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Prospective Comparative Study of Gefitinib Therapy for Postoperative Recurrent Non–small Cell Lung Cancer with Epidermal Growth Factor Receptor Mutations

Takao Ueno, Daisuke Hamatake, Takayuki Imakiire, Sou Miyahara, Takao Higuchi, Yasuteru Yoshinaga, Takeshi Shiraishi, Takayuki Shirakusa and Akinori Iwasaki

Department of Thoracic Surgery, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

Abstract：Purpose：This study was designed to investigate the efficacy and feasibility of gefitinib for the treatment of recurrent non-small cell lung cancer (NSCLC) patients after surgery with epidermal growth factor receptor (EGFR) mutations in comparison to conventional chemotherapy for those without EGFR mutations. Patients and Methods：The EGFR gene status of the recurrent NSCLC patients after surgery obtained from formalin-fixed and paraffin-embedded surgical specimens was examined by the DNA sequencing of EGFR exons 18 to 21. Patients with EGFR mutations received gefitinib (250 mg/day), and those without EGFR mutations received conventional chemotherapy. The response rate(RR), disease control rate(DCR), progression free survival (PFS), and toxicity profile were all assessed prospectively. Results：Between October 2005 and May 2007, 17 patients were examined for the EGFR status, and 7 patients(41%) harbored EGFR mutations. EGFR mutations were significantly more frequently found in females (P=0.021) and never smokers (P=0.021). Seven patients with EGFR mutations received gefitinib therapy and six patients without EGFR mutations received conventional chemotherapy. The response rate at 3 months in the gefitinib treated patients was 42.9% (95% CI, 6.2% to 79.6%), and the disease control rate was 71.4%(95% CI, 38% to 100%). The median PFS of these patients was 10.9 months (1.9 to 19.8 months). No life-threatening toxicity was observed. While these parameters in the conventional chemotherapy group were 0%, 16.7%(95% CI, 0% to 46.5%), and 5.4 months(1.1 to 14.2 months), respectively. Conclusion：Treatment with gefitinib for the recurrent NSCLC patients with EGFR mutations was thus found to achieve a high efficacy with acceptable toxicity.

Key words：Gefitinib, Non-small cell lung cancer, Prospective study, EGFR mutations, Postoperative recurrence

Introduction

Lung cancer is the leading cause of malignancy related death in Japan[1] and the world. Patients diagnosed to have metastatic and advanced non-small cell lung cancer (NSCLC) normally have a dismal prognosis that rarely reaches more than 1–2 years. Platinum doublet chemotherapy has been the basis of treatment of advanced NSCLC.[2] However, even the administration of platinum doublets plus bevacizumab, a vascular endothelial growth factor monoclonal antibody, could achieve response rates (RR) of at most about 30% in the phase II[3] and III[4] trials and the progression free survival (PFS) was less than 7.5 months. The median survival was hardly over 12 months.[4] In order to improve the outcomes for this heterogeneous disease, it is important to identify the subsets of NSCLC patients who can receive tailored therapies.

Correspondence to：Takao Ueno
Department of Thoracic Surgery, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
Tel：+81-92-801-1011 ext.3435 Fax：+81-92-861-8271 E-mail：uenot@fukuoka-u.ac.jp

Epidermal growth factor receptor (EGFR), a 170kDa protein containing tyrosine kinase domain (TK), is a member of the human epidermal receptor (HER) family.[5] The activation of this receptor transmits the downstream signal pathways and results in cell proliferation, angiogenesis, motility, protection from apoptosis and metastasis.[5] EGFR is highly expressed in many human cancers including lung cancer,[6)–8)] and therefore it is a target for cancer therapy.

Gefitinib (Iressa; AstraZeneca), an orally administered TK inhibitor (TKI), was the first targeted agent to be approved for the treatment of the patients with advanced NCSLC.[9)–10)] This drug binds to the adenosine triphosphate binding pocket of the EGFR TK domain, and blocks the downstream signaling pathways. In 2004, three groups of investigators identified somatic mutations in the TK domain of EGFR in patients with NCSLC which correlated with a dramatic response to gefitinib therapy.[11)–13)] Most of those mutations were found in the following two hotspots : in-frame deletions including amino acids at codons 746 to 750 (E746 to A750) in exon 19 and an amino acid substitution at codon 858 (L858R) in exon 21. A number of retrospective studies have shown those EGFR mutations to be more frequently detected in tumors from females, non-smokers, patients with an adenocarcinoma histology, and Japanese and East Asian patients. It is known that these features are clinical predictors of gefitinib sensitivity as well as indicators of favorable prognosis.[14)–24)]

The patients with recurrent NSCLC after a resection are often unable to tolerate aggressive cytotoxic chemotherapy. In chemotherapy for these patients, a high efficacy and low toxicity are needed. Gefitinib monotherapy (250 mg/day) is well tolerated and effective for patients with advanced NSCLC harboring EGFR mutations, so the patients with recurrent NSCLC after a resection harboring EGFR mutations are considered to receive some benefit from gefitinib therapy. However, no such prospective study has ever been reported. Therefore, we prospectively investigated the efficacy and toxicity of gefitinib monotherapy for these patients in comparison to conventional chemotherapy for those without EGFR mutations.

Materias and Methods

1. Eligibility criteria

Eligible patients postoperatively showed a relapse of NSCLC in which the diagnosis had been confirmed histologically at resection, and had not yet received systemic chemotherapy for recurrent disease either with or without a history of adjuvant chemotherapy. Other eligibility criteria included an age ≧20 years, measurable disease based on the RECIST guidelines,[25)] the availability of sufficient amounts of tumor specimens for an EGFR mutation analysis, an Eastern Cooperative Oncology Group performance status of 0–1, adequate organ function (WBC≧3,000/μl, Neutrophils ≧1,500/μl, platelets ≧100,000/μl, Hb≧8.0 g/dl, AST and ALT ≦twice the upper limit of the reference range, Total bilirubin and Serum creatinine ≦1.5 times the upper limit of the reference range, PaO2≧60 mmHg). The exclusion criteria included pulmonary fibrosis, thoracic irrdiation after a tumor resection, SVC syndrome, the history of severe drug allergy, active infection, the presence of symptomatic brain metastasis, active concomitant malignancy, severe heart disease, uncontrollable Diabetes mellitus, severe mental disorder, active gastrointestinal bleeding and continuous diarrhea. All patients were informed of the investigational nature of this study and signed a written informed consent form. The approval for both this study and the gene analyses was obtained from the Institutional Review Board and the Ethics Committee of our hospital.

2. EGFR gene analysis

Previous formalin-fixed and paraffin-embedded surgical specimens of primary NSCLC were used for the EGFR gene analysis. Tumor genomic DNA was prepared from paraffin-embedded sections using the microdissection method. The EGFR mutations in exons 18, 19 and 21, as previously reported,[11)–12)], were determined using polymerase chain reaction (PCR) amplification and intron-exon boundary primers according to the previously published method.[11)–12)] Polymerase chain reaction products were sequenced directly using the DNA sequencer (ABI PRISM 3100 Genetic

analyzer).

3. Study Design

Patients with EGFR mutations received Gefitinib therapy. Gefitinib (250 mg/day) was administered orally once daily. Treatment was continued either until disease progression or intolerable toxicity (Table 3). In contrast, the patients without EGFR mutations received conventional systemic chemotherapy. The regimen of anticancer drugs was not limited.

Routine clinical and laboratory assessments and blood gas analyses were performed either weekly or biweekly. Chest X-ray assessments were performed weekly during the first month of administration, thereafter biweekly or monthly. CT assessments of target lesions were performed monthly, while magnetic resonance imaging of the whole brain and a bone scintigraphy were performed every three months. The objective responses of the patients were evaluated every month according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[25] All adverse events during the gefitinib treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

4. Statistical Analyses

The primary endpoint of this study was the response rate at 3 months defined as the proportion of the patients whose response was CR or PR among all per-protocol patients. The secondary endpoints were the disease control rate (DCR) at 3 months, the progression free survival (PFS), and the overall survival (OS). The starting point of these analyses was the start of the treatment. PFS and OS probability estimates were based on the Kaplan-Meier method. The confidence intervals were calculated at the 95% level (95% CI). For comparisons of the proportions, Student's unpaired t-test and Fisher's exact test were used. A P value of <0.05 was considered to be statistically significant. The StatFlex software program (Artec, Inc. Japan) was used for the analyses.

Results

1. Patient characteristics

From October 2005 to May 2007, 17 relapsed NSCLC patients after resection were prospectively screened for this study (Figure 1). Of them, EGFR mutations were detected in 7 patients (41%), who received Gefitinib therapy (Group G). On the other hand, 4 of the 10 patients in whom no EGFR mutations were found, were ineligible for their choice of other treatments. As a result, 6 patients without EGFR mutations received conventional chemotherapy (Group C).

The patient characteristics are shown in Table

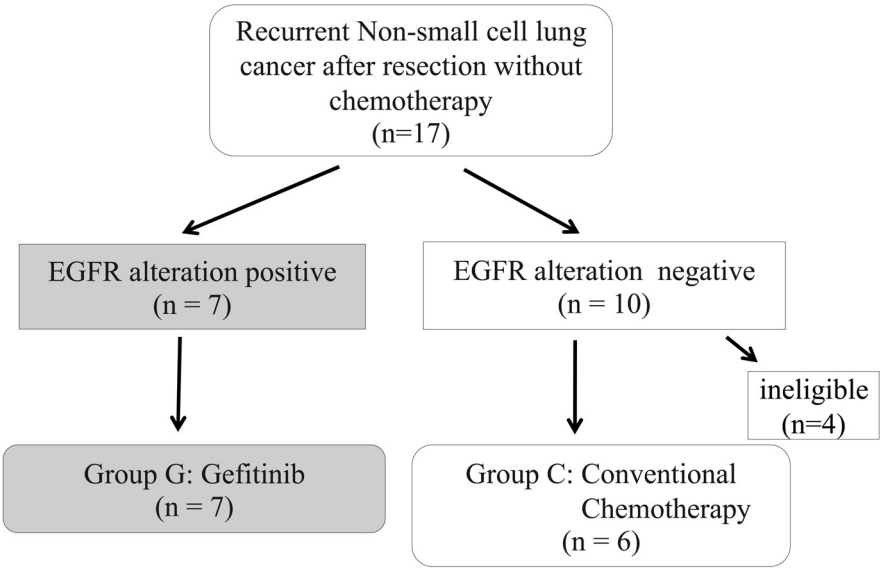

Fig. 1. Study Design (Prospective Study)

1. No significant differences were observed in the age, performance status, or the p-stage of primary tumor between Groups G and C. All patients with EGFR mutations were women, while two of six (33.3%) without EGFR mutations were women and the difference was significant (p=0.021). In addition, all patients with EGFR mutations were never smokers, but 4 of 6 patients (66.7%) without EGFR mutations were smokers (p=0.021). These features of the patients with EGFR mutations are similar to those described in many previous reports.[11)-24)] Regarding the histology type, all cases with EGFR mutations were adenocarcinomas with or without a bronchioloalveolar component (BAC), while in cases without EGFR mutations two non-adenocarcinoma types were observed.

Table 1. Patient Demographic

Characteristic	Group G (n=7) No.	%	Group C (n=6) No.	%	*p*
Median age, years	70.0		73.5		0.91
Range	54–78		51–78		
Sex					
Male	0	0	4	66.7	0.021
Female	7	100	2	33.3	
Performance status					
0	4	57.1	2	33.3	0.59
1	3	42.9	4	66.7	
Smoking status					
Current/former	0	0	4	66.7	0.021
Never smoked	7	100	2	33.3	
Histology					
Adeno	6	85.7	3	50	
Adeno w/BAC	1	14.3	1	16.7	0.097
Adenosq.	0	0	1	16.7	
Signet ring cell ca.	0	0	1	16.7	
Primary p-stage					
ⅠA	1	14.3	3	50	
ⅠB	2	28.6	0	0	0.16
ⅡA	2	28.6	0	0	
ⅡB	0	0	2	33.3	
ⅢA	1	14.3	1	16.7	
ⅢB	1	14.3	0	0	

Adeno：Adenocarcinoma, Adeno w/BAC：Adenocarcinoma with bronchioloalveolar carcinoma, Adenosq. ：Adenosquamous carcinoma
In Group G (with EGFR mutations), ratio of female and never smoker are significantly higher than in Group C (without EGFR mutations).

Table 2. Type of EGFR Alterations

Characteristic	No. of patients (n=7)	%
Exon 18		
G719A	1	14.3
Exon 19		
del E746–A750	1	14.3
Exon 21		
L858R	5	71.4
V834L	1	14.3

The TK domain of EGFR stretches from exon 18 to 24, somatic mutations are basically limited to exons 18–21 (687–875aa). L858R point mutations in exon 21 were most frequently detected in our study.

Table 3. Chemotherapy

EGFR alteration positive	EGFR alteration negative
Gefitinib：250 mg/day	Conventional cytotoxic chemotherapy
Oral administration until developing disease (PD) or appearance of severe adverse effects	No limitation of regimen

Regimen	No. of Patient
・GEM	3
・CDDP+DTX	1
・CBDCA+TXL	1
・CDDP	1

GEM：Gemcitabine, CDDP：Cisplatin, DTX：Docetaxel, TXL：Paclitaxel

Table 4. Clinical Efficacy

Condition	Group G (n=7) No.	%	95%CI	Group C (n=6) No.	%	95%CI	*p*
Complete response	0	0		0	0		
Partial response	3	42.9		0	0		
Overall response rate	3	42.9	6.2–79.6	0	0	0	0.067
Stable disease	2	28.5		1	16.7		
Disease control rate	5	71.4	38–100	1	16.7	0–46.5	0.048
Progressive disease	2	28.5		5	83.3		

Disease control rate of Group G was significantly higher than Group C. Two progressive disease cases of Group G showed Grade3 adverse effects and were stopped administration of Gefitinib. But during administration of Gefitinib, their clinical efficacy had been partial response.

However, in both groups adenocarcinomas either with or without BAC accounted for a majority of the tumors.

Type of EGFR alterations of Group G was shown in Table 2. L858R point mutations in exon 21 were detected in five patients (71.4%), a deletion E746－A750 in exon19 was detected in one patient(14.3%), and a G719A point mutation in exon 18 and a V834L point mutation in exon 21 were found in one same patient (14.3%).

2. Response and survival

The objective tumor responses are listed in Table 4. The response rate and DCR at 3 months were 42.9% (95% CI：6.2－79.6%) and 71.4% (95% CI：38.0–100%), respectively in group G. On the other hand, in group C they were 0% (95% CI：0－0%) and 16.7% (95% CI：0－46.5%), respectively. DCR in Group G was higher than Group C significantly (p＝0.048). In Group G, three of seven patients (42.9%) achieved PR, two (28.5%) exhibited SD, and two (28.5%) had PD, respectively. Two PD cases in Group G demonstrated grade 3 adverse effects (dyspnea and oral mucositis, respectively) and the administration of Gefitinib was stopped on the 54th. day and the 60th. day of treatment, respectively. However during the administration of gefitinib they achieved PR. Consequently, the best overall response rate and best overall DCR were 71.4% and 100% respectively, in Group G. In Group C three patients (50%) were treated with gemcitabine, while the other patients were treated with Cisplatin and Docetaxel, Carboplatin and Paclitaxel, and Cisplatin alone, respectively (Table 3). One (16.7%) of six patients in Group C exhibited SD, and five (83.3%) had PD. The best overall response rate and the best overall DCR were 0% and 16.7% respectively, in group C.

The Kaplan–Meier curve for PFS is shown in Fig. 2. The median follow－up time was 11.5 months (range：2.1－19.8 months). The median PFS time was 10.9 months (range:1.9–19.8 months) in group G, and 5.4 month (range：1.1－14.2 months), respectively. The median OS has not yet been reached. Two PD patients in group G died of cancer at 2.1 months and 3.5 months from treatment, respectively. While three of five PD patients in group C died of cancer at 3.2 months, 14.9 months, and 17.7 month, respectively.

3. Safety and toxicity

The Gefitinib related adverse events are shown in

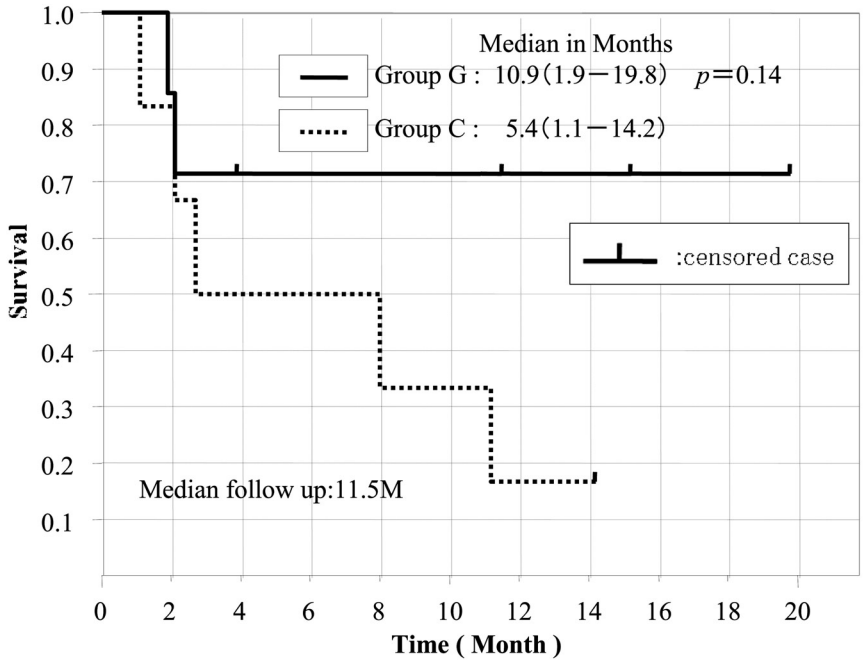

Fig. 2. Progression－Free Survival
Median time to progression was 10.9 months for Group G patients, on the other hand it was 5.4 months for group C.

Table 5. The most frequent adverse events were rashes in three patients (42.9%). Other adverse events included dyspnea in one patient (14.3%), elevated AST/ALT in one patient (14.3%). Grade 3 adverse events were found in 2 cases (Rash and Dyspnea). Due to the adverse events the administration of gefitinib was stopped in these 2 patients, while three continued to receive gefitinib every other day. No Interstitial Lung disease (ILD) was observed in this study.

Table 5. Gefitinib Related Adverse Events

	No. of patient (%) (n=7)			
Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Rash	1 (14.3)	1 (14.3)	1 (14.3)	0 (0)
Dyspnea	0 (0)	0 (0)	1 (14.3)	0 (0)
Elevated AST/ALT	0 (0)	1 (14.3)	0 (0)	0 (0)

Two cases of Grade 3 events were stopped administration of Gefitinib.

4. Gefitinib respondor in Group G

The most effective patient receiving gefitinib therapy in Group G is shown in Figure 3. A 78-year-old female who had undergone a right upper lobectomy due to advanced lung adenocarcinoma with pulmonary metastasis in the same lobe four years previously, received 5 courses of adjuvant chemotherapy with Gemcitabine, and subsequently had been maintained with the oral administration of UFT (300 mg/day). However, one year previously she had undergone a metastasectomy of two recurrent lesions in the right lower lobe, and thereafter new recurrent lesions developed on the right dorsal side of hilar region and the serum carcinoembryonic antigen (CEA) level also gradually increased. Since the start of gefitinib, the recurrent lesions decreased in size (Reduction ratio : 95.7%) and the serum CEA level also fell rapidly in one month. A Grade 1 rash appeared one month later, and gefitinib was thus administered every

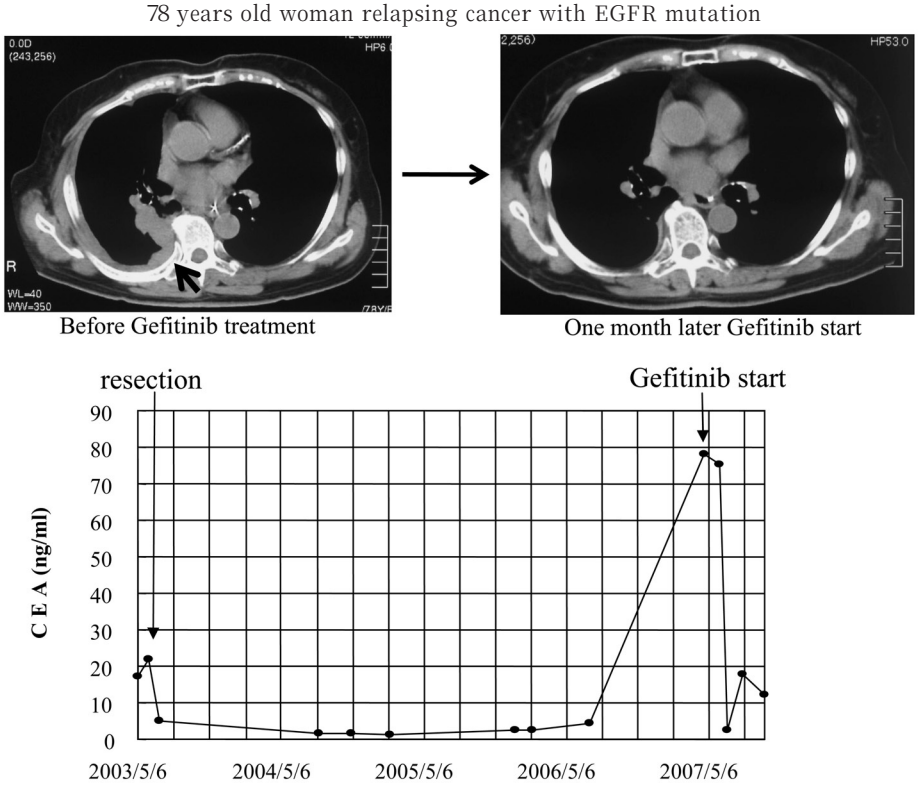

Fig. 3. Gefitinib Respondor
Black arrow shows recurrent lesion.
A 78 years old woman had recurrent disease 3 years after resection of Lung adenocarcinoma with EGFR mutations. One month later from the start of Gefitinib therapy, the size of recurrent lesion and serum carcinoembryonic antigen level had remarkably decreased.

other day, and the lesion has since remained well controlled.

Discussion

In this small scale prospective study, we reported the high best overall response rate (71.4%) and the best overall DCR (100%) to gefitinib monotherapy for recurrent NSCLC patients after surgery with EGFR mutations. According to 6 previous prospective studies of gefitinib monotherapy for advanced NSCLC,[26)-31)] the reported overall response rate, DCR, and the median PPFS are 75–90.5%, 87.5–99%, 7.7–12.9 months, respectively. In addition, Mitsudomi et al.[18)] in his retrospective study of gefitinib for recurrent NSCLC after surgery, reported the effective ratio of gefitinib to be 83%. Our data of gefitinib therapy for postoperative recurrent NSCLC are closely equivalent to those previously reported for advanced NSCLC.

In line with many previous reports, the cohort with EGFR mutations consisted of all women, never smokers, and patients with a histological finding of adenocarcinoma in our study. In some studies,[18) 26) 30)] most EGFR mutations were deletions in exon 19 (E746 to A750) followed by point mutations in exon 21 (L858R), but in our study most of the EGFR mutations were L858R. Jackman et al.[32)] and Riely et al.[33)] reported patients with exon 19 deletions to have a higher response rate than those with point mutations in exon 21. In this study, a patient with an exon 19 deletion has achieved PR. However, the patient with the most effective response to gefitinib had a point mutation in exon 21, and high serum carcinoembryonic antigen (CEA) level. Okamoto et al.[34)] reported the serum CEA level to be a predictive marker for sensitivity to gefitinib, thus supporting our findings. One woman with two EGFR mutations in exon 18 and 21 had a SD response to gefitinib and was well controlled without any disease progression.

Regarding toxicity, neither life-threatening ILD nor diarrhea occurred in our study. Two patients with grade 3 adverse events (rash, dyspnea, respectively) stopped gefitinib and thereafter their diseases became uncontrollable. They had achieved PR response until gefitinib administration was stopped. Due to rash and liver disorder, three of five patients have continued gefitinib every other day, and have been well controlled on an outpatient basis without any reduction in their quality of life. Hanaoka et al. reported a good controlled elderly patient with recurrent NSCLC treated with every other day administration of gefitinib.[35)] We therefore consider that such patients should continue gefitinib every other day as long as the adverse effects are tolerable and the disease is controlled. In addition, Ando et al. reported that, among 1976 NSCLC patients treated with gefitinib, 3.5% developed ILD and 1.6% died.[36)] They identified a male sex, smoking history and interstitial pneumonia as significant risk factors. Though there were no men and smoker in gefitinib therapy group in our study, the patients with such risk factors should be carefully monitored when receiving gefitinib therapy. As a result, gefitinib for recurrent NSCLC patients after surgery also seems to be safely administered on an outpatient basis.

Due to the slow case accumulation of cases, the sample size of our study was not large enough to detect the significant difference in the PFS between 2 groups. However, the PFS in Group G trended to be longer than that in group C. The overall survival could not be compared because of the small sample size, a short median follow-up time, and the heterogeneity of treatments after progressive disease between two groups. Indeed in conventional chemotherapy group, five patients with a PD response received various regimens of chemotherapy and irradiation, while two patients in whom gefitinib was stopped received best supportive care due to a drastic progression of disease.

Conclusion

This small scale study suggests that the recurrent NSCLC patients after surgery with EGFR mutations obtain substantial benefit from gefitinib therapy without reducing their quality of life. Large-scale trials are needed to develop more effective treatment strategies and to improve the clinical application of appropriate gefitinib administration in recurrent NSCLC patients after surgery.

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