Table 5. Multivariate Analysis Results Including Factors Available After Lung Resection

Variable	Hazard Ratio (95% CI)	*p* Value
Age	1.021 (1.006–1.037)	0.006
CEA	1.301 (0.970–1.744)	0.079
cT factor (2–4 vs 1)	0.971 (1.411–2.051)	0.071
cN factor (1–3 vs 0)	0.951 (0.652–1.388)	0.796
sP factor (1–3 vs 0)	1.244 (0.834–1.856)	0.284
pT factor (2–4 vs 1)	1.285 (1.181–1.399)	<0.001
pN factor (1–3 vs 0)	0.446 (0.316–0.629)	<0.001
p factor (1–3 vs 0)	0.726 (0.527–1.001)	0.050
Histology (Ad.[a] vs others)	1.100 (0.769–1.573)	0.602
Lymphatic invasion	1.495 (1.058–2.114)	0.023
Vascular invasion	2.161 (1.410–3.311)	<0.001
Scar grade (3–4 vs 1–2)	0.792 (0.453–1.383)	0.412
Nuclear atypia (3 vs 1–2)	0.634 (0.447–0.898)	0.010
Mitotic index (3 vs 1–2)	0.875 (0.617–1.239)	0.452
Resection completeness	0.676 (0.472–0.968)	0.033
Pre-PLC	1.833 (0.949–3.541)	0.071
Post-PLC	1.803 (1.077–3.018)	0.024

Ad.[a] = adenocarcinoma; CEA = serum carcinoembryonic antigen; PLC = pleural lavage cytology.

ipsilateral pleural space. Eight patients died of lung cancer, one recurring locally and seven having distant metastases. They concluded the prognostic role of PLC needed further study. The first report on pre-PLC was by Kondo and associates in 1989 [12], followed by their expanded result analyses in 1993 [13]. They reported that 42 (9.0%) of 467 lung cancer patients undergoing surgery with little or no pleural effusion had a positive pre-PLC result. The 3-year survival rates of the patients with negative and positive cytology results were 68.7% and 22.9%, respectively. The prognosis of the positive cytology group was as poor as that of stage IIIB or IV patients. They concluded that pre-PLC was an important prognostic factor, indicating microscopic cancer cell exfoliation into the pleural cavity and subclinical malignant pleural effusion. Okada and associates [14] reported, based on 1,000 patients in 2003, that 45 (4.5%) patients had positive pre-PLC findings. Positive cytologic findings were observed more frequently in patients with adenocarcinoma, advanced stage, extended lymph node involvement, pleural involvement, lymphatic invasion, vascular invasion, high serum CEA level, and male gender. The survival rate at 5 years was 28% in patients with a positive result and 67% in negative patients ($p < 0.001$). Multivariate analysis demonstrated that pre-PLC was an independent prognostic determinant ($p = 0.0290$). Higashiyama and associates [1] performed pre-PLC and post-PLC in 325 lung cancer patients without malignant pleurisy. Positive post-PLC patients especially with adenocarcinoma resulted in a poor outcome. The survival rate at 5 years was 71% in 250 patients with negative pre-PLC and post-PLC results, while it was 33% in 19 patients with positive results. However, in multivariate analyses, neither pre-PLC nor post-PLC result was an independent prognostic factor in their study. Dresler and associates [3] reported the pre-PLC and post-PLC analysis in 137 patients in 1999. The 3-year survival rates of the patients with negative and positive pre-PLC results were 55% and 0%, respectively ($p = 0.088$). The 3-year survival rates of the patients with negative and positive post-PLC results were 50% and 0%, respectively ($p < 0.04$). In the present study, we analyzed both pre-PLC and post-PLC in almost 1,200 patients, the largest cohort ever studied with regard to PLC. Both pre-PLC and post PLC were analyzed in a multivariable setting, together with conventional significant clinicopathologic prognostic factors we reported previously [15]. Although our study yielded results similar to previous studies and post-PLC proved to be an important prognostic predictor, we found no difference in PLC results in relation to histologic characteristics. There have been a considerable number of reports concluding positive pre-PLC to be a poor prognosis predictor since pre-PLC was first reported by Kondo and associates in 1989 [12]. However, positive pre-PLC is currently not recognized as equivalent to T4 or a factor indicating incomplete resection [16–18]. In our study, pre-PLC was an independent prognostic factor when analyzed with prognostic factors available before lung resection, but not when postoperative pathologic factors and post-PLC results were combined in analyses. Positive pre-PLC patient outcome, when post-PLC was negative, was not very poor, with the 5-year survival rate reaching almost 60%. Therefore, positive pre-PLC result alone does not contraindicate surgical resection. In contrast, post-PLC proved to be an independent prognostic factor as significant as other established prognostic factors, including pathologic TNM status. No positive post-PLC patients survived beyond 4 years. As the patient outcome was extremely poor when pre-PLC was also positive, adjuvant therapy may be needed in these patients. We conclude PLC should be recognized as an essential prognostic factor and should be performed in NSCLC patients without pleural effusion and dissemination. And post-PLC, compared with pre-PLC, had a greater and independent impact on survival and needs to be incorporated in the pathologic staging of NSCLC in the future. As Vicidomini and associates referred to in their recent article on PLC [19], the results of the American College of Surgeons Oncology Group's Z0040 trial, which has completed a 1,200 patient accrual, will further define the potential implications of PLC in the management of lung cancer.

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ORIGINAL REPORT

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

Seiji Niho, Kaoru Kubota, Koichi Goto, Kiyotaka Yoh, Hironobu Ohmatsu, Ryutaro Kakinuma, Nagahiro Saijo, and Yutaka Nishiwaki

From the Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan.

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Address reprint requests to Seiji Niho, MD, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan; e-mail: siniho@east.ncc.go.jp.

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ABSTRACT

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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INTRODUCTION

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.

PATIENTS AND METHODS

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 $\geq$ 60 mmHg; (5) adequate organ function (ie, total bilirubin $\leq$ 2.0, AST and ALT $\leq$ 100 U/L, serum creatinine $\leq$ 1.5 mg/dL, leukocyte count 4,000 to 12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, hemoglobin $\geq$ 9.5 g/dL, and platelets $\geq$ 100,000/mm^3); (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 $\geq$ 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.

RESULTS

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.

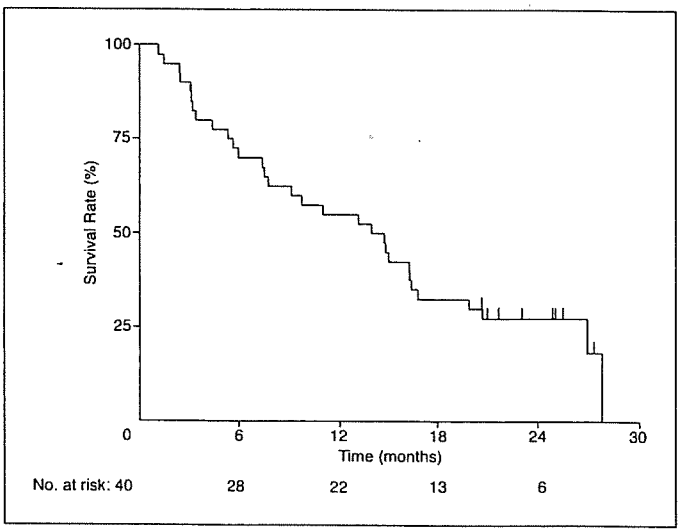

Fig 1. Overall survival of all eligible patients (n = 40) was calculated according to the Kaplan-Meier method. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%.

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 PaO2 was 43.7mmHg 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 Grade									
	1		2		3		4		5	
Toxicity	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% tol.9%). Multivariate analyses found that risk factors included 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)	*EGFR* 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.

gemcitabine, or irinotecan is probably acceptable as the current standard first-line chemotherapy.

First-line single agent with gefitinib is active, but produces unacceptably frequent ILD in the Japanese population. Being female, as well as adenocarcinoma, those who never smoked, and *EGFR* mutation were associated with response to gefitinib. Patients who responded to gefitinib did not experience ILD during gefitinib chemotherapy. Further research via genetics and image analysis is needed to avoid ILD and identify a subgroup of patients that benefit from gefitinib treatment. If this is realized, single agent treatment with gefitinib could be an option as first-line chemotherapy in selected patients with advanced NSCLC. Furthermore, randomized trials are warranted to compare first-line single agent treatment with gefitinib followed by second-line platinum-based chemotherapy with first-line platinum-based chemotherapy followed by second- or third-line gefitinib treatment.

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Author Contributions

Conception and design: Seiji Niho, Kaoru Kubota, Koichi Goto, Kiyotaka Yoh, Hironobu Ohmatsu, Ryutaro Kakinuma, Nagahiro Saijo, Yutaka Nishiwaki
Financial support: Yutaka Nishiwaki
Provision of study materials or patients: Seiji Niho, Kaoru Kubota, Koichi Goto, Kiyotaka Yoh, Hironobu Ohmatsu, Ryutaro Kakinuma, Yutaka Nishiwaki
Collection and assembly of data: Seiji Niho, Kaoru Kubota, Koichi Goto, Kiyotaka Yoh, Hironobu Ohmatsu, Ryutaro Kakinuma
Data analysis and interpretation: Seiji Niho, Nagahiro Saijo, Yutaka Nishiwaki
Manuscript writing: Seiji Niho
Final approval of manuscript: Seiji Niho, Kaoru Kubota, Koichi Goto, Kiyotaka Yoh, Hironobu Ohmatsu, Ryutaro Kakinuma, Nagahiro Saijo, Yutaka Nishiwaki

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Original Article

The Lung Cancer Database Project at the National Cancer Center, Japan: Study Design, *Corresponding Rate* and Profiles of Cohort

Naoki Nakaya[1], Koichi Goto[2], Kumi Saito-Nakaya[1], Masatoshi Inagaki[1], Tetsuya Otani[3], Tatsuo Akechi[1], Kanji Nagai[2], Fumihiko Hojo[2], Yosuke Uchitomi[1], Shoichiro Tsugane[3] and Yutaka Nishiwaki[2]

[1]Psycho-Oncology Division, Research Center for Innovative Oncology, [2]Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa and [3]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center Research Institute, Tokyo, Japan

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Background: The lung cancer database project was established in 1999 at the National Cancer Center Hospital East, Japan, as an ongoing project to integrate data on various factors in lung cancer patients. The aim of the project was to construct a *large-scale cancer registry* for lung cancer that would contribute to basic research and clinical research in the future.
Methods: Between July 1999 and July 2004, consecutive lung cancer patients were recruited into this project. The baseline survey consisted of self-administered questionnaires concerning various demographic data, health habits and psychological factors. Medical information was obtained from the patients' medical charts. Urine specimens and blood samples were collected, and DNA was extracted from blood lymphocytes.
Results: Out of the 2506 patients who were asked to participate in the project, 2036 (81%) patients with newly diagnosed, untreated primary lung cancer were enrolled. The final analytic cohort consisted of 1995 patients. Virtually all of the 1995 patients (*corresponding rate*, 99%) completed the questionnaires on demographic data and health habits. The corresponding rates for the questionnaires on psychological factors and dietary habits were 99 and 94%, respectively. In a follow-up survey conducted to determine vital status as of December 2004, a total of 1051 patients (53%) had died and 44 patients (2%) were lost to follow-up.
Conclusions: This paper overviews the rationale for initiating the lung cancer database project, Japan. This database should prove useful for researchers examining the pathogenesis of lung cancer and may contribute to the formulation of a framework for cancer treatment.

Key words: follow-up survey – health habits – large-scale cancer registry – lung cancer – psychological factors

INTRODUCTION

Lung cancer is the most common form of cancer and the most common cause of cancer-related deaths throughout the world (1,2). In Japan, lung cancer is the leading cause of death from cancer among men and women, and the incidence of lung cancer has been increasing in recent years (3). In 2003, the number of lung cancer deaths reached 41 615 (22% of all cancer-related deaths) in men and 15 086 deaths (12% of all cancer-related deaths) in women (3). Lung cancer is often resistant to treatment, so research programs designed to share epidemiologic, psychosocial and molecular biology data are needed to improve treatment efficacy and patient outcome. It is difficult to determine the factors associated with lung cancer outcome because of the marked clinical heterogeneity of patients. In earlier reports, various individual characteristics like age, sex, pathologic stage, performance status, co-morbidity, molecular biological markers, marital status, psychological factors and smoking status have all been implicated to contribute to the survival rate in lung cancer (4–7). Further clarification of the factors contributing to survival from lung cancer is needed.

For reprints and all correspondence: Yutaka Nishiwaki, Division of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Japan; E-mail: ynishiwa@east.ncc.go.jp

Approximately 400 newly diagnosed primary lung cancer patients visit the National Cancer Center Hospital East (NCCHE), Japan, for treatment each year. In 1999, the Lung Cancer Database Project was initiated as an ongoing project to integrate information on various factors in lung cancer patients. The aim of the project was to construct a large-scale cancer registry for lung cancer that would contribute to basic research and clinical research in the future. In addition, by investigating the factors that influence the outcome of patients with lung cancer, we hoped to clarify several specific points related to cancer treatment in order to improve patient outcome.

This paper describes the epidemiological background and the study design, the questionnaire corresponding rates, the cohort profile and the survival rates obtained in a follow-up survey of patients in the Lung Cancer Database Project.

METHODS

Study Setting

The NCCHE was founded in the city of Kashiwa in suburban eastern Japan on July 1, 1992. The NCCHE has 425 beds and consists of 9 clinical divisions. As of January 1, 2005, the hospital staff included 73 physicians, 17 pharmacists and 268 nurses. During 2004, this hospital took care of 146 802 outpatients, including 7706 newcomers and 7506 inpatients.

Study Cohort

The project was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan (in March, 1999). The Japanese Ministry of Health, Labour and Welfare established the two guidelines that follow ['the Ethical Guidelines Concerning Human Genome and Gene Analysis' (in March, 2001) and 'the Ethical Guidelines Concerning Epidemiologic Study' (in June, 2002)]. (http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/dl/shinkyu.pdf http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/genome/dl/shinkyu.pdf).

When we planned a new study based on this project, the study needed to be approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. Moreover, the study followed two guidelines by the Japanese Ministry of Health, Labour and Welfare.

Data from subjects who participated in the Lung Cancer Database Project at the NCCHE and at the National Cancer Center Research Institute East were used in this study. We distributed two self-administered questionnaires to the patients before the start of cancer treatment (at baseline). The first questionnaire included questions on various demographic data, health habits and psychological factors (including the Mental Adjustment to Cancer Scale, the Eysenck Personality Questionnaire-Revised and the Hospital Anxiety and Depression Scale), and the second was on dietary habits (the Food Frequency Questionnaire). Medical information was obtained from the patients' medical charts. After admission but before cancer treatment, urine specimens and blood samples were collected, and DNA was extracted and collected from blood lymphocytes. These samples were stored at 80 C until further use. We previously reported part of the information in a project (8).

The subjects enrolled in this study were all newly diagnosed primary lung cancer patients, who had visited the Division of Thoracic Oncology of the NCCHE, Japan. Patients were included in this database study if they met all of the following criteria: knowledge of their lung cancer diagnosis; new diagnosis of primary lung cancer; physically capable of completing the questionnaires; absence of cognitive impairment (i.e. dementia, delirium); ability to provide written consent; and no problems regarding the patients' participation in this project, as judged by their physicians.

Study Procedure

In the initial study plan, the sample size and accumulation period were decided as 1500 patients and 5 years, respectively. Approximately 400 newly diagnosed patients with primary lung cancer visit the NCCHE each year. We estimated that the rate of ineligible patients and/or patients who would refuse to participate in the project would be 25%.

Between July 1999 and July 2004, consecutive patients eligible for the project were recruited after disclosure of their diagnosis by their attending physician. The patients completed the questionnaires during the waiting period before admission, and the questionnaires were collected after the patients were admitted. All patients provided their written informed consent prior to enrolment in this project.

MEASUREMENTS

Demographic Data And Medical Information

Demographic factors (age at time of cancer diagnosis, sex, education level, marital status, smoking history, past history of cancer and family history of cancer) and medical information (histology, clinical stage, pathologic stage, cancer treatment of first line, performance status and symptoms) were obtained from the self-administered questionnaires and the patients' medical charts. Performance status (PS) was assessed by each attending physician using the Eastern Cooperative Oncology Group criteria (9).

Fagerström Tolerance Questionnaire [FTQ]/ Fagerström Test for Nicotine Dependence

Nicotine dependence was evaluated using the Fagerström Tolerance Questionnaire (FTQ) and the Fagerström Test for Nicotine Dependence (FTND). In 1978, Fagerström developed a self-rating scale (the FTQ) to assess nicotine dependence and used the questionnaire in a smoking cessation clinic (10). As a revised version of the FTQ, the FTND was developed by Heatherton et al. in 1991 (11). The Japanese version of the

FTND is a reliable and valid measure of nicotine dependence in patients with smoking-related cancers (12).

Mental Adjustment to Cancer (MAC) Scale

The patients' psychological response to their cancer diagnosis was measured using the Japanese version of the MAC scale, a 40-item, self-rating scale developed in England (13). The scale consists of five subscales: fighting spirit (16 items), anxious preoccupation (9 items), fatalism (8 items), helplessness/hopelessness (6 items) and avoidance (1 item). The respondents were asked to read a number of statements that might describe their reactions to having cancer and to circle the number indicating the degree to which each statement applied to them. Each item was rated on a scale of 1–4, ranging from 'definitely does not apply to me' to 'definitely applies to me'. Previous studies have revealed that the MAC scale is adequately valid and reliable (14).

Eysenck Personality Questionnaire-Revised

Personality was evaluated using the Eysenck Personality Questionnaire-Revised (EPQ-R). The Japanese translation of the original English version of the EPQ-R Short Form is one of a series of personality inventories developed by Eysenck and colleagues (15). It contains 48 questions with dichotomized responses (yes or no); there are 12 questions for each of the four subscales (extraversion, neuroticism, psychoticism and lie). The scores on each subscale ranged from 0 to 12, with higher scores indicating a greater tendency to possess the personality trait represented by each subscale. Extraversion represents sociability, liveliness and assurgency; neuroticism represents emotional instability and anxiousness; psychoticism represents tough-mindedness, aggressiveness, coldness and egocentricity; and lie represents unsophisticated dissimulation and social naivety or conformity (16). Previous studies have revealed that the EPQ-R is adequately valid and reliable (17).

Hospital Anxiety and Depression Scale

Anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS). The HADS (18) consists of a 7-item anxiety subscale and a 7-item depression subscale to assess symptoms of anxiety and depression during the preceding week in medically ill patients. The HADS has been used as a reliable and valid method of screening for depression in patients with cancer. Each item is rated on a scale of 0–3, with higher scores denoting a greater mood disturbance. The reliability and validity of the Japanese version of this questionnaire has been established in Japanese cancer patients (19).

Food Frequency Questionnaire

Dietary habits were assessed using the semiquantitative Food Frequency Questionnaire (FFQ), which was constructed for a population-based prospective study in Japan (20) and contains questions regarding 138 foods. For each food item, the participants reported the usual serving size. When the patient's dietary habits changed following the appearance of symptom(s) resulting in hospitalization, the dietary habits before the appearance of the symptom(s) was reported. Nine responses were possible for each food item, ranging from 'never' to '7 or more times per day'. The average daily intake of nutrients was calculated by multiplying the frequency of the consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items. The method used to calculate the average daily intake of each food and nutrient based on the FFQ responses has been described elsewhere (21).

Urine Specimens

Urine specimens (20 ml) were collected after admission but before treatment, and stored at 80 C until further use.

Blood Samples

Blood samples (20 ml) were collected after admission but before treatment. After storing the samples for about 2 h at 4 C, the serum was separated by centrifugation (1870 *g*, 10 min) and stored at 80 C until further use.

DNA

Peripheral blood samples (3 ml) were collected after admission. DNA was extracted from the blood lymphocytes *by a specialist at the Division of Thoracic Oncology, NCCHE, Japan*, and strictly stored at 80 C until further use.

Patients' DNA samples were analyzed after deleting their names and addresses. When we analyzed their DNA samples in planning a new study, these samples were labeled again with new identification numbers which could be linked to patients' information only by the specialist. Patients' DNA samples were strictly kept at the NCCHE, Japan. This project created the system concerning DNA sampling and reservation.

Follow-up Method

To assess vital status as part of a follow-up study, survival was confirmed by referring to the medical records, by normal postal mail, or using municipality registration data. Follow-up surveys were conducted once a year between July 1999 and December 2004 by members of our co-medical staff.

In order to protect patients' personal information, we planned a new study based upon this project, which needed to be approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. Each patient's information was analyzed after deleting his/her name and address. When we analyzed their information, we labeled again with new identification numbers which could be linked to patients' information. The clinical data included in this project was carefully managed by the researcher and the research secretariat.

RESULTS

Questionnaires concerning psychological factors and dietary habits achieved the target of 1500 participants within 4 years, and the questionnaires were completed in July 2003. The questionnaire on demographic variables was distributed for 5 years, and was completed in July 2004. In total, the project was explained to 2506 patients, of whom 2036 (81.3%) patients with newly diagnosed, untreated primary lung cancer were enlisted during the enrollment phase. A total of 470 cases were ineligible for the following reasons: could not be contacted (49 cases), lung cancer diagnosis not confirmed at time of admission (175 cases), non-lung cancer (120 cases), poor physical symptoms (77 cases), refusal to participate in the project (43 cases), treated for lung cancer at another hospital (5 cases), or not yet informed of their diagnosis (1 case). In 40 of the 2036 patients, written informed consent could not be confirmed, and one patient withdrew consent during the follow-up period. Finally, the analytic cohort consisted of 1995 patients.

For the corresponding rate according to baseline assessments among the patient, virtually all of the 1995 patients (corresponding rate, 99%) completed the questionnaires on demographic data and health habits. The corresponding rates for the questionnaires on psychological factors and dietary habits were 99 and 94%, respectively.

The demographic data and medical information is summarized in Table 1. Most of the patients were in their sixth decade at the time of their lung cancer diagnosis (38%), and there were more men than women (71 versus 29%, respectively). As for clinical stage, most of the patients (27%) had stage IV lesions, followed in descending order by IA (24%), IIIB (18%) and IB (14%). Histological classification revealed adenocarcinoma to be the most common lesion (58%), followed in descending order by squamous cell carcinoma (21%) and small cell carcinoma (11%). Most of the patients (44%) underwent surgery as their first-line treatment, followed in descending order by chemotherapy (37%) and chemotherapy plus radiotherapy (11%). Most of the patients were either PS 1 (50%) or PS 0 (44%).

For the vital status among this patient as of December 2004, out of the 1995 patients, 1051 patients had died (52.7%) and 44 patients had been lost to follow-up (2%). The proportion of patients lost to follow-up was low, ranging from 1 to 17%.

Table 1. Demographic and medical characteristics of the project subjects at the baseline

Variable	No. of subjects	%
Age in years at lung cancer diagnosis		
≤39	24	1
40–49	103	5
50–59	456	23
60–69	751	38
70–79	605	30
≥80	56	3
Sex		
Man	1,426	71
Woman	569	29
Clinical stage*		
IA	483	24
IB	285	14
IIA	20	1
IIB	114	6
IIIA	181	9
IIIB	367	18
IV	545	27
Histologic type		
Adenocarcinoma	1151	58
Squamous cell carcinoma	418	21
Large cell carcinoma	170	9
Cartinoid	10	1
Small cell carcinoma	218	11
Other	28	1
Treatment of first line		
Operation	880	44
Chemotherapy	736	37
Chemotherapy plus radiotherapy	228	11
Palliative care	91	5
Radiotherapy	36	2
Chemotherapy plus operation	13	1
Laser	6	0
Operation plus chemotherapy	3	0
Chemotherapy plus radiotherapy plus operation	2	0
Performance status at pre-treatment†		
0	886	44
1	993	50
≥2	116	6

*Defined by TNM classification: International Union Against Cancer.
†Defined by the Eastern Cooperative Oncology Group.

DISCUSSION

This paper overviews the rationale for initiating the Lung Cancer Database Project at the National Cancer Center, Japan. Few previous studies have analyzed such a wide variety of factors among lung cancer patients, making this a valuable clinical observation project.

The advantages of this cohort study were as follows: (1) as the corresponding rates to the baseline questionnaires on demographics, health habits, psychological factors and dietary habits were satisfactorily high, the data can be regarded as being representative of the subject; (2) because not only medical information but a variety of health habits and psychological factors were assessed using standardized questionnaires, valid evaluations of associations in the pathogenesis

of lung cancer can be made; (3) urine specimens, blood samples and DNA were collected from all patients so that when important new biomarkers are discovered, studies utilizing the database will be able to be promptly performed, hopefully leading to greater treatment efficacy in the future; and (4) the follow-up rate was satisfactorily high. The corresponding rate was high, despite the numerous questions on demographic data, health habits and psychological factors that were asked. For this reason, the research assistants reinvestigated patients who did not completely respond to the questionnaires.

The project had some limitations. First, a sampling bias existed because the project was conducted from only one institution, a teaching cancer center hospital in Japan. Care should be taken when generalizing the results of this project and applying them to other oncology settings. Second, we distributed the questionnaire on psychological variables and health habits only once before the patients underwent cancer treatment. Therefore, possible changes in these variables after cancer treatment remain unclear.

In summary, this project constructed a large-scale cancer registry containing data on the demographics, health habits, psychological factors and medical information on lung cancer patients. This database should prove useful for researchers examining the pathogenesis of lung cancer, and may contribute to the formulation of a framework for cancer treatment.

PARTICIPATING INSTITUTIONS

Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center Research Institute, Tokyo, Japan; Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan.

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Interstitial Shadow on Chest CT is Associated with the Onset of Interstitial Lung Disease Caused by Chemotherapeutic Drugs

Seiji Niho, Koichi Goto, Kiyotaka Yoh, Young Hak Kim, Hironobu Ohmatsu, Kaoru Kubota, Nagahiro Saijo and Yutaka Nishiwaki

Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan

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Objective: Pretreatment computerized tomography (CT) films of the chest was studied to clarify the influence of interstitial shadow on developing interstitial lung disease (ILD).
Methods: Eligible patients were those lung cancer patients who started to receive first-line chemotherapy between October 2001 and March 2004. Patients who received thoracic radiotherapy to the primary lesion, mediastinum, spinal or rib metastases were excluded. We reviewed pretreatment conventional CT and plain X-ray films of the chest. Ground-glass opacity, consolidation or reticular shadow without segmental distribution was defined as interstitial shadow, with this event being graded as mild, moderate or severe. If interstitial shadow was detected on CT films of the chest, but not via plain chest X-ray, it was graded as mild. Patients developing ILD were identified from medial records.
Results: A total of 502 patients were eligible. Mild, moderate and severe interstitial shadow was identified in 7, 8 and 5% of patients, respectively. A total of 188 patients (37%) received tyrosine kinase inhibitor (TKI) treatment, namely gefitinib or erlotinib. Twenty-six patients (5.2%) developed ILD either during or after chemotherapy. Multivariate analyses revealed that interstitial shadow on CT films of the chest and treatment history with TKI were associated with the onset of ILD.
Conclusions: It is recommended that patients with interstitial shadow on chest CT are excluded from future clinical trials until this issue is further clarified, as it is anticipated that use of chemotherapeutic agents frequently mediate onset of ILD in this context.

Key words: interstitial lung disease – interstitial shadow – chemotherapy – lung cancer – CT

INTRODUCTION

Interstitial lung disease (ILD) is known to be an adverse event in cancer chemotherapy and radiotherapy. Recently, ILD has attracted considerable attention in Japan since the observation that gefitinib caused ILD (1). Gefitinib is a tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor and is active in patients with recurrent non-small cell lung cancer (NSCLC) after platinum-based chemotherapy (2,3). Gefitinib was first approved for the treatment of advanced NSCLC by the Japanese regulatory agencies on 5 July 2002. From August 2002 to April 2003, ~28 000 patients with NSCLC were given gefitinib in Japan. However, 616 patients suffered from ILD and 246 patients died of ILD, according to a report from AstraZeneca. The West Japan Thoracic Oncology Group conducted a retrospective survey to clarify the risk factors related to ILD (4). Out of 1976 patients with NSCLC who received gefitinib across 84 institutions, 91 patients were suspected of having developed ILD. This group also analyzed the patients' background, together with computerized tomography (CT) films of the chest, before treatment and at the onset of ILD in this subcohort. Five experts in thoracic radiology in these extramural reviews diagnosed ILD in 64 patients. Multivariate analysis indicated that the predictive risk factors for the development of ILD were as follows: male, smoking and existence of idiopathic pulmonary fibrosis. However, this group did not review CT films of the chest in all 1976 patients. How much interstitial shadow on chest CT impacts ILD development remains unknown.

ILD has a high associated risk of death, even if steroid therapy resolves ILD temporarily. Furthermore, ILD affects salvage chemotherapy. In cases where patients are at a high risk of developing ILD, anti-cancer drugs that tend to cause ILD should be avoided. Previous analysis often included only those cases developing ILD, but not all cases undergoing chemotherapy (4,5). The frequency of interstitial shadow in

For reprints and all correspondence: Seiji Niho, the Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan. E-mail: siniho@east.ncc.go.jp

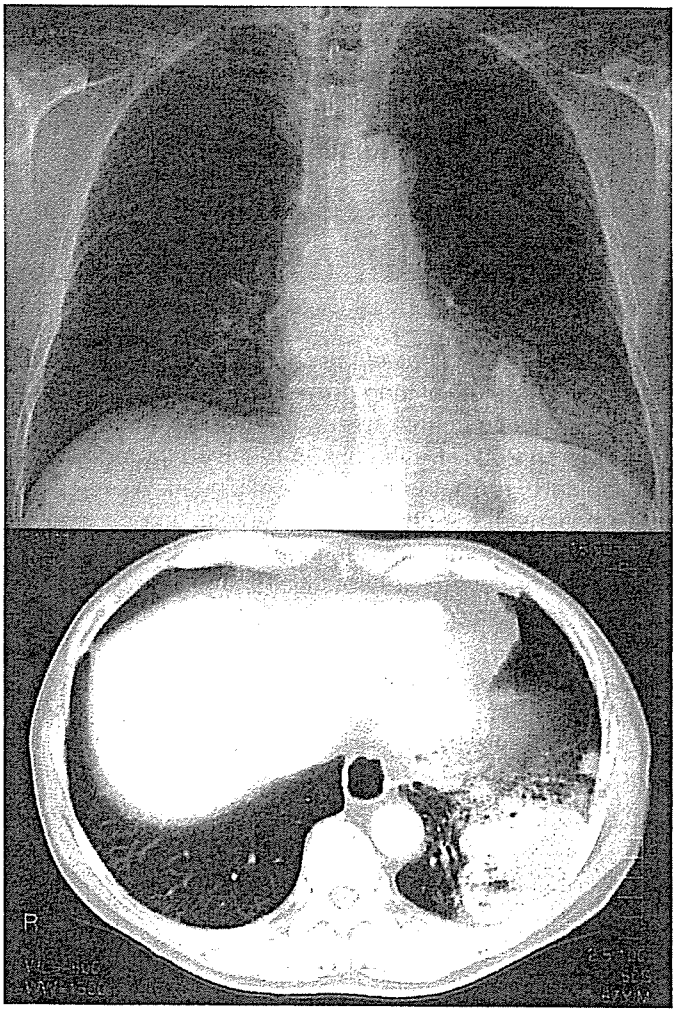

Figure 1. Mild interstitial shadow. An X-ray film of the chest shows no obvious interstitial shadow. A CT film of the chest demonstrated ground-glass opacity in the right basal lung. Interstitial shadow is classified as mild in this case.

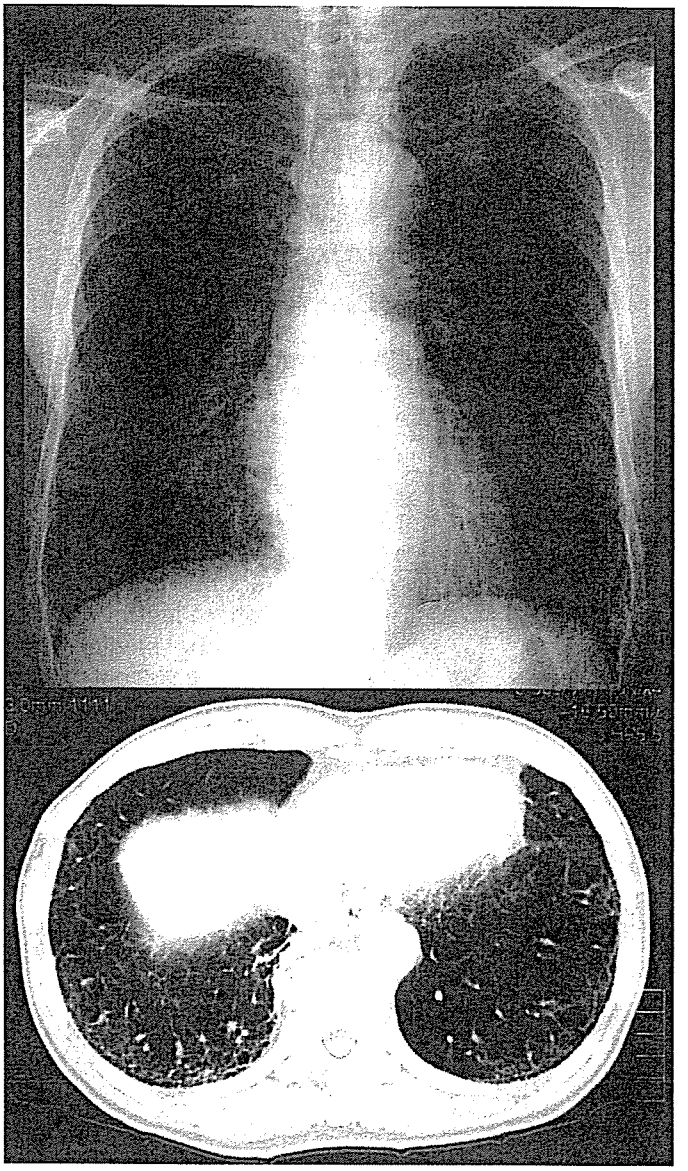

Figure 2. Moderate interstitial shadow. An X-ray film of the chest shows bilateral reticular shadow in the basal area. A CT film of the chest demonstrated bilateral reticular shadow just below the pleura. Interstitial shadow is distributed in 10–30% of the bilateral lower lobes, with this being classified as moderate.

pretreatment CT films of the chest in patients with lung cancer remains unknown, and also how much interstitial shadow confers a risk toward ILD. To further clarify the influence of interstitial shadow on developing ILD, we retrospectively analyzed pretreatment CT films of the chest in consecutive lung cancer patients receiving chemotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of lung cancer patients who began to receive first-line chemotherapy between October 2001 and March 2004 at the Division of Thoracic Oncology in the National Cancer Center Hospital East. Patients who received thoracic radiotherapy to the primary lesion, mediastinum, spinal or rib metastases were excluded. Plural pulmonologists (S.N., Y.H.K., K.Y., and K.G.) reviewed pretreatment conventional CT and plain X-ray films of the chest. Whether patients had developed ILD or not was blinded to the pulmonologists when they read the films. Conventional spiral CT films were used in our analysis, as high-resolution CT was not routinely conducted. Ground-glass opacity, consolidation or reticular shadow without segmental distribution was defined as interstitial shadow. Localized low attenuation area was defined as emphysema. The grading criteria for interstitial shadow was mild (<10% in bilateral lower lobes), moderate (10–30% in bilateral lower lobes) and severe (>30% in bilateral lower lobes) (Figs 1, 2, and 3). These breakpoints (10 and 30%) were chosen for convenience sake. Interstitial shadow detected on CT films of the chest, but not on plain X-ray, corresponded to mild interstitial shadow. The grading criteria for pulmonary emphysema were mild (<10% in bilateral lungs), moderate (10–30% in bilateral lungs) and severe (>30% in bilateral lungs).

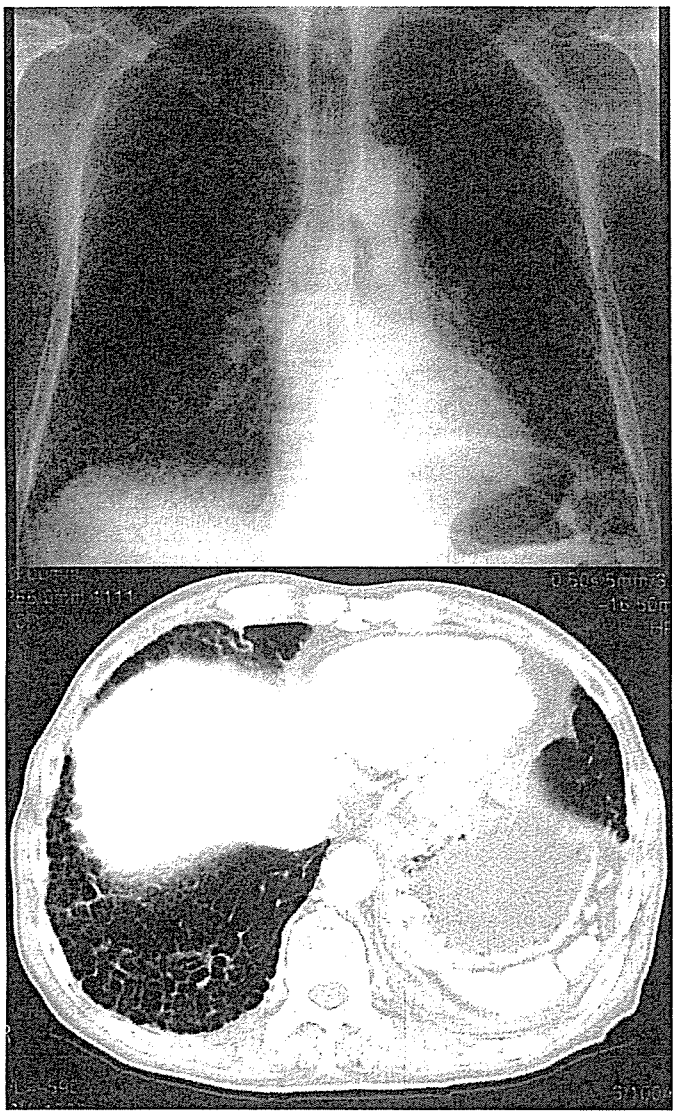

Figure 3. Severe interstitial shadow. An X-ray film of the chest shows bilateral reticular shadow. Reticular shadow is distributed in >30% of the bilateral lower lobes, with this being classified severe.

We identified patients developing ILD, utilizing medical records. ILD was diagnosed on the basis of standard or high-resolution CT findings of the chest (diffuse ground-glass opacity, reticular shadow or consolidation without segmental distribution), elevation of serum levels of lactate dehydrogenase (LDH) and/or KL-6, and lack of response to antibiotics. Bronchoalveolar lavage had not been performed to rule out infections. Most patients diagnosed as ILD were treated with corticosteroids. We compared patients who either had or had not developed ILD in terms of existence and severity of interstitial shadow, emphysema and/or pulmonary bullae on CT films of the chest, as well as patient characteristics including age, gender, smoking history and regimens of received chemotherapy. Comparisons between proportions were performed using a Fisher exact test or a Pearson chi-square test, as appropriate. Multivariate analyses were performed using the logistic regression procedure to determine the relationship between several factors and the onset of ILD.

RESULTS

A total of 502 patients were eligible, with the relevant patient characteristics shown in Table 1. A total of 74% of patients were male and 84% of patients had NSCLC, while the remaining 16% had small cell lung cancer; 79% of the patients were smokers, while 21% never smoked. Platinum-based chemotherapy was performed on 384 patients (76%). A total of 188 patients (37%) received tyrosine kinase inhibitor (TKI) treatment, namely gefitinib or erlotinib. TKI therapy was administered as a first-line (n = 48), second-line (n = 68), third-line (n = 62), fourth-line (n = 9) or fifth-line (n = 1) regimen. Out of 48 patients treated with TKI as a first-line treatment 41 had been entered into a phase II trial of single agent treatment with gefitinib (6).

Radiological findings on this patient cohort are listed in Table 2. Interstitial shadow was detected on chest X-ray and CT in 13 and 20% of patients, respectively. Mild, moderate or severe interstitial shadow was identified in 7, 8 or 5% of patients. Pulmonary emphysema was detected in 38% of patients. Mild, moderate or severe pulmonary emphysema was detected in 18, 10 or 10% of patients. Pulmonary bullae were detected in 20% of patients.

Twenty-six patients (5.2%) developed ILD either during or after chemotherapy. The last regimen of chemotherapy received prior to the onset of ILD included platinum plus vinorelbine or gemcitabine (n = 4), platinum plus taxane (n = 4), other platinum-based chemotherapy (n = 2), vinorelbine plus gemcitabine (n = 2), docetaxel plus gemcitabine (n = 2), single agent treatment with taxane (n = 2) and TKI treatment (n = 10). Out of 26 patients who developed ILD, 14 had a history of taking TKI. Four patients developed ILD after first- or second-line chemotherapy with TKI followed by combination chemotherapy of cisplatin plus vinorelbine (n = 2) or single agent treatment with docetaxel (n = 2).

Univariate analyses demonstrated that male gender (P = 0.0361) and interstitial shadow on CT films of the chest (P = 0.0096) were significantly associated with the onset of ILD (Tables 1 and 3). Multivariate analyses showed interstitial shadow on CT films of the chest [odds ratio (OR): 3.20, 95% confidence interval (CI): 1.34–7.59] and treatment history with gefitinib or erlotinib (OR: 3.17, 95% CI: 1.36–7.36) were associated with the onset of ILD. Male gender was not a significant risk factor for development of ILD in multivariate analysis (OR: 4.33, 95% CI: 0.97–19.38) (Table 4). Univariate and multivariate analyses demonstrated that neither interstitial shadow on X-ray films nor the number of chemotherapy regimens was associated with the onset of ILD.

DISCUSSION

Pulmonary fibrosis or interstitial pneumonia is considered to be a risk factor for ILD caused by drugs (5). In line with the

Table 1. Patient characteristics (n = 502)

	Total	Developed ILD	No ILD Development	P-value
Gender				
Male	371	24	347	0.0361
Female	131	2	129	
Age				
Median (range)	65 (33–83)	66 (53–77)	65 (33–83)	0.5253
ECOG PS				
0–1	443	26	417	0.0590
2–4	59	0	59	
Pathological type				
Adenocarcinoma	279	14	265	0.8775
Squamous cell carcinoma	84	6	78	
Poorly differentiated carcinoma	56	3	53	
Small cell carcinoma	79	3	76	
Others	4	0	4	
Smoking status				
Current smoker	272	14	258	0.1085
Former smoker	124	10	114	
Never smoked	106	2	104	
Clinical stage				
IB	10	0	10	0.6633
IIB	7	0	7	
IIIA	21	0	21	
IIIB	128	8	120	
IV or recurrence after operation	336	18	318	
Treatment history				
Platinum-based	384	18	366	0.3505
Vinorelbine-containing	295	13	282	0.4145
Gemcitabine-containing	110	7	103	0.4758
Taxane-containing	236	14	222	0.5470
Irinotecan-containing	72	2	70	0.5624
Etoposide-containing	67	2	65	0.5573
TKI	188	14	174	0.0954
Number of chemotherapy regimens				
1	212	9	203	0.7733
2	155	9	146	
3	106	7	99	
4 or 5	29	1	28	

ILD, interstitial lung disease; TKI, tyrosine kinase inhibitor.

Table 2. Radiological findings of plain X-ray and computerized tomography films of the chest

Interstitial shadow on plain X-ray films	65 (13%)
Interstitial shadow on CT films	102 (20%)
Mild	37 (7%)
Moderate	42 (8%)
Severe	23 (5%)
Pulmonary emphysema on CT films	189 (38%)
Mild	92 (18%)
Moderate	49 (10%)
Severe	48 (10%)
Pulmonary bullae	101 (20%)

Table 3. Radiological findings and interstitial lung disease

Radiological findings	Developed ILD	No ILD Development	P-value
Interstitial shadow on plain X-ray films of the chest			
No	23	414	1.000
Yes	3	62	
Interstitial shadow on CT film of the chest			
No	15	385	0.0096
Yes	11	91	
Severity of the interstitial shadow			
No	15	385	<0.0001
Mild	8	29	
Moderate	1	41	
Severe	2	21	
Pulmonary emphysema			
No	14	299	0.4075
Yes	12	177	
Severity of the emphysema			
No	14	299	0.6468
Mild	7	85	
Moderate	2	47	
Severe	3	45	
Pulmonary bullae			
No	18	383	0.2052
Yes	8	93	

ILD, interstitial lung disease.

information for prescription, patients with obvious interstitial shadow on chest X-ray should avoid gemcitabine or irinotecan. Although patients with interstitial shadow on chest X-ray were excluded in previous clinical trials in Japan, unexpectedly frequent ILD has been reported, as in the case of combination chemotherapy with docetaxel and gemcitabine (7). Is interstitial shadow on chest X-ray an appropriate criterion to detect interstitial pneumonia or pulmonary fibrosis and avoid ILD? Generally, chest CT can detect interstitial shadow more clearly than chest X-ray. Specifically, high-resolution CT of the chest is essential in diagnosing interstitial pneumonia. However, it has not been determined exactly how much more interstitial shadow detected by CT reveals the onset of ILD. We analyzed CT films of consecutive lung cancer patients who underwent

Table 4. Multivariate analysis of risk factors associated with the onset of interstitial lung disease

Variable	Odds ratio	95% CI	*P*-value
Interstitial shadow on CT films of the chest	3.20	1.34–7.59	0.0086
Treatment history with TKI	3.17	1.36–7.36	0.0073
Male gender	4.33	0.970–19.38	0.0551

CI, confidence interval; TKI, tyrosine kinase inhibitor.

chemotherapy without thoracic radiation therapy. Retrospective review of medical records identified that 26 out of 502 patients developed ILD. We found that interstitial shadow on CT films was associated with onset of ILD, but that interstitial shadow on X-ray was not. We divided interstitial shadow into three classes: mild, moderate and severe. Interstitial shadow on X-ray means moderate to severe interstitial pneumonia. Eight out of 37 patients (22%) with mild interstitial shadow not detected on chest X-ray developed ILD. The reason for the high rate of ILD in patients with mild interstitial shadow is unknown. The criteria of no interstitial shadow on chest X-ray did not sufficiently reduce the risk of ILD. Treatment history with TKI, either gefitinib or erlotinib, was also associated with onset of ILD in multivariate analysis. Conversely, treatment with gemcitabine or irinotecan was not associated with onset of ILD.

Our retrospective analyses have several limitations. We avoided treatment with gemcitabine, irinotecan or TKI in the case of patients with moderate to severe interstitial shadow detectable on chest X-ray films. Some patients who were transferred to another hospital just after chemotherapy may have developed ILD, but detailed clinical courses after transfer were not available. Early death after chemotherapy due to disease progression might conceal the onset of ILD. Although these biases may exist, our analyses were made with an extensive cohort of patients, and therefore the results obtained are of significance.

The frequency of ILD in Japanese patients was reported to range between 3 and 15% in previous clinical trials (6–8). This rate appears to be higher than that observed in the rest of the world. Explanations include the possibility that ILD may be more prevalent among the Japanese or, alternatively, that a greater awareness of the disease could lead to more frequent diagnosis. Furthermore, there may be an increased genetic susceptibility to ILD specifically among the Japanese population (5).

Patients with interstitial shadow on chest X-ray have been excluded in previous clinical trials to avoid ILD caused by chemotherapeutic agents. However, this criterion alone is considered insufficient. It is recommended that patients with interstitial shadow on chest CT are excluded from future clinical trials until this issue is clarified, as it is anticipated that use of chemotherapeutic agents frequently mediate onset of ILD in this context. Therefore, physicians need to understand the associated risk of ILD in patients with interstitial shadow on chest CT and obtain informed consent from patients before administering chemotherapy in clinical practice.

Acknowledgments

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Brief Communication

Psychometric properties of the Japanese version of the quality of life-Cancer Survivors Instrument

Maiko Fujimori[1], Makoto Kobayakawa[1], Naoki Nakaya[1,2], Kanji Nagai[3], Yutaka Nishiwaki[3], Masatoshi Inagaki[1] & Yosuke Uchitomi[1]

[1]*Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan (E-mail: yuchitom@east.ncc.go.jp);* [2]*Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan;* [3]*Thoracic Oncology Division, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

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Abstract

The purpose of this study was to describe the psychometric properties of the Japanese version of the Quality of Life-Cancer Survivors Instrument (QOL-CS-J) developed in the U.S. This study was conducted as a mail survey to survivors of more than 5 years post curative resection for non-small-cell lung cancer (NSCLC) and who had participated in an earlier survey. This survey included the medical and demographic factors, the QOL-CS scores, and the Medical Outcome Study 36-Item Short Form (SF-36). A total of 113 survivors completed the survey. To confirm the reliability, the Cronbach's α coefficient of each subscale was calculated as an internal consistency (α = 0.65–0.89). To confirm the validity of the trial as conducted, Pearson's correlation coefficients between the subscales of the QOL-CS and the subscales of the SF-36 were calculated. There were moderate correlations between associated subscales including QOL-CS physical to SF-36 bodily pain (r = 0.45) and vitality (r = 0.52), QOL-CS psychological to SF-36 mental health (r = 0.55), QOL-CS social to SF-36 general health perception (r = 0.31) and mental health (r = 0.47), and QOL-CS total to each subscale of SF-36 (r = 0.25–0.64). Findings demonstrated that the QOL-CS-J adequately measured the QOL in long-term NSCLC survivors.

Key words: Japan, Non-small-cell lung cancer, Reliability, The Quality of Life-Cancer Survivors Instrument, Validity

Introduction

The Quality of Life-Cancer Survivors Instrument (QOL-CS) was developed to evaluate the long-term QOL of cancer survivors, to identify enduring problems in adjustment after treatment, and to identify potential areas for support [1]. The QOL-CS has been widely used, although not the case in Japan. The purpose of this study was to evaluate the psychometric properties of the Japanese version of the QOL-CS (QOL-CS-J) tool in Japanese survivors of non-small-cell lung cancer (NSCLC).

Methods

Sample

The sample of survivors of NSCLC was derived from the database of an earlier study [2]. The initial study eligibility criteria required patients to

be of 18 years of age or older; to be aware of the diagnosis of cancer; to be able to speak Japanese; to have undergone a predetermined standard surgical procedure (lobectomy or pneumonectomy with mediastinal lymph node dissection); to have no evidence of brain tumor on computerized tomography or magnetic resonance images of the head; to have no history of or current use of chemotherapy, immunotherapy, or radiation therapy; to have no active concomitant cancer; to have undergone a curative resective procedure; and to have no other medical conditions. Detailed of the original study design and recruitment procedures have been published elsewhere [2]. An additional eligibility criterion of the current study required a survival period of the participants of five years and three months or more since the original curative surgical treatment.

Instruments

QOL Questionnaires

The QOL-CS includes 41 items representing the four domains (physical, social, psychological, and spiritual well-being) of cancer-specific quality of life [1]. The instructions for the survey include the statement "How your experience of having cancer affects your quality of life." The QOL total score (average across items) and the four QOL subscale scores were used as outcomes. Transformations were performed such that higher scores indicated a better QOL for all of the subscales. To create a QOL-CS-J, we obtained copyright permission from Dr. Ferrell who developed the original QOL-CS, and translated the QOL-CS into Japanese, then back-translated the scale into English using a native English speaker who was both conversant with the appropriate terminology and was fluent in Japanese. After that, two trained attending psychiatrists who were on the cancer center staffs, and five healthy volunteers confirmed the content of each item.

The SF-36 is a generic QOL instrument that assesses eight health concepts (physical functioning, role limitations caused by physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations caused by emotional problems, and mental health) [3]. Each scale is scored from 0 to 100. Higher scores indicate a better QOL. The validity and reliability of the Japanese version of SF-36 have been well established [4, 5].

Psychosocial demographic and medical background information

Medical information was assessed regarding the pathologic disease stage, performance status (0–4, defined by the Eastern Cooperative Oncology Group), and the presence or absence of pain and dyspnoea. Furthermore, the fighting spirit and helplessness/hopelessness as cognitive and behavior adjustment to cancer were assessed using the subscales of Mental Adjustment to Cancer scale (MAC) [6]. The validity and reliability of the Japanese version of the MAC have been confirmed [7]. Patients provided demographic information, including age, sex, occupation, and marital status.

Procedure

The Institutional Review Board and the Ethics Committee of the NCC, Japan approved this study, and each patient provided informed written consent.

All eligible outpatients were invited to participate in the study after their follow-up medical visit. The patients completed a series of questionnaires, and mailed them back. If the questionnaires contained any blanks and the patients had agreed to the terms of the study at the time of first contact, a single attempt was made to obtain the missing information by telephone.

Analysis

The Cronbach's α and the item-total correlation of each subscale of the QOL-CS-J were calculated to assess internal consistency reliability.

The Pearson's correlation coefficients between each subscale of the QOL-CS-J and SF-36 were computed to assess the concurrent validity. To test discriminant validity, *t*-tests or χ^2 tests were conducted with the medical background information as the independent variable and each subscale of QOL-CS-J as the dependent variable.

Data analyses were carried out with SPSS 12.0 statistical software. A significant difference was defined as $p < 0.05$.