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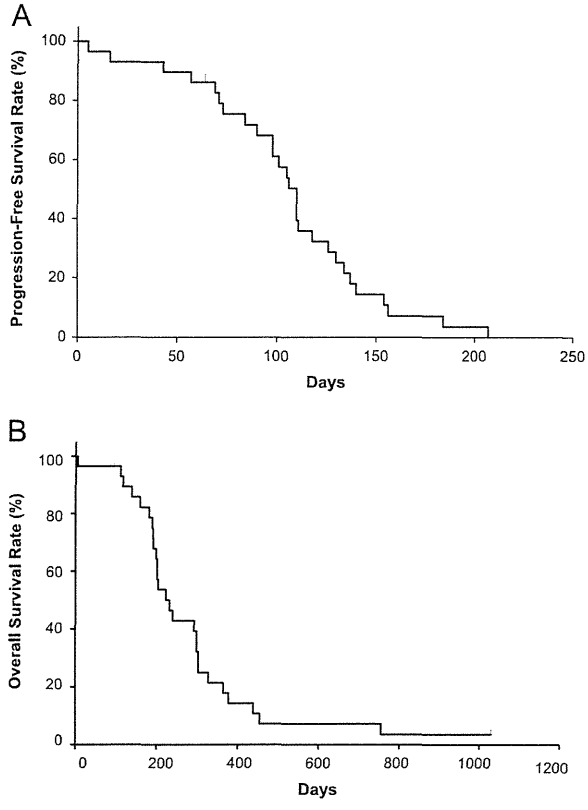

Fig. 1 – (A) Progression-free survival and (B) overall survival.

Table 3 – Toxicity profile.

Toxicity (≥ grade 2)	Grade (CTCAE)			
	Number of patients			
	2	3	4	Grade 3/4 (%)
Hematological				
Neutropenia	0	10	13	23 (79%)
Decreased hemoglobin	11	6	1	7 (24%)
Thrombocytopenia	6	4	3	7 (24%)
Febrile neutropenia	–	1	0	1 (3%)
Non-hematological				
Infection	4	2	0	2 (6%)
Nausea	2	0	0	0
Fatigue	1	0	0	0
Mucositis oral	1	0	0	1 (3%)
Stomach pain	1	0	0	0
Phlebitis	1	0	0	0
Hiccups	1	0	0	0
Pain	1	0	0	0
Interstitial lung disease	0	1	0	1 (3%)
Hyponatremia	0	2	0	2 (6%)
Hypoglycemia	0	0	1	1 (3%)

CTCAE, Common terminology criteria for adverse events.

SCLC, the combination of AMR and CBDCA is worth investigating. Contrary to our expectations, most patients in this study received sufficient cycles of platinum-doublet therapy as first-line chemotherapy. The ORR might have increased if more patients had been treated with insufficient first-line chemotherapy. According to subgroup analysis, this regimen might be suitable for patients treated with CBDCA as first-line chemotherapy. The efficacy of CBDCA plus AMR was not different in patients treated with ETP or CPT as first-line chemotherapy with platinum, which was consistent with our previous result of AMR as second-line chemotherapy [6]. Although the sample size was too small, the above-mentioned results require further validation.

In another Japanese study, even AMR alone demonstrated a quite high response rate (40%) in refractory relapsed SCLC [9], although the result might be biased due to its small sample size ($n=16$), considering the result of a subsequent larger study [7]. Other studies have used combined regimens for relapsed SCLC, some of which suggested high efficacy. However, most of those studies included both sensitive and refractory relapse patterns [4]; thus, their usefulness in refractory relapsed SCLC was unclear.

Toxicity is another important issue for such combination regimens. The above-mentioned previous regimens for relapsed SCLC were generally very toxic. For example, Kubota reported that dose-intensive CODE (CDDP, vincristine, doxorubicin, and ETP) could result in an ORR of approximately 80% in patients with refractory relapsed SCLC; however, that regimen required prophylactic G-CSF support due to severe neutropenia [10]. In contrast, AMR combined with CBDCA showed moderate toxicity in this study, which might be attributable to the dose of CBDCA being AUC 4. We reported this regimen in another study, where toxicity profiles tended to be similar and the efficacy for SCLC was sufficient (ORR was 89% as first-line treatment) [11]. Regarding the AMR dose, the current dose was one level lower than the recommended dose in our phase I and phase II studies of patients with chemotherapy-naïve SCLC because we considered that previously treated patients would be at a higher risk of myelosuppression. Although we believe this combination with the current dosage would be worth investigating in the second-line setting in terms of the risk–benefit balance, there might be scope for increasing the AMR dose to increase its efficacy.

This study has a few limitations. First, the sample size was too small to draw definite conclusions, the efficacy of this combination needs to be confirmed in a future phase III study in which the current regimen could be compared with AMR alone. Second, the drug dose might be insufficient for refractory relapsed cases. Considering that the toxicity of the current dose was moderate, there might be scope to increase the CBDCA or AMR dosage. In addition, the patients that would benefit most from the re-administration of platinum during second-line chemotherapy should be identified.

In conclusion, AMR combined with CBDCA was effective for refractory relapsed SCLC and demonstrated acceptable toxicity. Since treatment options for patients with refractory relapsed SCLC remain limited, further investigation of this regimen is warranted.

Conflict of interest

Akira Inoue received honoraria and research funding from AstraZeneca; Satoshi Oizumi received honoraria from AstraZeneca and research funding from Eli Lilly; Toshihiro Nukiwa received honoraria from Boehringer Ingelheim.

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First-line gefitinib for elderly patients with advanced NSCLC harboring EGFR mutations. A combined analysis of North-East Japan Study Group studies

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Objective: To assess outcomes of elderly patients with advanced NSCLC harboring an *EGFR* mutation treated with gefitinib, as well as safety and impact on quality of life (QoL).

Methods: We performed a retrospective analysis of pooled data from one Phase III and two Phase II studies of 71 patients aged ≥ 70 years with a performance status of 0 – 2. The main outcome measures were progression-free survival (PFS), overall survival (OS) and response rate (RR), as well as incidence of adverse events and time to 9.1% deterioration in QoL.

Results: Median PFS (14.3 vs 5.7 months, $p < 0.001$) and overall RR (73.2 vs 26.5%, $p < 0.001$) in the gefitinib group were superior to those in the standard chemotherapy group, whereas median OS was not significantly different (30.8 vs 26.4 months, $p = 0.42$). Elevation of aspartate transaminase and/or alanine transaminase (18.3%) was the most common adverse event, and one treatment-related death (pneumonitis) occurred. Time to 9.1% deterioration in the QoL domains of pain and dyspnea, anxiety, and daily functioning was similar between the two age groups.

Conclusion: First-line gefitinib is efficacious with acceptable toxicity in relatively fit elderly patients with advanced NSCLC harboring an *EGFR* mutation.

Keywords: EGFR tyrosine kinase inhibitors, elderly patients, gefitinib, NSCLC

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1. Introduction

Improved understanding of the molecular pathways underlying the pathogenesis of NSCLC has led to the development of agents that target specific components in these pathways. In particular, mutations of the *EGFR* gene result in aberrant growth of tumor cells in NSCLC, and targeted molecular therapy with EGFR tyrosine kinase inhibitors (TKI) has been developed to treat advanced NSCLC [1]. One such EGFR TKI is gefitinib [2]. In the PIONEER study that examined *EGFR* mutation frequency in 1482 Asian patients (in China, Hong Kong, Taiwan, Thailand, Vietnam, India and the Philippines) with advanced lung adenocarcinoma, the incidence of *EGFR* mutations in the Asian population was estimated to be ~ 51% (range, 22 – 64%) [3]. The relatively high incidence of *EGFR* mutation in Asian NSCLC patients suggests that a significant proportion of these patients may be eligible for EGFR TKI therapy.

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Several large clinical trials of gefitinib have demonstrated improved progression-free survival (PFS) but not overall survival (OS) in patients with advanced NSCLC containing an activating mutation in *EGRF* compared with platinum-based doublets. The IPASS trial of East Asian patients with untreated advanced lung adenocarcinoma showed that 12-month PFS was 24.9% in the gefitinib group (n = 609) compared with 6.7% in the carboplatin–paclitaxel group (n = 608), with the improvement in median PFS being dependent on the presence of an *EGFR* mutation [4,5]. In patients with *EGFR* mutations, the West Japan Oncology Group 3405 trial of 172 patients demonstrated that PFS was significantly longer in the gefitinib-treated group than in the cisplatin plus docetaxel group (9.2 vs 6.3 months, n = 86 in each group) [6], and longer PFS (10.8 vs 5.4 months) was also observed in the North-East Japan Study Group 002 trial examining gefitinib (n = 114) versus carboplatin–paclitaxel (n = 110) [7]. Gefitinib was generally well tolerated in these studies, with common adverse effects being rash, diarrhea and liver dysfunction.

EGFR TKI therapy has been studied in elderly patients with advanced NSCLC, but analyses were originally conducted in unselected populations. In the study by Maemondo *et al.* that evaluated gefitinib therapy for 31 chemotherapy-naive elderly Japanese patients with advanced NSCLC harboring an *EGFR* mutation, the overall response rate (RR) was 74% whereas medial PFS was 12.3 months [8]. Additional information on response to gefitinib in elderly patients with advanced NSCLC harboring an *EGFR* mutation is needed because of the relatively low numbers of elderly patients in individual studies. Therefore, the aim of this study was to evaluate the efficacy and feasibility of gefitinib as first-line therapy for elderly patients with advanced NSCLC harboring an *EGFR* mutation by examining the combined results of one Phase III trial (NEJ002) [7] and two Phase II trials (NEJ001 and NEJ003) [8,9].

2. Patients and methods

2.1 Study design

This was a retrospective analysis of a subgroup of elderly patients in multicenter Phase II and III studies that examined gefitinib therapy for advanced untreated NSCLC harboring EGFR mutations. Specifically, NEJ001 was a Phase II study examining the efficacy and feasibility of gefitinib for patients with poor PS; NEJ002 was a Phase III study on the efficacy and safety of gefitinib compared with carboplatin plus paclitaxel; and NEJ003 was a Phase II study examining the efficacy and feasibility of gefitinib in elderly patients (≥ 75 years). The presence of EGFR mutations in all patients was determined in cytological or histological specimens by the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, as described previously [10].

Gefitinib at 250 mg was administered orally once daily, and treatment was ceased when there was evidence of disease progression, intolerable or severe toxicity occurred, or if consent was withdrawn. The dose of gefitinib was reduced when severe toxicity occurred, in accordance with protocol. Those who received carboplatin plus paclitaxel (in NEJ002) were given paclitaxel at a dose of 200 mg/m^2 intravenously over a 3-h period and carboplatin (dose equivalent to an area under the curve of six, with the dose in milligrams calculated using the Calvert formula) intravenously over a 1-h period, with both agents administered on the first day of every 3-week cycle [7].

2.2 Patients

The institutional review board of each participating hospital approved the study, and patients had provided written informed consent in the respective studies.

A total of 174 patients with advanced NSCLC received gefitinib as initial treatment in the three studies (NEJ001 [n = 29], NEJ002 [n = 114] and NEJ003 [n = 31]). Common inclusion criteria of the three studies were stage IIIb/IV NSCLC with an EGFR mutation and no prior chemotherapy. Eastern Cooperative Oncology Group performance status (ECOG PS) and age limit differed between the studies. ECOG PS 1 – 4 was permissible for NEJ001 whereas only ECOG PS of 0 – 1 was allowed in NEJ002 and NEJ003. Age of participants was restricted to 75 years or older for NEJ003. Those with the *EGFR* mutation T790M were excluded.

In the present study, patients aged ≥ 70 years with ECOG PS of 0 – 2 were selected from the three studies for further analysis, resulting in a cohort of 71 elderly patients who had been treated with gefitinib. A total of 34 patients who received carboplatin plus paclitaxel in the NEJ002 study were included for comparison.

2.3 Outcome measures

Clinical assessment using computed tomography every 1 – 2 months was conducted to determine the clinical response, with the adoption of unidirectional measurements based on Response Evaluation Criteria in Solid Tumors (RECIST). The primary endpoint was PFS, which was defined as the period from randomization to observation of disease progression or death. The secondary endpoints were OS – defined as time from randomization to death or the most recent follow-up date – and RR, which was the rate of complete plus partial responses. Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for AEs (version 3.0).

An analysis of quality of life (QoL) was conducted using care notebooks, specifically examining the QoL domains of pain and shortness of breath, anxiety, and daily functioning [11]. The care notebook is a 24-item, self-administered, cancer-specific questionnaire on the patient's condition during a 1-week period, separated into categories of physical, mental and life well-being. Each item is rated on an 11-point linear scale. The care notebook was completed once a week.

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Table 1. Patient numbers and characteristics.

Characteristic	Gefitinib (n = 71)	Carboplatin–Paclitaxel (n = 34)	p value
Eligible patients: no. (%)			
NEJ 001 study	7 (10)		
NEJ 002 study	33 (46)	34 (100)	
NEJ 003 study	31 (44)		
Sex: no. (%)			0.37
Male	19 (27)	13 (38)	
Female	52 (73)	21 (62)	
Age: years			< 0.001
Mean	76.8	71.9	
Median	75	72	
Range	70 – 89	70 – 75	
Smoking status: no. (%)			0.29
Never smoked	53 (75)	22 (65)	
Previous or current smoker	18 (25)	12 (35)	
ECOG PS: no. (%)			
0	34 (48)	17 (50)	PS 0 – 1 vs 2
1	31 (44)	17 (50)	0.16
2	6 (8)	0 (0)	
Histologic diagnosis: no. (%)			0.54
Adenocarcinoma	67 (94)	33 (97)	
Other	4 (6)	1 (3)	
Clinical stage: no. (%)			1.00
IIIB/ IV (UICC 6th Edition)	64 (90)	31 (91)	
Postoperative relapse	7 (10)	3 (9)	
Type of EGFR mutation no. (%)			
Exon19del	35 (49)	16 (47)	
L858R	32 (45)	16 (47)	
Other	4 (6)	2 (6)	

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2. Treatment response.

Response	Gefitinib (n = 71) Number of patients (%)	Carboplatin–Paclitaxel (n = 34)
Complete response	3 (4.2)	0 (0.0)
Partial response	49 (69.0)	9 (26.5)
Stable disease	15 (21.1)	16 (47.1)
Progressive disease	4 (5.6)	5 (14.7)
Response that could not be evaluated	0 (0.0)	4 (11.8)
Response rate (%)	73.2*	26.5
95% CI (%)	61.3 – 83.0	12.9 – 44.5
Disease control rate (%)	94.4‡	73.6
95% CI (%)	86.2 – 98.4	55.5 – 87.4

*$p < 0.001$.
‡$p = 0.003$.

Time to 9.1% deterioration in QoL was chosen as an endpoint based on prior studies [11], which recognized deterioration on the basis of a QoL score change from baseline by one point on the 11-point scale (9.1%), or more, in a direction indicating worse QoL at any time point.

2.4 Statistical analysis

Categorical variables were analyzed using the chi-square test with Fisher's exact test used for small sample sizes (when a value of five is expected in any cell of the contingency table). Two-sided tests were performed except for the trend test for which a one-sided test was applied. Survival estimation was carried out using the unstratified log-rank test for between-arm comparison and Kaplan–Meier estimations for medians, and Kaplan–Meier curves were created for PFS and OS. Differences in QoL parameters between age groups were assessed using the log-rank test. Statistical significance was set at a level of 0.05.

3. Results

3.1 Patient characteristics

Data for 71 elderly gefitinib-treated patients (NEJ001, n = 7; NEJ002, n = 33; NEJ003, n = 31) were examined in this study (Table 1). Their median age was 75 years (range, 70 – 89) and the proportion of women was 73%. The proportion of never smokers was 75 and 92% had a PS of 0 or 1. Apart from age, there were no significant differences between the carboplatin–paclitaxel and gefitinib-treated elderly groups. The median age of gefitinib-treated patients was relatively high in this study because no upper age limit was imposed in the NEJ003 study.

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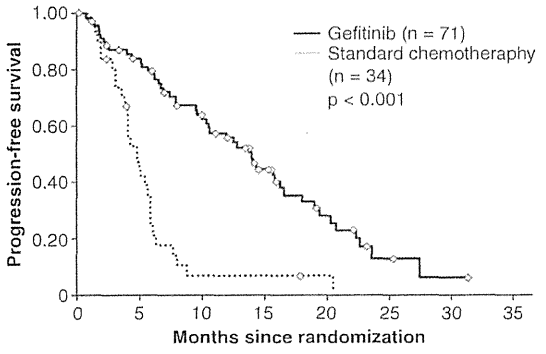

Figure 1. Progression-free survival.

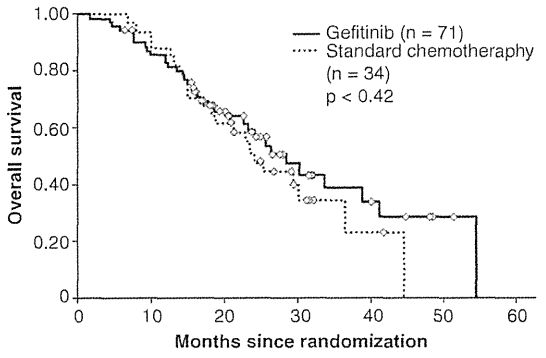

Figure 2. Overall survival.

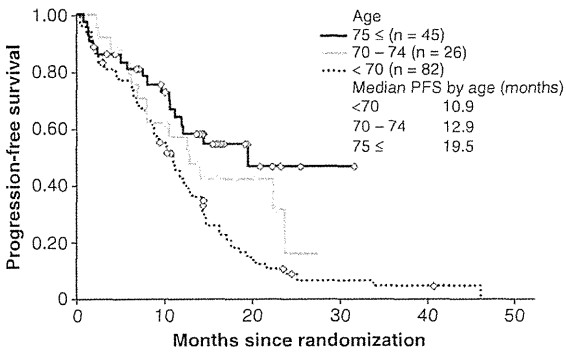

Figure 3. Progression-free survival by age in the gefitinib group.
PFS: Progression-free survival.

With respect to the type of *EGFR* mutation, the majority of cases demonstrated either exon 19 deletion or exon 21 L858R point mutation in both the gefitinib (35/71 [49%] and 32/71 [45%], respectively) and chemotherapy (16/34 [47%] for both types) groups.

3.2 Gefitinib efficacy

The overall RR was 73.2% (52/71) in the gefitinib group and 26.5% (9/34) in the carboplatin–paclitaxel group ($p < 0.001$) whereas the disease control rate (DCR; the sum of patients achieving a complete response, partial response or stable disease – that is, the sum of patients achieving non-progressive disease) was 94.4% in the former and 73.6% in the latter ($p = 0.003$) (Table 2). As shown in Figure 1, the median PFS was 14.3 months and 5.7 months in the gefitinib and standard chemotherapy groups, respectively, with a significant difference in PFS between the two groups ($p < 0.001$). Figure 2 shows the OS rates in the two groups. The median OS was 30.8 months and 26.4 months in the gefitinib and standard chemotherapy groups, respectively, with no significant difference in OS between the two groups ($p = 0.42$). Despite the fact that few patients in the gefitinib group received second-line chemotherapy, the median OS was not inferior to that in the standard chemotherapy group, possibly because all 34 patients who received chemotherapy as initial therapy received gefitinib as second-line treatment.

On further analysis of PFS in the gefitinib group stratified by age (< 70, 70 – 74, and ≥ 75 years), no significant differences in median PFS between the three age groups were seen (Figure 3). Compared with the 82 patients aged < 70 years in the NEJ002 study, PFS of elderly patients (i.e., those aged ≥ 70 years) was longer.

3.3 Gefitinib safety

Table 3 shows AEs in the gefitinib group. The most common AE was elevation of aspartate transaminase and/or alanine transaminase (18.3%), followed by rash and other non-hematological toxicity (4.2% each). Elevation of aspartate transaminase/alanine transaminase was also the most common grade ≥ 3 AE, whereas the most frequent grade 2 AE was rash. One treatment-related death (grade 5 pneumonitis) occurred. The type and incidence of AEs were not significantly different from those in non-elderly patients in the NEJ002 study [7].

3.4 QoL assessment

The results of the QoL assessment that examined time to 9.1% deterioration are shown in Figure 4. No differences in the QoL domains of pain and dyspnea, anxiety, and daily functioning were seen between the < 70 years and ≥ 70 years age groups.

4. Discussion

The present retrospective study verified the efficacy and safety of gefitinib in elderly patients using data compiled from

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Table 3. Adverse events of grade 2 or worse in the gefitinib group.

Toxicity	Grade 2 No.	Grade 3 No.	Grade ≥ 4 No.	Total no. of grade ≥ 3 toxicity No.	%
Hematologic					
Leukocytopenia	3	0	0	0	0
Neutropenia	1	0	0	0	0
Anemia	4	0	0	0	0
Thrombocytopenia	1	0	0	0	0
Non-hematologic					
Pneumonitis	0	1	1	2	2.8
aspartate transaminase/alanine transaminase	8	12	1	13	18.3
Rash	22	3	0	3	4.2
Diarrhea	4	1	0	1	1.4
Other non-hematologic toxicity	3	3	0	3	4.2

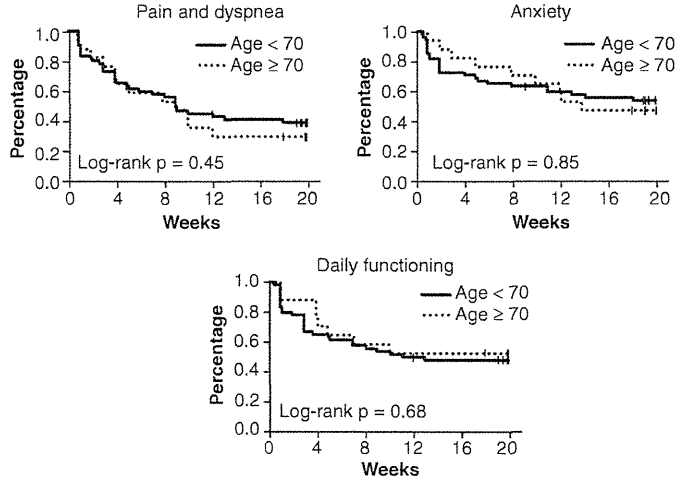

Figure 4. Quality of life (QoL) by age in the gefitinib group. The graphs show the percentages of patients without a 9.1% deterioration in QoL score from baseline at each time point (QoL endpoint).

two Phase II studies and one Phase III study of gefitinib as first-line therapy for advanced NSCLC harboring an *EGFR* mutation. When the data on elderly patients from the three studies were pooled, RR and DCR were found to be 73.2 and 94.4%, respectively, whereas median PFS was 14.3 months. These findings confirmed the results of NEJ003, in which elderly patients aged 75 years or older achieved overall RR of 74%, DCR of 90%, and a median PFS of 12.3 months [8]. Moreover, median PFS (14.3 vs 5.7 months) and RR (73.2 vs 26.5%) were more favorable in the gefitinib group than in the carboplatin–paclitaxel reference group.

Specific information on the efficacy of gefitinib in elderly patients with advanced NSCLC has been relatively limited. A Phase II study of gefitinib (n = 97) versus vinorelbine (n = 99) in chemotherapy-naive, unselected elderly patients (≥ 70 years; INVITE study [12]) reported no significant difference in efficacy between the two agents. A Phase II study of another EGFR TKI, erlotinib, in unselected chemotherapy-naive elderly patients (≥ 70 years) with advanced NSCLC, showed that median time to progression was 3.5 months, with a median survival time of ~ 11 months [13].

Several Phase III open-label trials of EGFR TKI therapy for advanced *EGFR* mutation-positive NSCLC demonstrated improved PFS compared with standard chemotherapy even with the inclusion of a cohort of elderly patients [14-17], suggesting that EGFR TKI therapy is efficacious regardless of age. However, the elderly subgroup was not analyzed in detail and the age definition of the elderly group has been inconsistent. Therefore, further accumulation of data is required to

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determine whether EGFR TKI therapy provides a robust survival benefit and is safe in elderly patients. Studies are currently underway to examine the potential enhanced therapeutic effect of EGFR TKI combined with either chemotherapy [18] or an angiogenesis inhibitor [19] in patients with advanced NSCLC with EGFR mutations. Such therapies should also be considered for elderly patients in the future, and evidence of the efficacy of EGFR TKI monotherapy forms the basis for future studies on combined therapy. Thus, we believe that our study is invaluable and provides a platform for further studies of EGFR TKI therapy in elderly patients.

Given that standard chemotherapy for advanced NSCLC is associated with significant side effects, QoL is also an important consideration in weighing the benefits of EGFR TKI therapy versus standard chemotherapy. In an analysis of QoL of patients in the NEJ002 trial that examined the time to deterioration of QoL categories of physical, mental and life wellbeing, gefitinib proved to be more favorable than chemotherapy [11]. Specifically, time to 27% deterioration of pain and shortness of breath, anxiety, and daily functioning were significantly longer in the gefitinib arm. As an extension of that study, we examined whether there was a difference in the time to deterioration of pain and shortness of breath, anxiety, and daily functioning between elderly (≥ 70 years of age) and non-elderly (< 70 years of age) patients receiving gefitinib in the present study. No significant difference was seen in the three QoL domains between the two groups, suggesting that gefitinib maintains QoL to the same extent in elderly patients as in younger patients.

In the present study, the incidence and toxicity profile of gefitinib were comparable between elderly and younger patients in the NEJ002 study. However, it has been reported that elderly patients (≥ 70 years of age) suffer from more erlotinib toxicity overall, and that the percentage of elderly affected by severe toxicity (grade ≥ 3) was almost double that of younger patients. (35 vs 18%, $p < 0.001$). They were also more likely to discontinue erlotinib because of drug toxicity (12 vs 3%, $p < 0.0001$) [20]. Notably, there was one grade 3 and one fatal grade 5 gefitinib-related pneumonitis. Older age is reported to be a risk factor for interstitial lung disease in NSCLC patients receiving either gefitinib or chemotherapy [21]. Close monitoring of elderly patients on EGFR TKI therapy is warranted because of their greater susceptibility to drug toxicity and development of interstitial lung disease.

Several limitations of this study exist. The study was retrospective in design and involved the pooling of data from three studies that were conducted at different times. A prospective, multicenter study of elderly patients with the same characteristics is needed to confirm the results of the present study. Second, a direct comparison between standard chemotherapy and gefitinib groups may not be valid because the treatment arms were not conducted in parallel, and thus caution is advised with the interpretation of the data. Third, only elderly patients in the NEJ002 study underwent QoL assessment, so QoL results were derived from a relatively small number (n = 33) of patients, which might limit its applicability to other elderly patients.

5. Conclusion

Gefitinib is highly efficacious in relatively fit elderly patients as first-line therapy for advanced NSCLC harboring an *EGFR* mutation with an acceptable level of toxicity. In contrast to younger patients, elderly patients tend to be ineligible for multiple treatment lines; thus, gefitinib is an important and recommended first-line therapy for this population.

Acknowledgements

We thank patients and their families as well as site investigators, and Koichi Yamazaki (deceased), former associate professor of the First Department of Medicine, Hokkaido University School of Medicine. Results of this study were presented at the 2012 American Society of Clinical Oncology Annual Meeting, Chicago, IL, USA (June 1 – 5, 2012).

Declaration of interest

K Kobayashi and K Hagiwara have received research support from AstraZeneca. The NEJ002 study was supported by Grants-in-Aid from the Japan Society for Promotion of Science and the Japanese Foundation for Multidisciplinary Treatment of Cancer and a grant from the Tokyo Cooperative Oncology Group. We wish to thank William Ng for providing medical writing support, which was funded by AstraZeneca K.K. (Osaka, Japan) according to a publication support agreement. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Annals of Oncology Advance Access published February 10, 2015

Randomized Phase II Study of Concurrent Versus Sequential Alternating Gefitinib and Chemotherapy in Previously Untreated Non-small Cell Lung Cancer with Sensitive *EGFR* Mutations: NEJ005/TCOG0902

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ABSTRACT

Background: The first-line combination of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) plus platinum-based doublet chemotherapy has not been sufficiently evaluated for patients with *EGFR*-mutant non-small cell lung cancer (NSCLC). This randomized phase II study was designed to select a combination regimen for phase III evaluation.

Patients and methods: Chemotherapy-naïve patients with advanced non-squamous *EGFR*-mutant NSCLC were randomly assigned to receive either a concurrent or a sequential alternating regimen with gefitinib (250 mg) and carboplatin/pemetrexed (area under the curve [AUC] = 6 and 500 mg/m^2; 3-weekly). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), response, and safety.

Results: All 80 patients enrolled were eligible and evaluable for efficacy (41 and 39 patients in the concurrent and sequential alternating regimen groups, respectively). Median PFS was 18.3 months for the concurrent regimen and 15.3 months for the sequential alternating regimen (hazard ratio [HR] 0.71 [0.42-1.20], p = 0.20). Although OS data are immature (16 and 24 death events), median survival times were 41.9 and 30.7 months in the concurrent and sequential alternating regimen groups, respectively (HR 0.51 [0.26-0.99]; p = 0.042). Response rates were similar in both groups (87.8% and 84.6%). Hematological

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and non-hematological adverse events were common and reversible; interstitial lung disease was neither frequent nor fatal (two cases in each group; 5% of all patients).

Conclusion: This is the first randomized study to investigate the efficacy of combinational EGFR-TKI and chemotherapy in the *EGFR*-mutated setting. Both regimens had promising efficacy with predictable toxicities, although concurrent regimens might provide better OS. The concurrent regimen was chosen to compare with gefitinib monotherapy in our ongoing phase III study.

Clinical Trials registration: University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN C000002789)

KEY WORDS

Non-small cell lung cancer, First-line, EGFR-TKI, Chemotherapy, Combination, *EGFR* mutation

KEY MESSAGE

EGFR-TKI therapy produces a dramatic clinical response in patients with NSCLC harboring *EGFR* mutation. However, clinical outcomes should be further improved in this cohort. Thus, we conducted a randomized phase II study to investigate the efficacy and safety of combinational EGFR-TKI and chemotherapy, demonstrating that the combination might be a promising strategy for advanced *EGFR*-mutant NSCLC.

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INTRODUCTION

A growing body of evidence, together with our North East Japan Study Group (NEJ) 002 study, demonstrated the superiority of first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) over standard chemotherapy with regards to progression-free survival (PFS) and response for non-small cell lung cancer (NSCLC) with sensitive *EGFR* mutations [1-6]. Furthermore, a supplemental analysis of NEJ002 demonstrated that quality of life was also improved with EGFR-TKI therapy [7]. Thus, first-line EGFR-TKI therapy became a standard first-line treatment for *EGFR*-mutant NSCLC.

Most previous clinical trials failed to show a benefit for EGFR-TKI plus platinum-based doublet chemotherapy in unselected or clinically selected NSCLC patients [8-12]. However, in the TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin) study, median time to progression was improved in a subgroup analysis of *EGFR*-mutated NSCLC [13]. Likewise, continuous erlotinib in combination with carboplatin and paclitaxel conferred a better response and survival outcomes in an *EGFR*-mutant population [12]. Collectively, these results indicate that the first-line combination of EGFR-TKI and platinum-based doublet chemotherapy might improve clinical outcomes for NSCLC harboring *EGFR* mutations. However, to the best of our knowledge, this concept has not been sufficiently evaluated in the *EGFR*-mutated setting.

This multi-center randomized phase II trial, NEJ005 and Tokyo Cooperative Oncology Group (TCOG) 0902, was designed to explore the efficacy and safety of gefitinib plus carboplatin/pemetrexed and to select a

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proper regimen for phase III evaluation in advanced NSCLC harboring active *EGFR* mutations.

PATIENTS AND METHODS

Patient Eligibility

This study was approved by the ethics review boards at each participating institute and was conducted according the Declaration of Helsinki. Each patient provided written informed consent prior to enrollment.

The main eligibility criteria were: chemotherapy-naïve; stage IIIB, IV, or relapsed non-squamous NSCLC with *EGFR* mutations (exon 19 deletions [Del19], L858R, L861Q, G719A, G719C, or G719S); over 20 and under 75 years of age; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; and adequate organ functions. Main exclusion criteria included serious concomitant systemic disorders, including interstitial pneumonia, another primary malignancy, presence of T790M, symptomatic brain metastases and pregnancy.

Study Design

Patients were stratified according to sex and clinical stage of NSCLC (IIIB, IV, or postoperative relapse). Eighty patients were randomly assigned to receive either concurrent or sequential alternating regimen. Details of the study treatment are shown in Supplementary Figure S1. Patients in the concurrent regimen group received concurrent gefitinib (250 mg daily) and carboplatin (6 × area under the curve [AUC], day 1)/pemetrexed (500 mg/m^2, day 1) in a 3-week

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cycle for up to six cycles, followed by concurrent gefitinib and pemetrexed maintenance until disease progression, unacceptable toxicity, or death. Patients in the sequential alternating regimen group initially received 8 weeks of gefitinib and then two cycles of carboplatin/pemetrexed; this sequential treatment was repeated up to three times (carboplatin/pemetrexed was repeated for up to six cycles), followed by alternating gefitinib and pemetrexed maintenance. When patients received four cycles or more of carboplatin/pemetrexed with gefitinib, the induction therapy was considered complete. Dose modification and treatment assessment are described in Supplementary Materials.

Patients were enrolled from January 2010 to April 2012. Protocol-defined final analysis was planned after a 2-year follow-up period (March 31, 2014).

Statistical Analysis

The primary objective was to select the arm with superior PFS. In subgroup analysis for *EGFR*-mutated NSCLC in the TRIBUTE study, median time to progression was 12.5 months [13]. The arm with the superior PFS was selected, provided that the related PFS was at least 12 months and resulted in PFS prolongation of 4 or more months with a probability of 90% or higher. The planned sample size was 40 eligible patients per arm. Secondary endpoints included overall survival (OS), objective tumor response, and toxicity profile. This study was not designed to have adequate power to detect a statistically significant difference in efficacy and safety between the two regimens, thus the *p* value reported for the difference was to be interpreted as exploratory.

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PFS was evaluated for the period from the date of randomization to the date on which progression was first confirmed by assessment by the investigator. OS was evaluated for the period from the date of randomization to the date of death from any cause. For patients without any events, data were censored on the last date with non-event status. The probability of PFS or OS was estimated using the Kaplan-Meier method, and survival curves were compared using a log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using a Cox proportional-hazards analysis with gender and clinical stage as covariates. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test. Statistical analysis was carried out using the SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

From January 2010 to April 2012, 80 patients were randomly assigned: 41 to the concurrent regimen and 39 to the sequential alternating regimen (Figure 1). All the patients received at least one dose of the study treatment. The median follow-up period was 30.7 months (range, 4.9 to 50.1 months). The demographics and disease characteristics of the patients were well-balanced between the treatment groups (Table 1). One patient with PS 2 was enrolled because the PS had changed from 1 to 2 during the screening process. Of note, all patients had adenocarcinoma, and the majority had stage IV disease. In addition to the Del19 and L858R, two patients exhibited minor *EGFR* mutations in the sequential alternating regimen group (one G719A, one coexistence of

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G719A and Del19). Treatment delivery is described in Supplementary Material.

Efficacy

Data for patients without progression (eight patients in the concurrent and six patients in the sequential alternating regimen group) or for those who started off-study second-line treatment before confirmation of progression (one patient in the concurrent and two patients in the sequential alternating regimen group) were censored at the time of data cutoff (March 31, 2014). PFS curves were identical between the two groups (Figure 2A). Median PFS was 18.3 months (95% CI, 9.7-21.9 months) for patients in the concurrent regimen group and 15.3 months (95% CI, 11.3-17.4 months) for patients in the sequential alternating regimen group (HR 0.71 [95% CI, 0.42-1.20]; $p = 0.20$).

However, OS time between the groups was significantly different (Figure 2B). Although survival data are immature, with 50% of patients censored (25 patients in the concurrent and 15 patients in the sequential alternating group), median OS was 41.9 months (95% CI, 35.1 months-Not reached) in the concurrent regimen group and 30.7 months (95% CI, 23.2-40.5 months) in the sequential alternating regimen group (HR 0.51 [95% CI, 0.26-0.99]; $p = 0.042$).

The objective response rates in the concurrent and sequential alternating regimen group were 87.8% and 84.6% ($p = 0.75$, Supplementary Table S1), respectively, whereas the disease control rates were 100% and 92.3% ($p = 0.11$). As shown in a representative waterfall plot (Figure 3), deep tumor regression in a substantial proportion of the patients was observed with seven patients (four and three patients for the concurrent and sequential

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alternating regimen, respectively) exhibiting CR response. Treatment post RECIST progression is shown in Supplementary Table S2. Subset analyses by types of common *EGFR* mutations are shown in Supplementary Figure S2 and S3.

Safety

The most common grade 3 or 4 hematological adverse events were neutropenia (48.8% vs. 46.2%), anemia (34.1% vs. 12.8%) and thrombocytopenia (41.5% vs. 28.2%) (Table 2). In contrast, adverse non-hematological events were not severe. The most commonly reported grade 3 or 4 adverse events likely related to carboplatin and pemetrexed were vomiting (2.4% vs. 0.0%), appetite loss (7.3% vs. 0.0%), fatigue (2.4% vs. 0.0%), and febrile neutropenia (2.4% vs. 5.1%). The most commonly reported grade 3 or 4 adverse events likely related to gefitinib included diarrhea (9.8% vs. 0.0%), rash (2.4% vs. 0.0%), stomatitis (4.9% vs. 0.0%), paronychia (2.4% vs. 2.6%), and AST/ALT elevation (9.8% vs. 20.5%). We recorded no increase in fatal events; a total of 4 interstitial lung diseases (5% of all patients) occurred (grade 1 and 2 events in the concurrent; and grade 2 and 4 events in the sequential alternating regimen group), but they were reversible and not fatal.

DISCUSSION

To the best of our knowledge, this is the first randomized study to examine the efficacy of first-line combination of EGFR-TKI and chemotherapy in patients with NSCLC harboring *EGFR* mutations. Although not formally

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compared, PFS with both regimens was improved when compared to that with gefitinib monotherapy in previous phase III studies (median, 9.2-10.8 months) [2, 3, 14].

The results of the current selection-design study indicate that the concurrent regimen with superior PFS (median) should be selected for further evaluation. Before this final analysis, we had already initiated the phase III NEJ009 (UMIN000006340) study, which is comparing this combination strategy with standard gefitinib monotherapy in the *EGFR*-mutated setting, with OS as the primary endpoint. Efficacy, safety, and feasibility in clinical practice by interim monitoring were considered when choosing the concurrent regimen as an experimental arm in the NEJ009 study.

In the NEJ002 study, OS was improved in patients who received both TKI and platinum-based doublet chemotherapy sequentially [15]. In addition, pemetrexed maintenance therapy extended both OS and PFS, and therefore became a standard treatment option for advanced non-squamous NSCLC [16, 17]. These results encouraged us to adopt carboplatin and pemetrexed induction followed by pemetrexed maintenance as a partner for gefitinib in this combinational strategy.

However, it is still controversial whether patients can benefit from the combination of EGFR-TKI and chemotherapy. Mahaffey et al. reported that EGFR-TKIs caused G1 cell-cycle arrest in *KRAS*-mutant and *EGFR* wild-type NSCLC cell lines, thereby inhibiting the cell-cycle-dependent cytotoxic effects of chemotherapy [18]. Although it remains unknown whether the G1 phase arrest also occurs in *EGFR*-mutant tumors, it was hypothesized that an intercalated or

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