Clinical Outcomes in Elderly Patients Administered Gefitinib as First-line Treatment in Epidermal Growth Factor Receptor-mutated Non-small Cell Lung Cancer: Retrospective Analysis in a Nagano Lung Cancer Research Group Study

Kazunari Tateishi 1), Takashi Ichiyama 1), Kazuya Hirai 2), Toshihiko Agatsuma, 3), Shigeru Koyama 4), Tsutomu Hachiya 5), Nobutoshi Morozumi 6), Takayuki Shiina 7), Tomonobu Koizumi 8)

1) First Department of Internal Medicine, 7) Department of Second Surgery, and 8) Comprehensive Cancer Center, Shinshu University, Matsumoto City, 2) Department of Pulmonary Diseases, Nagano Municipal Hospital, Nagano City; 3) Department of Respiratory Medicine, National Hospital Organization Shinshu Ueda Medical Center, Ueda City, 4) Department of Pulmonary Diseases, Nagano Red Cross Hospital, Nagano City, 5) Department of Pulmonary Diseases, Suwa Red Cross Hospital, Suwa City, 6) Department of Pulmonary Disease, Saku Central Hospital, Saku City

Corresponding Author: Tomonobu Koizumi, MD, PhD,

Comprehensive Cancer Center, Division of Clinical Oncology, Shinshu University Hospital, 3-1-1 Asahi Matsumoto Nagano 390-8621 Japan

Phone: +81-263-37-2631

Fax: +81-263-36-3722

Email: tomonobu@shinshu-u.ac.jp

ABSTRACT[214 words (do not exceed 250)]

Purpose: The clinical efficacy and outcomes of gefitinib therapy as a first-line treatment for elderly patients with non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) mutations were analyzed retrospectively.

Patients and methods: We analyzed chemotherapy-naïve NSCLC patients aged 75 years or older who had *EGFR* mutations (exon 19 deletion mutation or L858R), who were initially treated with gefitinib (250 mg) once daily in Nagano Prefecture.

Results: A total of 55 patients (16 men, 39 women) with a median age of 81.1 years (range: 75 – 94 years) treated between April 2007 and July 2012, were analyzed. The overall response rate and disease control rate were 72.7% (95% confidence interval (CI); 59.5% – 82.9%) and 92.7% (95% CI: 82.0% – 97.6%), respectively. Median progression-free survival and overall survival from the start of gefitinib treatment were 13.8 months (CI: 9.9 – 18.8 months) and 29.1 months (95% CI: 22.4 – not reached), respectively. Two-year survival rate was 59.5% (95% CI; 41.0% – 78.8%). Major grade 3 toxicities were skin rash (1.8%) and increased levels of aspartate aminotransferase or alanine aminotransferase (7.3%).

Conclusion: First-line treatment with gefitinib for elderly *EGFR*-mutated NSCLC patients was effective and well tolerated. The results suggest that first-line gefitinib should be considered as a preferable standard treatment in elderly patients with advanced NSCLC harboring *EGFR* mutations.

Key Words: non-small cell lung cancer, elderly patients, first-line, *EGFR* mutations, gefitinib

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in Japan and throughout the world [1, 2]. Non-small cell lung cancer (NSCLC) accounts for 80% – 85% of all lung cancers, and half of all patients already have metastatic disease with no indications for local therapy, such as surgery or radiotherapy, at the time of diagnosis. Furthermore, approximately 50% of patients diagnosed with or dying from NSCLC are 70 years or older around the world [1-4]. In general, doublet combinations of platinum compounds are standard regimens as first-line treatment in advanced-stage NSCLC [5, 6]. However, only 13% – 17% of patients over 70 years old were enrolled in previous studies [6, 7]. In addition, although it has been shown that the efficacy of chemotherapy for the elderly is similar to that in younger patients, it is generally more toxic in elderly patients in terms of both incidence and severity [5, 8]. Thus, based on several clinical studies [5, 8], monotherapy with vinorelbine, gemcitabine, or docetaxel is recommended in advanced and non-selected NSCLC, especially in patients aged 75 years or older [9, 10].

On the other hand, the current treatment paradigm focused on identifying potential predictors for treatment benefits, especially in molecular targeted agents. Gefitinib, an oral small molecule agent that acts as an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), is the first molecular targeted agent to be approved for the treatment of NSCLC patients. The extremely high response rate (RR) for gefitinib is associated with the presence of active *EGFR* mutations in tumor cells, such as in-frame deletions in exon 19 or point mutations in exon 21 (*e.g.*, L858R) [11 – 13]. Several phase III

trials comparing chemotherapy to gefitinib in a first-line setting demonstrated that gefitinib could produce improved progression-free survival (PFS) compared to platinum-containing chemotherapy in patients harboring *EGFR*-activating mutations [14 – 16]. However, these trials targeted NSCLC patients aged ≤ 75 years, and the clinical benefit of EGFR-TKI in *EFGR*-mutated NSCLC patients over 75 years old remains undetermined.

We previously conducted a prospective phase II study in elderly (≥ 75 years old) *EGFR*-mutated patients with advanced NSCLC and reported RR of 58.6% and median PFS of 12.9 months [17]. Subsequently, Maemondo et al. [18] reported RR of 74% and PFS of 12.3 months in the same clinical setting. These results suggest that first-line gefitinib would be preferable to standard therapy in elderly patients. However, the numbers of patients enrolled in these studies were too small to elucidate the efficacy of first-line gefitinib. In the present study, we retrospectively evaluated the clinical outcomes in elderly patients (≥ 75 years old) with advanced NSCLC and gefitinib-sensitive *EGFR* mutations in Nagano prefecture, Japan.

PATIENTS AND METHODS

We retrospectively analyzed patients aged 75 years or more treated in Shinshu University Hospital and associated hospitals in Nagano prefecture, Japan, from April 2007 to July 2012, who were *EGFR*-mutated NSCLC and received gefitinib as first-line therapy. The histological diagnosis and stage of NSCLC were based on the World Health Organization (WHO) classification version 3 [19, 20] and

Tumor-node-metastasis (TNM) staging system [21], respectively. Performance status (PS) was estimated according to the Easterm Cooperative Oncology Group (ECOG) classification.

Before therapy, each patient underwent physical examination, chest radiography, computed tomography scans of the thorax and abdomen, bone scintigraphy or F-18 fluorodeoxyglucose positron emission tomography, and magnetic resonance imaging scan of the brain to evaluate the TNM stage. If patients were diagnosed as having local NSCLC but were not suitable for thoracic surgery because of poor PS or other diseases, subjects treated with first-line gefitinib were included in the present analysis. We examined *EGFR* mutation status using the peptide nucleic acid-locked nucleic acid (PNA-LNA; Mitsubishi Chemical Medicine, Tokyo, Japan) PCR clamp method with paraffin sections of histological or cytological specimens. We defined gefitinib-sensitive *EGFR* mutations as exon 19 deletion mutation and L858R point mutation in the present study. For the identified and selected subjects, an electronic clinical record search was performed in each hospital and patient privacy was protected when using individual information.

Gefitinib (250 mg) was administered orally once daily and continued until disease progression or intolerable toxicity. The response to gefitinib therapy was evaluated using the response evaluation criteria in solid tumors (RECIST) version 1.0 [22]. Disease control rate (DCR) was defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). Progression-free survival (PFS) was defined as the period from initiation of gefitinib therapy to the date of progressed disease (PD)

confirmation or death from any cause. Overall survival (OS) was defined as the interval between the date of therapy initiation and the date of death from any cause or last follow-up. The survival curves were calculated using the Kaplan–Meier method. Toxicities associated with gefitinib therapy were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [23]. After failure of first-line gefitinib therapy, patients were permitted any subsequent treatments desired, including continuation of gefitinib treatment. Statistical analyses were performed using SPSS ver. 11.0 for Windows (IBM, Chicago, IL).

RESULTS

Patient Characteristics

Fifty-five patients harboring *EGFR*-mutated NSCLC were included in the analysis. The characteristics are listed in Table 1. Thirty-nine were women (70.9) , with a median age of 81.1 years (range: 75 – 94 years). Thirty-nine patients were never smokers. The mean number of pack years in patients with smoking history was 22.7, ranging from 1.3 to 40. Forty-three patients (83.7%) had PS of 0 or 1 according to ECOG, followed by 7 patients with PS 2 and 2 with PS 3 – 4. Histological type in all patients was adenocarcinoma. According to the TNM staging system, 3 patients had stage IIA disease, but they were considered to be medically inoperable because of poor PS and cerebrovascular disease. Two patients had stage IIIA disease, 4 patients had stage IIIB disease, and 40 patients had stage IV disease. There were 6 patients with postoperative recurrence. In terms of *EGFR* mutation 31 patients had exon 19

deletion mutation and 24 patients had L858R point mutation. There were medical complications in the listed subjects. Four patients had concomitant malignant diseases, such as prostate and breast cancer, which were well controlled with hormonal therapy.

Response to gefitinib therapy and survival

The objective tumor response rate (RR) is described in Table 2. One patient reached CR and 39 patients met the criteria of PR. Eleven patients showed SD during the observation period. Four patients showed PD. Thus, overall RR and DCR were 72.7% (95% confidence interval (CI); 59.5% – 82.9%) and 92.7% (95% CI; 82.0% – 97.6%), respectively. The median follow-up time was 16.0 months (range: 1 – 48 months). The survival curves are shown in Figures 1A and B. Median PFS was 13.8 months (95% CI: 9.9 – 18.8 months; Figure 1A), and median survival time (MST) was 29.1 months (95% CI: 22.4 – not reached; Figure 1B). Two-year survival rate was 59.5% (95% CI : 41.0% – 78.0%).

Toxicities

Toxicities were evaluated in all patients and the main toxicities of first-line gefitinib therapy are summarized in Table 3. The most common adverse event was skin toxicity. Skin rash was observed in 41.8% of patients. Increased levels of AST or ALT appeared in 20.0% of patients, and grade 3 or more was observed in 7.3%. These serious adverse events were improved with temporary withdrawal of gefitinib or alternate-day administration. Alternate-day administration was performed in 13 patients (23.6%) . Other toxicities observed were mild. Interstitial lung disease (ILD) was observed in three

subjects but improved with cessation of gefitinib therapy or corticosteroid therapy. Thus, none of the patients developed acute respiratory failure.

Treatment after progression of disease

Information about second-line therapy after PD was unknown in 6 cases. Twenty patients were still receiving first-line gefitinib therapy without developing PD during the observation period. Table 4 lists the second-line therapy in the remaining 29 patients. Cytotoxic chemotherapy was performed in 7 patients. Three patients received carboplatin plus pemetrexed, and 4 patients received monochemotherapy with cytotoxic agents, including docetaxel, pemetrexed, or S-1. Eight patients continued EGFR-TKI by switching to erlotinib or continuing gefitinib. Thirteen patients received best supportive therapy without any second-line treatment. One patient received thoracic radiotherapy to the metastatic site.

DISCUSSION

In the present study, we found that first-line gefitinib showed a high RR and extended survival time in elderly NSCLC patients harboring *EGFR* mutations. We reported in a previous prospective study that RR was 58.6%, which was slightly less than in the present study (72.7%) and another prospective study (74%) [17]. The difference was due to the small number of patients enrolled in our previous trial (n = 17). The median PFS and two-year-survival rate in two previous prospective studies [17, 18] were reported to be 12.9, 12.3 months and 63%, 61%, respectively. The median PFS of 13.8 months and two-year-survival rate of 59.5% obtained here were identical to the values in these previous prospective

studies. In addition, several clinical phase III trials involving *EGFR*-mutated NSCLC patients demonstrated significantly longer PFS, than in those receiving platinum-based combination chemotherapy [14-16]. These trials involved patients aged ≤ 75 years old, but the PFS ranged from 9.2 to 10.8 months. It is noteworthy that first-line gefitinib therapy in elderly *EGFR*-mutated NSCLC showed a prolonged PFS in comparison with younger patients. As the reason for this remains unclear, further clinical studies to determine the differences in efficacy of EGFR-TKI between age groups are warranted.

Toxicities with first-line gefitinib therapy in elderly patients were generally mild and predictable. The incidence and severity were also identical to those observed in patients aged ≤ 75 years old [14-16]. Three patients developed ILD, but responded well to corticosteroid treatment. No patients discontinued therapy due to gefitinib-related adverse events except ILD in this study.

A number of the patients in the present study suffered from other medical complications. Furthermore, the incidence of PS > 2 was 16.4% in the present analysis. These patients had a relatively low tolerance to standard first-line chemotherapy. As the introduction of first-line gefitinib in each case was dependent on the decision of the attending physician, our results may have included the clinical outcomes in elderly patients who were reluctant to receive first-line cytotoxic chemotherapy. For frail patients with *EGFR*-mutated NSCLC, e.g., poor PS over grade 3 or elderly (> 75 years old) with PS > 2, it was demonstrated that first-line gefitinib therapy showed a high RR (66%) and relatively long OS

(17.8 months) [12]. Therefore, we believe that gefitinib is a good alternative as a first-line treatment for elderly patients.

At the time of data analysis, 7 of 29 relapsed subjects (24.1%) received subsequent cytotoxic chemotherapy after failure of gefitinib therapy. Most patients (13/29; 44.8%) eventually selected treatment with the best supportive care available. In the MILES study, which compared three groups over 70 years old [24], only 6% – 13% of patients received second-line treatment with cytotoxic agent chemotherapy, In a Japanese study [10], which compared docetaxel with vinorelbine in a population > 70 years old, 47.5% of patients received second-line chemotherapy; however, gefitinib was used as second-line chemotherapy in most cases (63.5%). Thus, subsequent chemotherapy using cytotoxic agents in elderly patients with NSCLC was limited in elderly NSCLC patients in contrast to non-elderly patients. In addition, standard second-line treatments in elderly NSCLC have not been established. The influence of second-line or later therapies on overall survival in patients with *EGFR*-mutated NSCLC remain unknown. We postulated that PFS extension may be evident in elderly patients, although the extension of PFS using gefitinib in non-elderly NSCLC was not reflected by achieving extension of OS. Thus, we suggest that elderly patients with sensitive *EGFR* mutations could be treated with first-line EGFR-TKI and should not miss out on the chance to receive EGFR-TKI therapy simply due to poorly timed administration.

NEJ002, a phase III trial comparing gefitinib with carboplatin-paclitaxel as the first-line treatment

for advanced NSCLC with sensitive *EGFR* mutations [14], demonstrated that quality of life (QOL) was maintained much longer in patients treated with gefitinib than in those treated with standard chemotherapy [25]. Unfortunately, we were unable to evaluate QOL in the present study. However, we speculated that maintenance of QOL in elderly patients with *EGFR*-mutated NSCLC would be similar to that in patients less than 75 years old based on the results of prospective studies [13]. Thus, we recommend that first-line gefitinib therapy should be considered even focusing on the maintenance of QOL.

In conclusion, our results demonstrated remarkable efficacy and tolerance of first-line gefitinib in elderly *EGFR*-mutated patients. Although this was a retrospective study, our results suggest that first-line gefitinib should be considered as a preferable standard treatment in elderly patients with advanced NSCLC harboring *EGFR* mutations.

Acknowledgements

We thank the patients and their families for their support and participation in this study. We also thank Akihiro Tsukadaira in Iida Municipal Hospital, Muneharu Hayasaka in Chushin Matsumoto Hospital, Akio Morokawa in Showa Inan Hospital and all of the members of Nagano Lung Cancer Research Group for their helpful support.

Conflict of interest

Conflict of interest: Nil.

FIGURE LETTERING

Fig. 1 Kaplan–Meier plot of progression-free survival (A) and overall survival (B) in elderly *EGFR*-mutated non-small cell lung cancer patients treated with first-line gefitinib.

Median progression-free survival was 13.8 months (95% CI : 9.9 – 18.8 months; Figure 1A), and median survival time was 29.1 months (95% CI: 22.4 – not reached; Figure 1B). The two-year survival rate was 59.5% (95% CI : 41.0% – 78.0%)

References

1. Matsuda T, Marugame T, Kamo, et al. Cancer incidence and incidence rates in Japan in 2006: based on data from 15 population-based cancer registries in the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol. 2012;42:139-47.

2. Marugame T, Matsuda T : Comparison of time trends in lung cancer incidence (1973-2002) in Asia, from cancer incidence in five continents Vols IV-IX. Jpn J Clin Oncol. 2009;39:133-5.

3. Lee-Chiong TL Jr, Matthay RA: Lung cancer in the elderly patient. Clin Chest Med. 1993;14: 453-78.

4. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol. 2007;25:5570-7.

5. Azzoli CG, Baker S Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small Cell Lung Cancer J Clin Oncol. 2009;27:6251-66.

6. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346:92-8.

7. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst. 2002;94:173-81.

8. Provencio M, Camps C, Alberola V, et al. Lung cancer and treatment in elderly patients: The Achilles

Study. Lung Cancer. 2009;66:103-6.

9. The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) Group: Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. J Natl Cancer Inst. 1999;91:66-72,

10. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol. 2006;24:3657-63.

11. Morita S, Okamoto I, Kobayashi K, et al. Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. Clin Cancer Res. 2009;15:4493-8.

12. Inoue A, Kobayashi K, Usui K, et al. North East Japan Gefitinib Study Group. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol. 2009;27:1394-400.

13. Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol. 2012;30:1122-8.

14. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380-8.

15. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor

(WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11:121-8.

16. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-57.

17. Asami K, Koizumi T, Hirai K, Ameshima S, et al. Gefitinib as first-line treatment in elderly epidermal growth factor receptor-mutated patients with advanced lung adenocarcinoma: results of a Nagano Lung Cancer Research Group study. Clin Lung Cancer. 2011;12:387-92.

18. Maemondo M, Minegishi Y, Inoue A, et al. First-Line Gefitinib in Patients Aged 75 or Older With Advanced Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutations: NEJ 003 Study. J Thorac Oncol. 2012;7:1417-22.

19. Travis WD, Colby TV, Corrin B, et al. Histological typing of lung and pleural tumors. In: World Health Organization international histological classification of tumors. 3rd ed. Berlin:Springer, 1999.

20. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Pathology and genetics. In: Tumors of the lung, pleura, thymus and heart. Lyon: IARC Press, 2004.

21. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposalsfor the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol. 2007;2:706-14.

22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer

Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92: 205–16.

23. Title of subordinate document. In: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. National Cancer Institute.2012. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 of subordinate document. Accessed 28 Nov 2012.

24. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst. 2003;95:362-72.

25. Oizumi S, Kobayashi K, Inoue A, et al. Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial. Oncologist. 2012;17:863-70.

Figure 1.

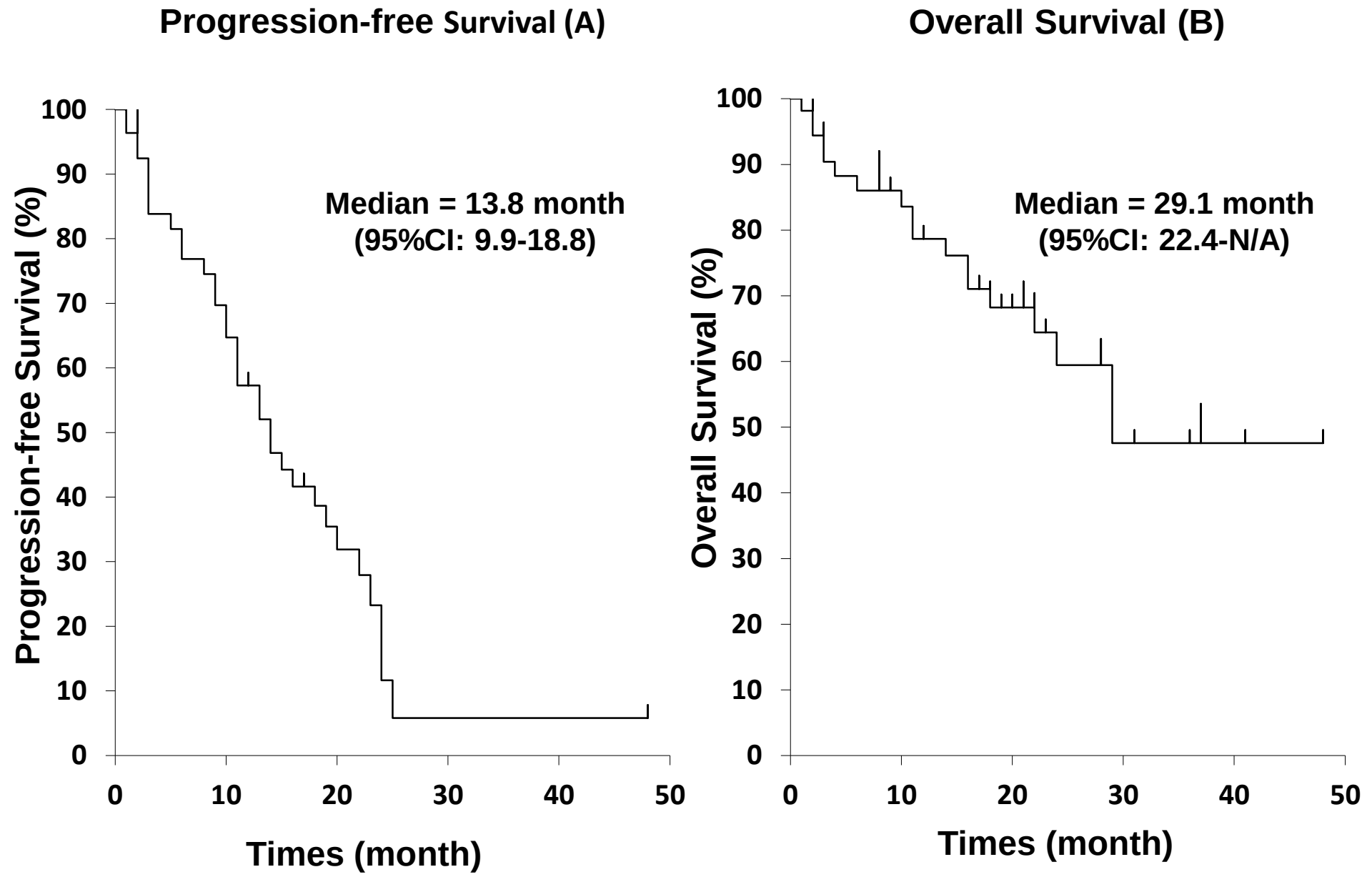
Progression-free Survival (A)
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Median = 13.8 month
(95%CI: 9.9-18.8)
0
10
20
30
40
50
Times (month)
Overall Survival (B)
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Median = 29.1 month
(95%CI: 22.4-N/A)
0
10
20
30
40
50
Times (month)

Table 1 Patient Characteristics (*n* = 55)

Characteristic	Number of patients
Median age, (range)	**81.1 (75 – 94)**
Sex	
Male / Female	**16 (29.1%) / 39 (70.9%)**
Smoking status	
Never / Former or Current / Unknown	**39 (70.9%) / 7 (12.7%)/ 9 (16.4%)**
Median pack years * (range)	**22.7 (1.3 – 40)**
Performance status (ECOG)	
0 / 1 / 2 / 3 / 4	**21 (38.2%) / 25 (45.5%) / 7 (12.7%) / 1 (1.8%) / 1 (1.8%)**
Histology	
Adenocarcinoma	**55 (100%)**
Stage	
IIA / IIIA / IIIB / IV	**3 (5.5%) / 2 (3.6%) / 4 (7.3%) / 40 (72.7%)**
recurrence after surgery	**6 (10.9%)**
***EGFR* mutation**	
Exon 19 deletion mutation / Exon 21 L858R	**31 (56.4%) / 24 (43.6%)**
Complication	
Hypertension	**21 (38.2%)**
Diabetes mellitus	**5 (9.1%)**
Heart diseases	**6 (10.9%)**
Digestive system disease	**8 (14.5%)**
COPD	**3 (5.5%)**
Cerebrovascular disease	**3 (5.5%)**
Other concomitant malignant tumors	**4 (7.3%)**

ECOG: Eastern Cooperative Oncology Group, EGFR: epidermal growth factor receptor, Heart disease: valvular disease, arrhythmia, ischemia; COPD: chronic obstructive pulmonary disease.

*** Subjects were current or former smokers.**

Table 2 Response to first-line gefitinib therapy in elderly patients with *EGFR*-mutated NSCLC

Response	Number of Patients	Response Rate (%)	95% CI
Complete Response	**1**	**1.8%**	
Partial Response	**39**	**70.9%**	
Stable Disease†	**11**	**20.0%**	
Progressive Disease	**4**	**7.3%**	
Overall response rate		**72.7%**	**59.5% – 82.9%**
Disease control rate‡		**92.7%**	**82.0% – 97.6%**

EGFR: epidermal growth factor receptor, NSCLC: non-small cell lung cancer, CI: confidence interval

†Stable disease was confirmed and sustained for 8 weeks or longer.

‡Disease control rate is defined as CR + PR + SD.

Table 3 Toxicities in first-line gefitinib therapy in elderly patients with *EGFR*-mutated NSCLC

Toxicity (*n* = 55)	Grade				Number of toxicities	
	1	2	3	4	≥ Grade 1 (%)	≥ Grade 3 (%)
Skin rash	18	4	1	0	41.8%	1.8%
Dry skin	16	1	0	0	30.9%	0.0%
Itching	11	2	0	0	23.6%	0.0%
Diarrhea	10	0	0	0	18.2%	0.0%
AST or ALT	4	3	4	0	20.0%	7.3%
Stomatitis	6	1	0	0	12.7%	0.0%
Pneumonitis	1	2	0	0	5.5%	0.0%

EGFR: epidermal growth factor receptor, NSCLC: non-small cell lung cancer, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Table 4

After first-line gefitinib therapy (*n* = 29)

Therapies	Number of Patients	Rate (%)
Chemotherapy	**7**	**24.1%**
EGFR-TKI	**8**	**27.6%**
Radiotherapy	**1**	**3.4%**
Best Supportive Care	**13**	**44.8%**

EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor