Cover page

Title: The Effect of Gefitinib in Patients with Postoperative Recurrent Non-small Cell Lung Cancer Harboring Mutations of the Epidermal Growth Factor Receptor

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ABSTRACT

Background: It is unclear whether there is a difference in the effect of gefitinib treatment between patients with postoperative recurrent non-small cell lung cancer (NSCLC) and those with stage IV NSCLC harboring mutations in the epidermal growth factor receptor (EGFR).

Methods: We retrospectively reviewed the medical records of consecutive patients with postoperative recurrent NSCLC (postoperative group) or stage IV NSCLC harboring EGFR mutations (stage IV group) who were treated with gefitinib at the Shizuoka Cancer Center between September 2002 and March 2012 to compare the effect of gefitinib and survival from treatment initiation.

Results: A total of 168 patients were treated with gefitinib (postoperative group, 49 patients; stage IV group, 119 patients). The response rate of gefitinib treatment in the postoperative group was similar to that in the stage IV group (58 versus 61%, $p = 0.613$). In contrast, median progression-free survival (PFS; 15.8 versus 9.8 months, $p < 0.001$) and median overall survival (OS; 51.1 versus 22.2 months, $p < 0.001$) were significantly longer in the postoperative group. In addition, postoperative recurrent disease, performance status (0–1), and a single metastatic organ were independent favorable prognostic factors in the multivariate analysis of survival.

Conclusions: PFS and OS were superior in patients with postoperative recurrent NSCLC harboring EGFR mutations treated by gefitinib than in those with stage IV disease. These results suggested that postoperative recurrent disease may be considered a stratification factor in clinical trials for NSCLC with

EGFR mutations.

Key words: Non-small cell lung cancer, Epidermal growth factor receptor mutations, Postoperative recurrence, Stage IV, Gefitinib

Introduction

Surgical resection is considered the most effective treatment for early stage non-small cell lung cancer (NSCLC), and can provide the maximum opportunity for cure and to improve survival. However, despite complete surgical resection, 50%–60% of patients with stage I-IIIA NSCLC relapse and die [1,2]. Postoperative NSCLC relapse is seldom curable, and the median survival time after recurrence is estimated at 8.1–17.7 months [3,4]. An optimal treatment strategy for postoperative recurrence is designed for each patient to relieve clinical symptoms, maintain quality of life, and delay disease progression.

Gefitinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor with reported efficacy in limited populations, harboring EGFR mutations including activating mutations such as a deletion in exon 19 and the L858R point mutation in exon 21 [5]. Several clinical trials in patients with advanced NSCLC harboring EGFR mutations have demonstrated that as compared with chemotherapy, gefitinib results in significantly longer progression-free survival (PFS) and higher response rates[6,7]. According to these results, gefitinib can be considered a standard therapy for patients with stage IV NSCLC harboring EGFR mutations.

Therefore, gefitinib is frequently used for treatment of patients with postoperative recurrent NSCLC harboring EGFR mutations in clinical practice, in accordance with treatment for patients with stage IV

NSCLC. However, it remains unclear whether there is a difference in the effect of gefitinib treatment between patients with postoperative recurrent NSCLC and stage IV NSCLC harboring EGFR mutations. The objectives of this retrospective study were to evaluate effect of gefitinib and survival between these two patient groups.

Patients and methods

Patients

We retrospectively reviewed clinical data from the medical records of consecutive patients with postoperative recurrent or stage IV NSCLC harboring EGFR mutations, who were treated with gefitinib, at the Shizuoka Cancer Center between September 2002 and March 2012. Gefitinib was administered at 250 mg/day until disease progression or unacceptable toxicity. Treatment change such as dose reduction or skipping was based on the physician's decision. Patients were excluded if they had received other EGFR tyrosine kinase inhibitors before gefitinib administration.

Evaluation of patient characteristics

All pretreatment and treatment parameters were compared between the following two groups: one group with postoperative recurrent NSCLC (postoperative group) and a second group with stage IV NSCLC at diagnosis (stage IV group). All patients underwent a systematic evaluation and standardized staging procedures before the start of systemic treatment. Clinical stage was assigned based on the results of a physical examination, chest radiography, computed tomography scans of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bone scintigraphy or positron emission tomography. Patients were excluded if they had only postoperative local recurrence without distant metastases. Performance status (PS) was evaluated based on the Eastern Cooperative Oncology Group (ECOG) PS scale. EGFR mutations were examined by commercial clinical laboratories. Only one patient with a single brain metastasis was diagnosed as pathological stage IV NSCLC and was included in the postoperative group. Although both the primary lesion and brain metastasis were completely resected, the patient experienced postoperative disease recurrence. On the other hand, patients who received only exploratory thoracotomy were included in the stage IV group. Adjuvant chemotherapy in the postoperative group was not considered as first line chemotherapy in this study. If patients have symptomatic brain metastases, we selected stereotactic radiotherapy or whole brain radiotherapy before gefitinib treatment in our institution.

Evaluation of efficacy

The response to gefitinib treatment was evaluated according to the guidelines of the Response Evaluation Criteria in Solid Tumors version 1.1 [8]. After the start of gefitinib, chest radiography was performed every 1 month. And, computed tomography of the chest and abdomen was performed every 2 to 3 months. When patients have been treated with gefitinib longer than 1 year, the frequency of radiologic examination was suitably adjusted by the physician's judgment. If disease progression was suspected by chest radiography, additional computed tomography was performed as necessary. Magnetic resonance imaging of the brain and positron emission tomography were performed based on the physician's decision, when clinical signs and symptoms suspicious for brain and bone involvement were present. PFS was defined as the period between the start of gefitinib treatment and progressive disease or death from any cause. Overall survival (OS) was defined as the period between the start of gefitinib treatment and the date of death from any cause.

Statistical analyses

The chi-squared and Mann–Whitney U tests were used to evaluate differences in categorical and continuous variables between the two groups, respectively. OS and PFS were evaluated using the Kaplan–

Meier method and compared using the log-rank test. Cox proportional hazards models were used to adjust for potential confounding factors. A p value of <0.05 was considered statistically significant. All analyses were performed using JMP 10 for Windows statistical software (SAS Institute Japan Inc., Tokyo, Japan). This study was approved by the institutional review board of Shizuoka Cancer Center.

Results

Patient characteristics

A total of 168 patients with postoperative recurrent NSCLC (49 patients, 29.2%) or stage IV NSCLC (119 patients, 70.8%) were included in this study. In the postoperative group, pathological stages I, II, III, IV, and multiple primary sites were noted in 14 (28.6%), 17 (34.7%), 15 (30.6%), 1 (2.0%), and 2 (4.1%) patients, respectively. The median interval from surgical resection for the primary disease to the start of cytotoxic chemotherapy or gefitinib was 17.0 months. The baseline characteristics stratified by the groups are summarized in Table 1. The distribution of gender and age were similar between the two groups. Patients in the postoperative group showed better PS than those in the stage IV group (p = 0.049). Almost all patients were pathologically diagnosed with adenocarcinoma. The type of EGFR mutation did not differ between the two groups. About 30% patients in both groups received cytotoxic chemotherapy

before gefitinib treatment.

Metastatic sites

Metastatic sites stratified by the groups are summarized in Table 2. At the start of gefitinib treatment, 20 (40.8%) patients in the postoperative group and 71 (59.7%) in the stage IV group had multiple metastatic organs. Patients in the stage IV group had significantly more metastatic organs than those in the postoperative group ($p = 0.033$). The predominant metastatic organs differed between the two groups, because bone and liver metastases were more common in the stage IV group ($p < 0.001$ and $p = 0.034$, respectively), while pulmonary metastases were more common in the postoperative group ($p = 0.003$).

Responses and survival

The median follow-up period from the start of gefitinib treatment was 24.6 months. Of the 168 patients, 153 (91.1%) were observed until disease progression and 103 (61.3%) until death. The response rate (RR) of gefitinib treatment in the postoperative group was comparable with that in the stage IV group (57.1 versus 61.3%, $p = 0.613$). However, the median PFS was significantly longer in the postoperative group than in the stage IV group (15.8 versus 9.8 months, $p < 0.001$) (Figure 1). The median OS was also

significantly superior in the postoperative group than in the stage IV group (51.1 versus 22.2 months, $p < 0.001$) (Figure 2).

Prognostic factor

The results of univariate and multivariate analyses for OS are shown in Table 3. In the univariate analysis for OS, postoperative group, PS (0–1), and a single metastatic organ were associated with favorable survival. Multivariate analysis showed that postoperative group (hazard ratio (HR) = 0.389, 95% confidence interval (CI) = 0.220–0.657, $p < 0.001$), PS (0–1) (HR = 0.461, 95% CI = 0.272–0.787, $p = 0.005$), and a single metastatic organ (HR = 0.442, 95% CI = 0.279–0.690, $p < 0.001$) were independent favorable prognostic factors.

Discussion

In our study, the RR of gefitinib treatment was comparable between both groups, but PFS and OS were significantly superior in patients with postoperative recurrent NSCLC harboring EGFR mutations than in those with stage IV disease. To our knowledge, there are only two reports in literature that have presented similar results. Mitsudomi et al. reported the results of phase III study (WJTOG3405) that compared the

effect of gefitinib with that of cisplatin plus docetaxel in patients with NSCLC harboring EGFR mutations. In this study, 71 of 172 (41.3%) patients had postoperative recurrent disease. Exploratory analyses of PFS in this study showed that patients with postoperative recurrent disease had a significantly better prognosis than those with stage IIIB/IV disease (HR = 0.433, 95% CI = 0.290–0.649, $p < 0.001$) [7]. Sekine et al. conducted a retrospective study to compare the effects of chemotherapy in postoperative recurrent NSCLC patients with stage IV NSCLC patients regardless of EGFR mutations. Although the RR of chemotherapy was comparable between postoperative recurrent NSCLC patients and stage IV NSCLC patients, PFS and OS were superior in the former (median PFS; 5.5 versus 4.2 months, $p = 0.007$ and median OS; 21.3 versus 13.3 months, $p < 0.001$). Multivariate analysis showed that patients with postoperative recurrent NSCLC had a better prognosis than those with stage IV NSCLC (HR = 0.66, 95% CI = 0.540–0.810, $p < 0.001$) [9]. In our study, the HR of the postoperative group to the stage IV group for OS was 0.389 (95% CI = 0.220–0.657, $p < 0.001$). These results suggested that patients with postoperative recurrent NSCLC may have better prognosis than those with stage IV. These results were also confirmed in a report by ECOG [10].

Although the reasons for these results remain unclear, there are several hypotheses. These results may be related to tumor heterogeneity and burden because tumor heterogeneity may contribute to resistance, and small cell subpopulations may acquire or stochastically already possess some features that enable them to emerge under selective drug pressure [11–15]. Most patients with postoperative recurrent NSCLC

received regular follow-ups after surgical resection; thus, the tumor burden may be lower than in patients with stage IV NSCLC at diagnosis. These differences in tumor heterogeneity and burden may be associated with favorable PFS and OS in patients with postoperative recurrent NSCLC [12,15–17]. In our study, patients in the postoperative group had less metastatic sites than those in the stage IV group. The results may support the difference in tumor burden between the two groups [16]. These results suggest that surgical reduction of tumor burden may improve the effectiveness of gefitinib treatment in patients with stage IV NSCLC harboring EGFR mutations. Several types of cancer (such as ovarian cancer and renal cell carcinoma) are treated by surgical reduction of tumor burden in clinical practice [15,18–20]. In addition, the efficacy of surgical reduction has been reported in selected patients with stage IV NSCLC [21–23]. Therefore, further clinical trials are warranted to develop and evaluate new treatment methods for patients with stage IV NSCLC harboring EGFR mutations.

In addition to postoperative recurrent disease, good PS and a single metastatic organ were independent favorable prognostic factors in our study. Good PS has been widely accepted as one of the most important favorable prognostic factors in lung cancer patients [10,24–26]. Previous studies have reported that a number of metastatic organs were associated with survival [10,16,25] in accordance with the results presented in the present study. Although age, gender, and smoking history were also reported as prognostic factors in extensive stage NSCLC [10,24–27], they were not significantly associated with survival in our study. However, these reports evaluated patients with NSCLC regardless of EGFR

mutations, whereas our study included only patients harboring EGFR mutations of whom 70% were female and 65% had no history of smoking. Thus, this patient distribution may have influenced these results.

There were several limitations to our study. First, we retrospectively collected the data from a single institution. Second, the number of patients in the postoperative and stage IV group was imbalanced. Therefore, further multiinstitutional studies are warranted to confirm our results.

In conclusion, PFS and OS were superior in patients with postoperative recurrent NSCLC harboring EGFR mutations treated by gefitinib than in those with stage IV disease. However, the RR of gefitinib treatment demonstrated no difference between the two groups. These results suggested that postoperative recurrent disease may be an independent prognostic factor, and should be considered as a stratification factor in clinical trials for NSCLC with EGFR mutations.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Table 1 Patient characteristics at the start of gefitinib treatment

	Postoperative group (n = 49)	Stage IV group (n = 119)	
	n (%)	n (%)	*p*
Sex			0.951
Male	15 (30.6)	37 (31.1)	
Female	34 (69.4)	82 (68.9)	
Age median (range)	71 (42–85)	66 (31–92)	0.077
Performance status			0.049
0–1	43 (87.8)	88 (73.9)	
2–4	6 (12.2)	31 (26.1)	
Smoking status			0.479
Never	31 (63.3)	82 (68.9)	
Previous/Current	18 (36.7)	37 (31.1)	
Histology			—
Adenocarcinoma	46 (93.9)	119 (100)	
Nonadenocarcinoma	3 (6.1)	0	
Type of EGFR mutation			0.970
Exon 19 deletion	25 (51.0)	59 (49.6)	
L858R	20 (40.8)	49 (41.2)	
other	4 (8.2)	11 (9.2)	
Prior chemotherapy before gefitinib treatment			0.525
No	35 (71.4)	79 (66.4)	
Yes	14 (28.6)	40 (33.6)	

EGFR, epidermal growth factor receptor

Table 2 Metastatic sites

	Postoperative group (n = 49)	Stage IV group (n = 119)	
	n (%)	n (%)	*p*
Number of metastatic organs			0.033
1	29 (59.2)	48 (40.3)	
>2	20 (40.8)	71 (59.7)	
Metastatic sites			
Brain			0.181
No	35 (71.4)	72 (60.5)	
Yes	14 (28.6)	47 (39.5)	
Bone			<0.001
No	34 (69.4)	49 (41.2)	
Yes	15 (30.6)	70 (58.8)	
Lung			0.003
No	27 (55.1)	93 (78.2)	
Yes	22 (44.9)	26 (21.8)	
Liver			0.034
No	48 (98.0)	104 (87.4)	
Yes	1 (2.0)	15 (12.6)	

Table 3 Univariate and multivariate analysis for overall survival

	Hazard Ratio (95% Confidence Interval)			
	Univariate Analysis	*p*	Multivariate Analysis	*p*
Group				
Stage IV group	1		1	
Postoperative group	0.323 (0.188–0.528)	<0.001	0.389 (0.220–0.657)	<0001
Type of EGFR mutation				
Exon 19 deletion	1		1	
L858R	1.276 (0.843–1.928)	0.248	0.920 (0.595–1.422)	0.708
Other	1.282 (0.630–2.384)	0.471	0.957 (0.456–1.850)	0.901
Sex				
Female	1		1	
Male	0.980 (0.639-1.471)	0.923	0.936 (0.555-1.564)	0.824
Age				
75≤	1		1	
<75	0.771 (0.496–1.240)	0.275	0.718 (0.453–1.172)	0.180
Performance status				
2–4	1		1	
0–1	0.342 (0.222–0.539)	<0.001	0.461 (0.272–0.787)	0.005
Smoking				
Previous/Current	1		1	
Never	1.046 (0.695–1.611)	0.831	0.776 (0.469–1.307)	0.336
Chemotherapy before gefitinib				
Yes	1		1	
No	1.165 (0.775–	0.467	0.982 (0.611–	0.940

		1.786)		1.595)	
Number of metastatic organs					
	Multiple	1		1	
	Single	0.401 (0.264–0.560)	<0.001	0.442 (0.279–0.690)	<0.001

EGFR, epidermal growth factor receptor

Fig. 1.

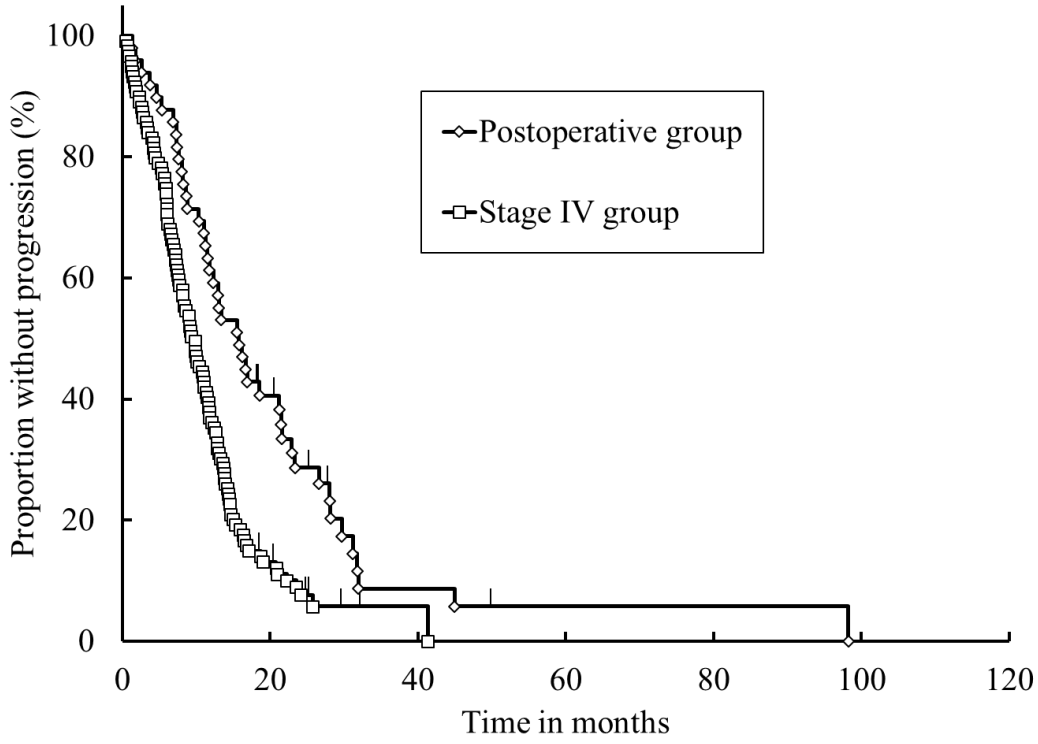
Proportion without progression (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Time in months
Postoperative group
Stage IV group

Fig. 2.

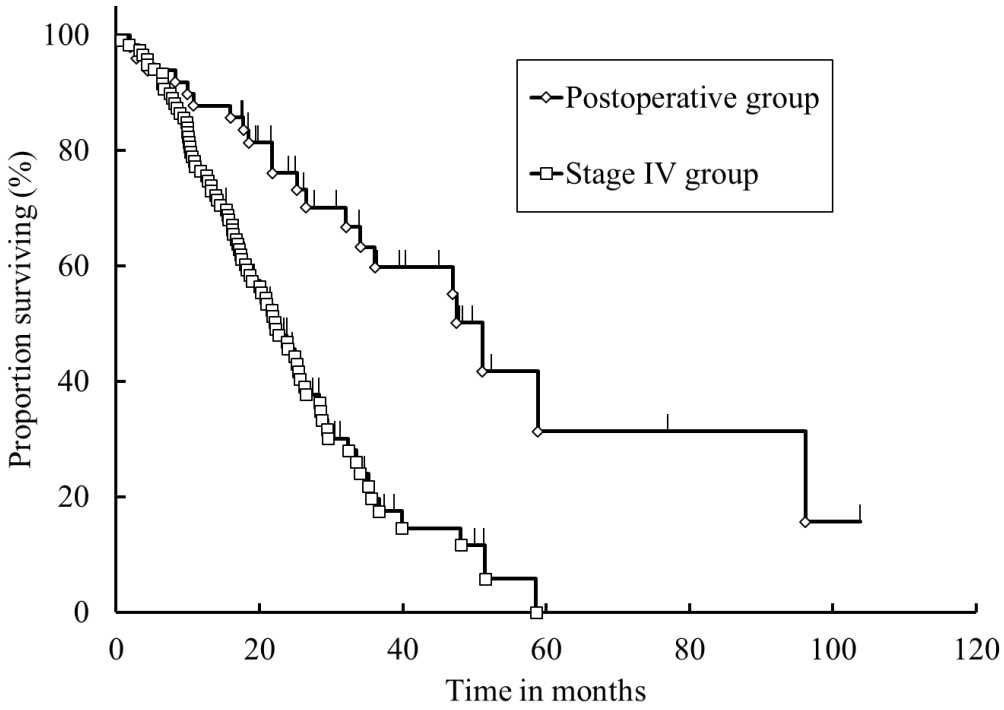
Proportion surviving (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Time in months
Postoperative group
Stage IV group

Figure legends

Fig. 1. Progression-free survival of patients in the postoperative (n = 49) and stage IV groups (n = 119).

Fig. 2. Overall survival of patients in the postoperative (n = 49) and stage IV groups (n = 119).