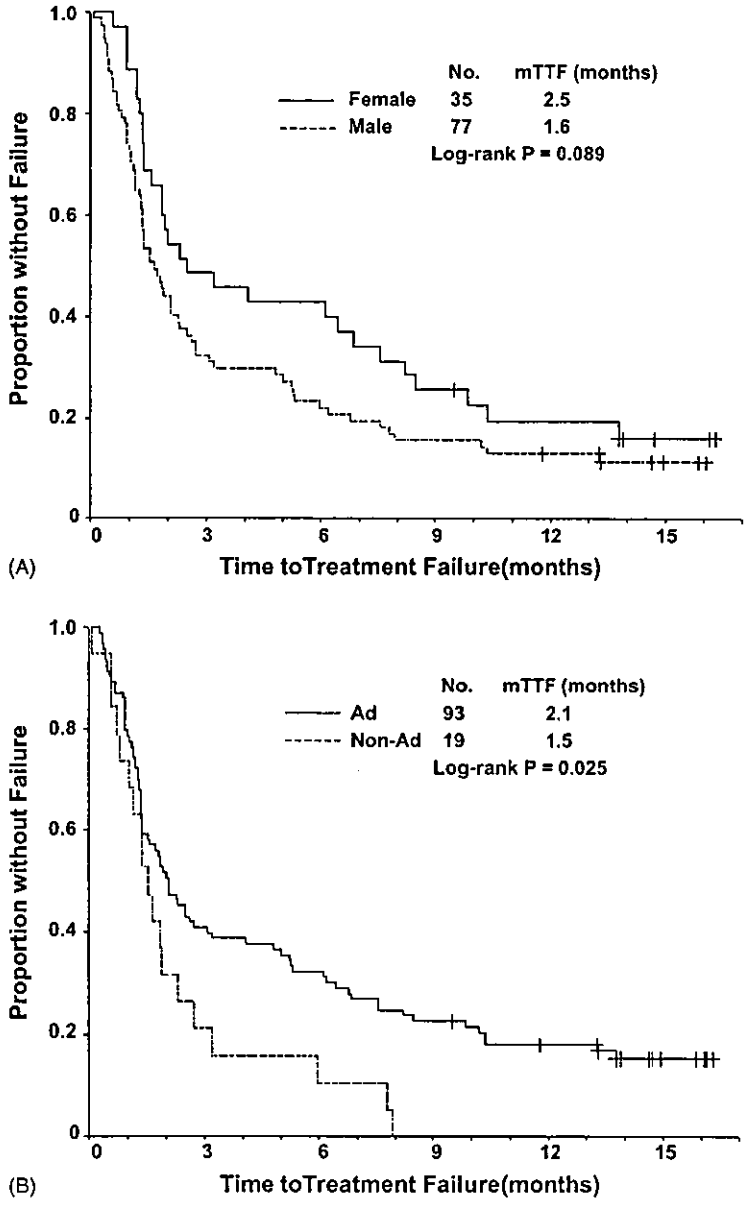


Fig. 1 Kaplan–Meier plot of time to treatment failure according to subgroups: (A) female versus male; (B) adenocarcinoma versus non-adenocarcinoma; (C) never-smokers versus moderate/heavy smokers. mTTF: median time to treatment failure, Ad: adenocarcinoma.

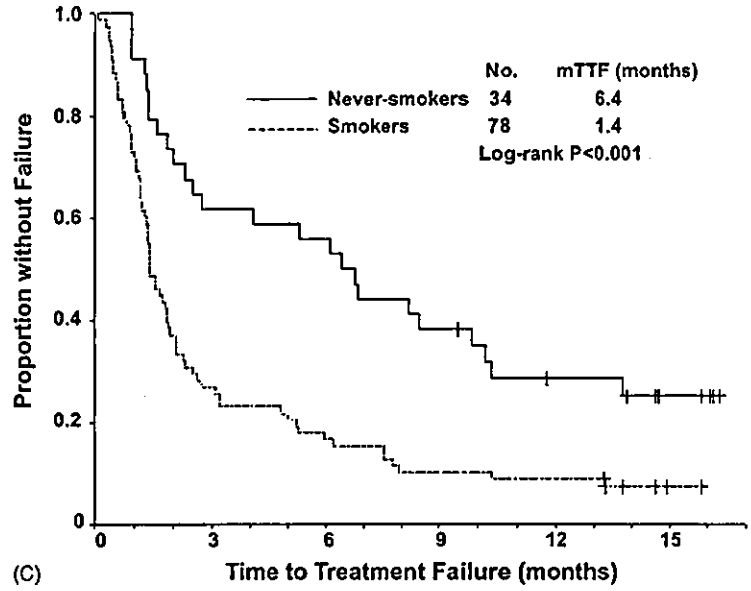


Fig. 1 (*Continued*).

The median follow-up time for survivors was 14.7 months, and ranged from 11.0 to 16.8 months. Sixty-nine patients (62%) died: 65 of disease progression and 4 of toxicity. Gefitinib treatment was terminated in 97 patients (87%) because of disease progression (68 patients), no tumor shrinkage (7 patients), toxicity (19 patients), or at the patients' request (3 patients). The median TTF and the median survival time (MST) for all patients were 1.9 and 10.7 months, respectively. The 1-year survival rate was 45%. The Kaplan–Meier plots of TTF and OS in each subgroup are shown in Figs. 1 and 2. The women had a longer TTF and OS than the men, but the difference was not significant. Patients with adenocarcinoma had a significantly longer TTF than those with non-adenocarcinoma, and "adenocarcinoma" was a marginally significant predictor of longer survival. "No history of smoking" was a highly significant predictor of longer TTF ($P < 0.001$) and longer survival ($P = 0.007$); the MST was 15.3 months in never-smokers and 8.8 months in moderate/heavy smokers.

We observed an association between efficacy and toxicity. As shown in Table 6, those who experienced skin rash or elevation in GOT/GPT levels tended to

Table 6 Association between efficacy and toxicity

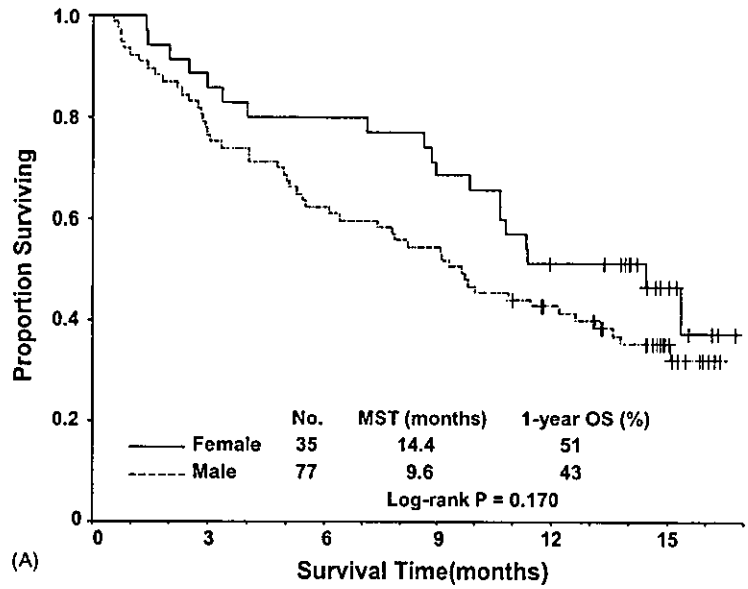
	No. of patients	Response rate (%)	*P*-values*	Median survival (months)	1-year survival (%)	*P*-values†
Skin rash						
Grade 0	21	12	0.043	3.0	24	0.011
Grade 1	59	33		10.6	44	
Grade 2	29	46		15.3	66	
Diarrhea						
Grade 0	48	33	0.903	9.3	35	0.037
Grade 1–2	61	32		13.6	54	
GOT/GPT						
Grade 0	57	21	0.004	7.8	31	0.006
Grade 1	31	48		15.1	55	
Grade 2–3	18	50		Not reached	83	

* *P*-values for chi-square test between grade 0 and 1–3.
† *P*-values for log-rank test.

exhibit a response, and skin rash, diarrhea and elevation in GOT/GPT levels were significant prognostic factors of survival.

4. Discussion

Gefitinib is a promising agent for the treatment of advanced NSCLC, but risk assessment is of critical importance to using it properly. Gefitinib was thought to be a relatively safe agent at first, and physicians in Japan tended to prescribe it without careful consideration of risks. In the first 4 months after its approval, 17,000 patients began taking gefitinib, the most rapid adoption of any antitumor agent in Japan. The Ministry of Health, Labour and Welfare has estimated that the incidence of ILD was 2.2%. However, since a follow-up survey of all of the cases has not been conducted and only limited data from sporadic reports by physicians were available, many ILD cases may not have been reported, and the actual incidence may have been higher than 2.2%. Although the sample size in the present study was small, the incidence of ILD was



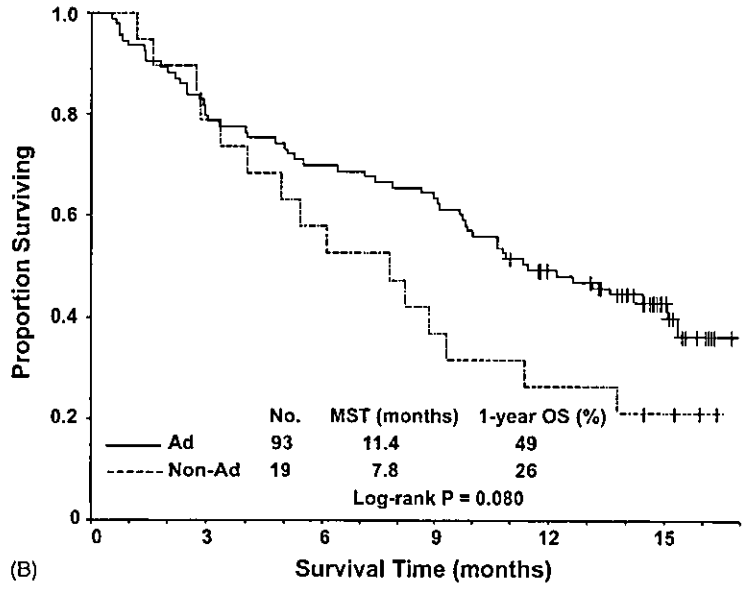


Fig. 2 Kaplan–Meier plot of overall survival according to subgroups: (A) female versus male; (B) adenocarcinoma versus non-adenocarcinoma; (C) never-smokers versus moderate/heavy smokers. MST: median survival time, OS: overall survival, Ad: adenocarcinoma.

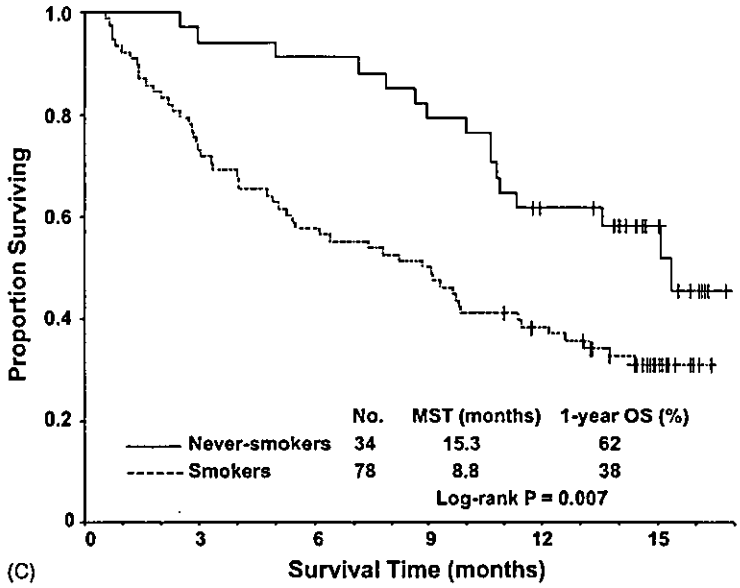


Fig. 2 (*Continued*).

as high as 5.4%. The risk of ILD appears to be around 2–5% if gefitinib is given to patients without careful risk assessment. We think that the incidence can be reduced by patient selection after a thorough risk assessment and that the proper use of gefitinib may enable great benefit, far exceeding its potential risks.

Our analysis of the risk factors for the development of ILD revealed pre-existing PF as a strong risk factor. Of the 112 patients in this study, 12 had PF at the start of gefitinib administration. Four (33%) of these patients subsequently developed ILD, 3 (25%) died as a result, and no response was seen in any of these 12 patients. A panel of experts convened by AstraZeneca Japan retrospectively analyzed 104 patients with NSCLC who developed ILD during gefitinib therapy in Japan and reported that 30 (29%) of them were diagnosed as pre-existing PF by chest X-rays or computed tomography scans taken before gefitinib administration [8]. The panel also noted that the patients with PF had a significantly higher mortality rate after the onset of ILD: it was 77% (23/30) among the patients with PF and 34% (25/74) among the patients without PF ($P < 0.001$) [8]. We conclude that gefitinib treatment may be harmful to patients with PF and recommend that gefitinib not be used if PF is apparent on the chest X-rays.

In our study, all patients were Japanese and a 33% response rate was observed. In the IDEAL 1 trial, 102 Japanese and 106 non-Japanese patients received gefitinib, and the response rate was 27.5% in the Japanese and 10.4% in the non-Japanese [5]. Whether this difference was attributable to ethnicity or an imbalance in other characteristics is unknown, but a high response rate in Japanese patients has been consistently observed in clinical practice.

Both the IDEAL 1 and 2 trials suggested "female gender" and "adenocarcinoma" as predictive factors for tumor response to gefitinib [5,6], and a retrospective analysis of gefitinib monotherapy for advanced NSCLC showed that "adenocarcinoma" (especially with bronchioloalveolar features) and "no history of smoking" were significantly correlated with response to gefitinib [9]. We observed the same tendency with a response rate of 53% in women, 38% in patients with adenocarcinoma, and 63% in never-smokers. "No history of smoking" was a significant predictive factor for response in multivariate analysis, and it was also a significant predictor of longer TTF and longer survival. Since both female gender and adenocarcinoma were significantly associated with no history of smoking, which of these characteristics are true predictive factors remains uncertain. It was also suggested that heavier smokers and male smokers specifically had a lower response rate among the patients with smoking history. Since heavier smokers tended to have a higher risk of ILD, we should carefully assess their risk-benefit ratio of gefitinib therapy before selecting therapeutic strategies.

There are some biological explanations for these clinical characteristics associated with response to gefitinib [10]. Although gefitinib inhibits the intracellular tyrosine kinase domain of EGFR, no correlation between expression of EGFR and response

has been demonstrated [11]. When EGFR and human epidermal growth factor receptor 2 (HER2) are coexpressed, HER2 is the preferred dimerization partner of EGFR, and EGFR-HER2 heterodimers have more signaling potency than EGFR homodimers [12]. Preclinical studies have indicated that tumor cell lines overexpressing HER2 or coexpressing EGFR and HER2 are sensitive to gefitinib [13–16]. Since EGFR/HER2-coexpression is more common in adenocarcinoma of the lung than in squamous cell carcinoma [13,17], the high response rate in adenocarcinoma may be attributable to it. In women, estrogens and estrogen receptors are involved in the development of NSCLC [18], and estrogens binding to its receptors upregulates EGFR and EGFR ligands [19]. The presence of estrogens and its receptors may impact EGFR signaling and the response of NSCLC to gefitinib in women. NSCLC in never-smokers may also have a different biology. Since several studies have indicated fewer mutations of the p53 and K-ras genes in never-smokers than in smokers [20,21], the relation between such tobacco-related mutations and gefitinib response should be investigated. Subgroups of patients who obtain a clinical benefit from gefitinib administration are needed to be identified more precisely, and molecular markers predictive of tumor response should be sought by using DNA microarrays and a proteomics-based approach.

Our analysis suggests that patients who suffer from skin toxicity, diarrhea, or liver toxicity have a greater clinical benefit from gefitinib treatment. A correlation between skin toxicity and survival has also been shown in a study of gefitinib for head and neck cancer [22] and in studies of erlotinib, another EGFR tyrosine kinase inhibitor [23]. Because these findings may be attributable to the responders having taken gefitinib for longer periods and the toxicities in these patients being evaluated more carefully, further studies are needed to confirm them. If the early onset of toxicities has predictive value for survival, it can be used for clinical decision making regarding continuation of gefitinib treatment.

5. Conclusion

When gefitinib is used to treat advanced NSCLC, it confers a higher risk of ILD on patients with PF and a greater clinical benefit on never-smokers, women, patients with adenocarcinoma, and patients with no history of thoracic radiotherapy. Gefitinib therapy is an important treatment option for patients with advanced NSCLC, but the proper use of it based on individual risk-benefit assessments is crucial.

Acknowledgements

This study had no specific funding source.

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ANTI-TUMOUR TREATMENT

Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials

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KEYWORDS
Small cell lung cancer;
The elderly;
Chemotherapy;
Radiotherapy

Summary At diagnosis, 25–40% of patients with small cell lung cancer (SCLC) are 70 years of age or older, and many of them have been undertreated because of fear of excessive toxicity associated with chemotherapy. Papers retrieved by a Medline search using the key words "elderly or older" and "small cell lung cancer" and by a manual search were classified into the three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. Treatment regimens, delivery, toxicity, antitumor activity, and patient survival were reviewed in elderly patients with good and poor general condition. The standard chemotherapy regimens for the general population could be applied to elderly patients in good general condition (performance status of 0–1, normal organ function, and no comorbidity), but etoposide and carboplatin regimen with dose modification was frequently used for unselected elderly patients. A combination of full-dose thoracic radiotherapy and chemotherapy was the treatment of choice for limited SCLC in the elderly. Full cycles of chemotherapy were tolerable by 80% of the elderly patients with good general condition, but two cycles may be optimal for unselected elderly patients. Although the evidence levels based on clinical trials available today are low, these results are helpful for clinical practice and future clinical trials for elderly patients with SCLC.

Introduction

Lung cancer is currently the most common cancer in the world, and it is the leading cause of cancer death in many countries.[1,2] Small cell lung cancer (SCLC) accounts for 15–25% of all lung tumors. For treatment purposes, it is considered separately from other histological types, which are known as non-small cell lung cancer, because by the initial diagnosis SCLC has already metastastized to distant organs in 60–70% of patients, and it is highly sensitive to chemotherapy and radiotherapy. The prognosis of the disease is extremely poor. The 5-year survival rate of patients with limited disease (LD), which is a disease confined to one hemithorax that can be encompassed in a tolerable radiation field, is less than 15–25%, and most patients with extensive disease (ED), which has spread

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doi:10.1016/j.ctrv.2003.12.006

beyond the range of LD, die within two years after diagnosis.[3]

At diagnosis, 25–40% of patients with SCLC are 70 years old or older, and the number of patients is expected to increase, because the geriatric population is growing.[3-5] There has been a general tendency among physicians to consider aged people to always have poor tolerance for chemotherapy, and as a result many elderly cancer patients have been undertreated because of fear of excessive toxicity.[5] Thus, it is one of the immediate tasks for medical oncologists to establish treatment of SCLC in the elderly based on evidence obtained in clinical trials.

The decreases in lean body mass, hepatic blood flow, and renal function that accompany aging affect drug distribution, metabolism, and excretion. The clearance of anticancer agents commonly used for the treatment of SCLC, including cisplatin, doxorubicin, etoposide, and ifosfamide, has been shown to be decreased in the elderly.[6] Myelotoxicity is also sometimes severer in this population than in younger populations, because the absolute amount of hematopoietic marrow decreases with age. The incidence of doxorubicin-induced cardiotoxicity is also increased in the elderly, although the mechanism is unknown.[6] These age-related changes in pharmacokinetics and phamacodynamics, however, have not been fully evaluated in the treatment for SCLC in the elderly.

Studies on the treatment of SCLC in the elderly can be classified into the following three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. The first type of studies retrospectively analyzes all the elderly cases of SCLC diagnosed at an institution in a given period. They may provide information on the general aspects of elderly patients with SCLC, including performance, comorbidity, and percentages of patients treated with chemotherapy or supportive care alone. The results for outcome of treatment, however, are thought to be highly biased, because the patient populations in these studies are heterogeneous in terms of various prognostic factors. In the second type of studies, treatment outcome is retrospectively compared between an elderly group and a younger group. The patients in these studies are highly selected, because only those who meet strict eligibility criteria are included in clinical trials. Thus, the results of the analyses are understandable, but they are only applicable to the limited population of elderly patients. The most reliable and clinically useful results are obtained in the third type of studies, because the subjects can be freely defined and biases are controlled. Thus far, however, only a limited number of prospective studies on elderly patients with SCLC have been available.

The interpatient variability in activities of daily living, performance status, and comorbidity in elderly patients is so large that it is difficult to establish a standard treatment applicable to all patients. In this review, treatments for patients with good and poor general condition were summarized separately. We believe these summaries are helpful for clinical practice and future clinical trials for elderly patients with SCLC.

Methods

We retrieved papers published during the period from 1981 to 2000 by means of a Medline search using the key words "elderly or older" and "small cell lung cancer" in the Medical Subject Headings and a manual search. The papers were then classified into the three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. Among the retrospective studies in the first two categories, only those in which "elderly" was defined as 70 years or older were selected for the analysis. Prospective trials of infirm as well as elderly patients, however, were included in the analysis, because both populations were frequently included in the same trial. Patient characteristics, treatment regimens, treatment delivery, toxicity, antitumor activity, and patient survival were reviewed. The general clinical characteristics of the elderly SCLC patients are summarized on the basis of the results of the first type of studies. In principle, our summary of treatment for elderly patients with good performance status and no comorbidity is based on the results of the second type of studies, and our summary for unselected elderly patients is based on the third type of studies. Evidence levels are provided according to the previously described scale (Table 1).[7]

General clinical characteristics of elderly patients with SCLC

Elderly patients 70 years of age or older accounted for 26–38% (average, 31%) of all of the patients (Table 2). The percentage of limited disease ranged from 36% to 50% in both age groups. The general condition of the elderly patients was worse than in the younger patients; patients with PS 0 or 1 accounted for only 52–69% of the elderly patients, and comorbidity was noted in 63–78%. Optimal treatment, defined as four or more treatment