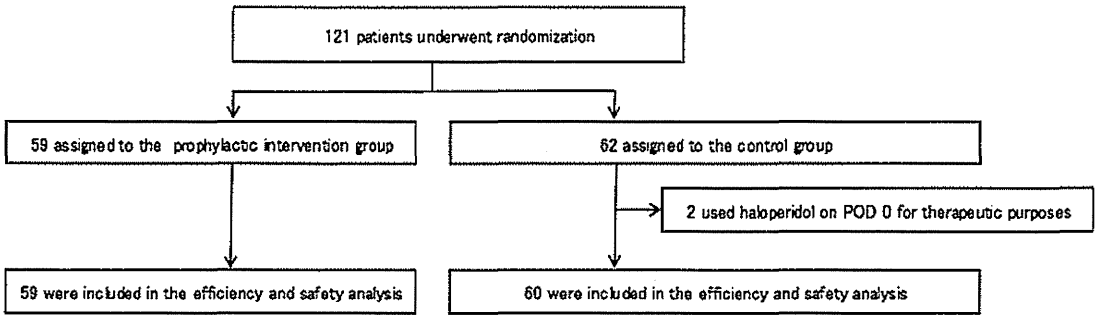

Fig. 2 A flow diagram of the study

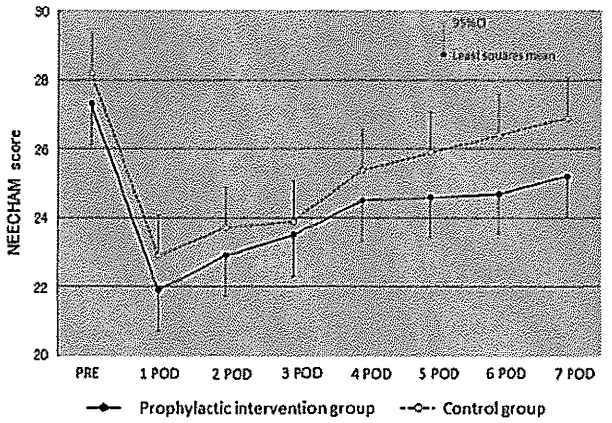

Fig. 3 The preoperative and postoperative changes in the NEECHAM scores in the prophylactic intervention group and control group The preoperative and postoperative (POD1-7) changes in the NEECHAM score in the prophylactic intervention and control groups. The percentages of patients with postoperative delirium (NEECHAM <20) in the prophylactic intervention and the control groups were 42.4 and 33.3 %, respectively (95 % confidence intervals (CI) 29.6–55.9 and 21.7–46.7 %; $p = 0.309$). The duration of the delirium (NEECHAM <20) was 1.38 versus 1.10 days in the intervention and control groups, respectively (95 %CI 0.83–1.95 days and 0.58–1.62 days; $p = 0.356$). *Open circle* shows the least-squares mean score of the control group. *Filled circle* shows the least-squares mean score of the prophylactic intervention group. The *vertical line* in the least-squares mean score shows the 95 %CI

in Table 4, which are consistent with the data shown in Table 3. The odds ratio of the prophylactic administration of haloperidol was 1.48 (95 %CI 0.33–6.71), which indicated no postoperative delirium-decreasing effect ($p = 0.611$). The age, preoperative MMSE score and number of days after surgery were significantly correlated with the development of postoperative delirium.

Regarding postoperative adverse events, grade 2 events were noted in two patients (convulsions and temporary loss of consciousness 2 days after completing the preventive administration of haloperidol and T-tube removal) and grade 3 events occurred in one (no abnormality was noted during haloperidol administration, but the patient fell on

Table 3 The results of the multivariate analysis of the factors affecting the development of postoperative delirium (logistic regression analysis)

	Odds ratio	95 % CI	*p* value
Prophylactic administration of haloperidol	1.30	0.54–3.17	0.558
Age	1.12[a]	1.01–1.27	0.043
Gender (male)	1.03	0.41–2.60	0.953
Preoperative NEECHAM score	1.23[b]	1.01–1.51	0.037
Preoperative MMSE score	1.15[b]	1.03–1.30	0.014

The multivariate logistic regression analysis was performed to include the patient age, gender, preoperative MMSE score and preoperative NEECHAM score as covariates to evaluate the effects of prophylactic haloperidol treatment after adjustments for potential confounding factors. An odds ratio >1 indicated that the factor conferred a greater risk of severe postoperative delirium

NEECHAM NEECHAM confusion scale, *MMSE* Mini-Mental State Examination

[a] For each 1-year increase

[b] For each 1-point decrease in the score

day 7, leading to a femoral neck fracture) in the intervention group. However, the grade 3 event was unlikely to have had any causal relationship with the preventive haloperidol treatment, considering that the half-life of intravenous haloperidol is 14.1 ± 3.2 h [28], and no other adverse events of grade 3 or more were noted.

Discussion

No significant preventive effect of the daily administration of low-dose haloperidol on postoperative delirium was noted in this randomized, open-label prospective study. The incidence of postoperative delirium was not significantly lower in the intervention group than in the control group, and no significant effect was noted on the severity or persistence of the delirium. Moreover, no significant effect was observed even in the group at high

Table 4 The results of the multivariate analysis of the factors affecting the development of postoperative delirium (GEE analysis)

	Odds ratio	95 %CI	*p* value
Prophylactic administration of haloperidol	1.48	0.33–6.71	0.611
Age	1.30[a]	1.07–1.58	0.008
Gender (male)	0.39	0.08–1.86	0.238
Preoperative NEECHAM score	1.05[b]	0.78–1.40	0.752
Preoperative MMSE	1.69[b]	1.05–2.73	0.032
Postoperative day (postoperative days 1–7)	0.67[c]	0.52–0.85	0.001

A supportive analysis using the generalized estimating equation regression model was conducted to compare the incidence of severe delirium between the treatment groups throughout first 7 days after the operation

GEE generalized estimating equation, *NEECHAM* NEECHAM confusion scale, *MMSE* Mini-Mental State Examination

[a] For each 1-year increase

[b] For each 1-point decrease in the score

[c] For each 1-day increase

risk for postoperative delirium with preoperative MMSE and NEECHAM scores below 25 and 27, respectively.

There have been several contradictory reports regarding the efficacy of haloperidol in preventing delirium. Kaneko et al. [13] reported that it significantly decreased the incidence of delirium after surgery involving the digestive organs in a small-scale clinical study, and Wang et al. [14] reported that 12-h continuous preventive administration of haloperidol significantly decreased the incidence of delirium in elderly patients admitted to an ICU, excluding those after cardiac surgery. In contrast, Kalisvaart et al. [15] reported that haloperidol reduced the severity and persistence of delirium, but did not decrease its incidence in patients following orthopedic surgery in a RCT where they received oral preventive treatment with low-dose haloperidol.

The absence of a preventive effect of haloperidol on postoperative delirium may have been due to the low dose used and short administration period. However, although the dose was lower than 5 mg/day for 5 days, as reported by Kaneko et al., the preventive administration of the dose of 2.5 mg/day for 3 days was still markedly higher than the intravenous bolus injection of 0.5 mg of haloperidol, followed by continuous infusion at a rate of 0.1 mg/h for 12 h (total dose per day: 1.7 mg) reported by Wang et al. High-dose haloperidol may be necessary for the primary prevention of delirium, but such treatment may increase the frequency and severity of adverse effects, particularly in vulnerable patients. It has been suggested that haloperidol should ideally be administered to elderly patients at a low dose for a short time [29].

It is also possible that the initiation of preventive administration in the present study may have been too late. In the time-course of the NEECHAM scores after surgery (Fig. 3), the lowest score was noted on postoperative day 1 in both the intervention and control groups, and it slowly improved thereafter. The NEECHAM score may have rapidly decreased immediately after surgery within one postoperative day. The drug was administered early after surgery in the studies by Kaneko et al. and Wang et al., in which an effect was observed. We performed our study on the assumption that the intervention would be administered in general wards of general hospitals, and decided to start haloperidol administration on postoperative day 1 in consideration of the patient safety; however, this timing was not before the decrease in the NEECHAM score was observed. This may have been the reason for the absence of an effect due to the intervention. Although it may have been better to initiate the intervention on the night after the surgery, an intervention immediately after surgery to patient in unstable general conditions is difficult unless it is strictly monitored in the ICU, as reported by Wang et al. When preventive administration is initiated immediately after surgery, the influence of anesthesia remains, and the respiratory and circulatory dynamics are unstable, which may have a negative influence on the postoperative course and increase the possibility of severe adverse events.

It should be noted that we were unable to exclude the possibility of a psychological effect arising from the patients' awareness of having received a haloperidol drip infusion, because this trial was not performed in a double-blinded manner. However, a lack of blinding would introduce potential bias in favor of the haloperidol prophylactic group, which was not observed in the present study. Therefore, the non-double-blinded nature of the study does not appear to have affected the conclusions regarding the treatment.

No severe adverse event corresponding to grade 3 or more that was assumed to be associated with the preventive haloperidol administration was noted. Although high-dose haloperidol administration (from 5 mg to more than 20 mg) was necessary when postoperative delirium developed, no adverse event assumed to be induced by the haloperidol was noted even in these cases, which suggested that haloperidol can be relatively safely administered even during the unstable postoperative period. The safety of haloperidol for postoperative elderly patients has also been confirmed in other studies [13–15]. Combining its high tolerability and low cost, expanding the clinical experience using this antipsychotic drug will broaden the range of applications for other conditions.

Nevertheless, this study suggests that intravenous treatment with low-dose haloperidol is unlikely to be used widely in hospital wards as prophylactic intervention to prevent postoperative delirium in elderly surgical patients who are not orally treatable. High-dose haloperidol may be

effective, but it has been advised that haloperidol should be administered to elderly patients at a low dose to prevent adverse effects [25, 26, 29].

Several studies have shown various non-pharmacological measures that can contribute to reducing the incidence of delirium [30–33]. Inouye et al. [30] proposed a multifactorial intervention that included specific protocols for cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration by showing significant reductions in the number and duration of episodes of delirium in hospitalized general medicine patients aged 70 or older. Marcantonio et al. [32] reported that geriatric consultation decreased delirium in elderly surgical patients after hip fracture by over one-third. More recently, Colombo et al. [33] showed that the timely use of a re-orientation strategy was correlated with a significantly lower occurrence of delirium in patients admitted to the ICU. In fact, the proportion of patients who developed postoperative delirium in the present study (38 % of all patients) was lower than that reported in our previous study (55 %) [7]. This may have been due to the protocol used in this study, in which patients who developed delirium on the day of surgery or on the following morning were not included. However, alternatively, it could have been because the preceding studies on delirium motivated the participating medical staff and nurses to be more aware of postoperative delirium, thus promoting the care of patients at risk and decreasing the incidence of delirium.

The NEECHAM score was employed to diagnose delirium and to evaluate its severity. A pattern similar to that in our previous report [7] was noted in the present study, which confirmed its reproducibility and usefulness as a score to evaluate delirium. The incidence of postoperative delirium has been shown to vary markedly (10 % to higher than 50 %) among reports [29, 34–38], and this may have been due to the fact that many studies were retrospective, and the definition of the development of delirium has been ambiguous or different among these studies. The DMS-IV [39] and Delirium Rating Scale (DRS) [40] are known as diagnostic criteria that can also be used to evaluate delirium; however, it is difficult for nurses who directly take care of patients with postoperative delirium to judge delirium accurately using the DMS-IV and DRS. On the other hand, the severity and condition of delirium can be simply and objectively determined by general physicians and nurses using the NEECHAM score. In this study, postoperative delirium was continuously and prospectively evaluated in consecutive cases using the NEECHAM score by nurses in direct contact with patients all day at clinical sites. The efficacy of the intervention was judged based on this evaluation, and its reliability should have been high.

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Conflict of interest The authors of this report have no conflicts of interest.

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ORIGINAL ARTICLE

First-line gefitinib therapy for elderly patients with non-small cell lung cancer harboring EGFR mutation: Central Japan Lung Study Group 0901

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Abstract

Background The population of elderly patients with lung cancer is increasing worldwide. Although first-line gefitinib is one of the standard treatments for advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation, few data have been reported regarding gefitinib and elderly patients.

Patients and methods Chemotherapy-naïve patients aged 70 years or older with stage IIIB or IV NSCLC harboring EGFR-activating mutation were enrolled and treated with 250 mg of gefitinib daily until disease progression. The primary end point was response rate, and secondary end points were survival, safety, and quality of life.

Results Twenty patients were enrolled, and the median age was 79.5 years (range 72–90). Overall response rate was 70 % (95 % CI 45.7–88.1 %), and the disease control rate was 90 % (95 % CI 68.3–98.7 %). The median progression-free survival and overall survival time were 10.0 and 26.4 months, respectively. The Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) scores improved significantly 4 weeks after the initiation of gefitinib ($P = 0.037$) and maintained favorably over a 12-week assessment period. Among the seven items of FACT-LCS, shortness of breath and cough improved

This trial is registered at UMIN-CTR, Number UMIN000001863.

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significantly after 4 weeks of treatment ($P = 0.046$ and $P = 0.008$, respectively). The most common adverse events were rash and liver dysfunction. Although Grade 1 pneumonitis developed in one patient, no treatment-related death was observed.

Conclusion First-line gefitinib therapy is effective and feasible for elderly patients harboring EGFR mutation, and improves disease-related symptoms, especially pulmonary symptoms like shortness of breath and cough.

Keywords Non-small cell lung cancer · EGFR mutation · Elderly · Gefitinib · Quality of life · First-line treatment

Introduction

Lung cancer is the leading cause of cancer mortality. Non-small cell lung cancer (NSCLC) accounts for 85 % of lung cancer cases, with at least 40 % of the patients at an advanced stage. The population of elderly patients with lung cancer is increasing worldwide. Two-thirds of the lung cancer cases are diagnosed in patients over the age of 65, and the median age at diagnosis is 70 years [1, 2].

Aging is associated with physiologic changes in organ function and altered drug pharmacokinetics. Furthermore, the presence of comorbidities and polypharmacy is frequent in elderly populations. Elderly patients are more likely to experience severe hematologic and non-hematologic toxicity from conventional chemotherapy than their younger counterparts [3]. Before the discovery of driver mutations including epidermal growth factor receptor (EGFR) mutation, single-agent chemotherapy was considered to be a standard of care for elderly patients with advanced NSCLC [4–6]. Although carboplatin and weekly paclitaxel doublet chemotherapy improved overall survival compared with vinorelbine or gemcitabine monotherapy in the IFCT-0501 trial, accompanying toxicity such as Grade 3 or Grade 4 neutropenia, febrile neutropenia, and asthenia was more frequent in the doublet chemotherapy arm [7]. Therefore, investigations of effective treatments with less toxicity are needed for this population.

Gefitinib is an orally administered EGFR tyrosine kinase inhibitor (TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells. Since EGFR somatic mutation was reported to be strongly related to the response of EGFR-TKI therapy, several studies have demonstrated the efficacy of gefitinib for NSCLC harboring EGFR-activating mutation [8–11]. Two phase III studies comparing gefitinib with platinum doublet chemotherapy as a first-line treatment for NSCLC patients with EGFR mutation showed that the gefitinib group had a higher response and longer progression-free survival than a standard chemotherapy group [12, 13]. However, these studies targeted patients aged 75 years or younger, and few data were available on the efficacy and feasibility of first-line gefitinib therapy for elderly NSCLC patients with EGFR mutation. Therefore, we started our current study of this population. The present study included the assessment of quality of life (QOL) besides the efficacy and feasibility of treatment.

Patients and methods

Patient eligibility

Patients aged 70 years or older with a histologically or cytologically proven diagnosis of non-small cell lung cancer were eligible for this study. Other eligibility criteria included the following: EGFR-activating mutation (either exon 19 deletion or L858R in exon 21); measurable disease; stage IIIB/IV or postoperative recurrence; no prior therapy including chemotherapy or radiotherapy of the primary tumor; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; an adequate organ function defined as leukocyte count $\geq$3,000/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dl, aspartate aminotransferase and alanine aminotransferase $\leq$100 IU/l, total bilirubin $\leq$1.5 mg/dl, serum creatinine $\leq$1.5 mg/dl, and PaO_2 at rest $\geq$60 mmHg. Patients with any of the following criteria were ineligible: superior vena caval syndrome; history of serious drug allergy; massive pleural or pericardial effusion or ascites that required drainage; interstitial lung disease or pulmonary fibrosis detected by conventional computed tomography of the chest; symptomatic brain metastasis; other concurrent active malignancy; pregnancy, lactation, or other concomitant serious medical conditions. All patients gave written informed consent before enrollment. The study protocol was approved by each institutional review board and was carried out in accordance with the Declaration of Helsinki 1964 (as revised 2000).

Study design and treatment

This was a single-arm, prospective, multicenter, phase II trial. Patients were treated with 250 mg of oral gefitinib daily. Therapy was continued unless there was evidence of disease progression, unacceptable toxicity, or withdrawal of consent. If Grade 3 toxicity other than pneumonitis was observed, gefitinib was discontinued for a maximum of 4 weeks. After the toxicity recovered to the level of Grade 2, gefitinib was given every other day. If toxicity further improved, gefitinib was given daily. If Grade $\geq$1 pneumonitis or Grade 4 toxicity other than pneumonitis was observed, the patient was removed from the study.

Evaluation of response and toxicity

The pretreatment baseline evaluation included a complete medical history and physical examination, complete blood cell count, blood chemistry studies, computed tomography scan of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, bone scintigraphy or positron emission tomography, arterial blood gas analysis, pulmonary function tests, and electrocardiography. Tumor response was assessed every 2 months during the first year after enrollment and every 3 months between 12 and 18 months. Thereafter, the interval was at the physician's discretion.

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for response assessment [14]. Disease control rate (DCR) was defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). An extramural review was conducted to validate staging and response. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria (version 3.0).

Quality of life (QOL) was assessed with the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) questionnaire version 4. The maximum attainable score on the FACT-LCS was 28, with which the patient was considered to be asymptomatic. Patients were asked to complete the FACT-LCS questionnaire at the time of enrollment and at 4, 8, and 12 weeks after the initiation of treatment.

Mutational analysis of EGFR

Epidermal growth factor receptor (EGFR) genetic testing methods included either direct sequencing, PCR invader, peptide nucleic acid-locked nucleic acid PCR clamp, or the combination of fragment analysis and the Cycleave method.

Statistical analyses

The primary end point of this study was the response rate. We calculated the sample size based on Simon's two-stage design of the phase II study [15]. Assuming that a response rate of 60 % from eligible patients would indicate potential usefulness, and that a rate of 30 % would be the lower limit of interest (with a power of 0.8 at a one-sided significance level of 0.05), accrual of 17 eligible patients was required. Therefore, we planned to accrue a total of 19 patients, assuming there would be a 10 % dropout rate. The duration of survival was measured from the day of enrollment, and the overall survival curve and progression-free survival curve were calculated according to the method of Kaplan and Meier [16]. Repeated-measures analysis of variance was used to assess the differences in the FACT-LCS between baseline and each point during the treatment. Comparisons of the FACT-LCS scores with the baseline scores were adjusted for multiple comparisons using the Dunnett–Hsu test. The software SAS/Proc Mixed version 9.2 (SAS Institute Inc., Cary, NC) was used for statistical analysis. All comparisons were two-sided, and the statistical significance level was set at $P < 0.05$.

Results

Patient characteristics

Between April 2009 and March 2011, 20 patients were enrolled in this study. Sixteen patients (80 %) were aged 75 years or older, and the median age was 79.5 years (range 72–90 years old) (Table 1). All of the 20 patients had adenocarcinoma, 13 (65 %) were female, two (10 %) had an ECOG performance status of 2, and 12 (60 %) had exon 19 deletion mutations.

Tumor responses and survival

Overall response rate was 70 % (95 % CI 45.7–88.1 %), and the disease control rate was 90 % (95 % CI 68.3–98.7 %) (Table 2). Although the response of one patient who developed pneumonitis was not evaluable, progressive disease was observed in only one patient. The median progression-free survival and overall survival time were 10.0 and 26.4 months, respectively (Figs. 1, 2).

Table 1 Patient characteristics

Characteristics	$N = 20$	(%)
Age, years		
Median (range)	79.5 (72–90)	
Sex		
Male	7	35
Female	13	65
Smoking status		
Never smoker	14	70
Former/current smoker	6	30
ECOG performance status		
0	13	65
1	5	25
2	2	10
Stage		
IIIB	4	20
IV	15	75
Postoperative recurrence	1	5
Type of EGFR mutation		
Exon 19 deletion	12	60
L858R	8	40

ECOG Eastern Cooperative Oncology Group

Table 2 Response rate

Response	$N = 20$	% (95% CI)
Partial response	14	70
Stable disease	4	20
Progressive disease	1	5
Inevaluable	1	5
Overall response rate	14	70 % (45.7–88.1)
Disease control rate	18	90 % (68.3–98.7)

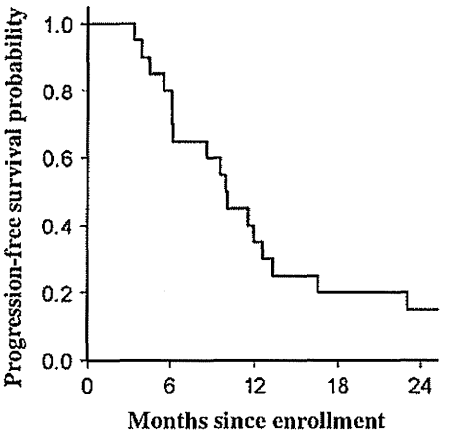

Fig. 1 Kaplan–Meier progression-free survival curve with gefitinib

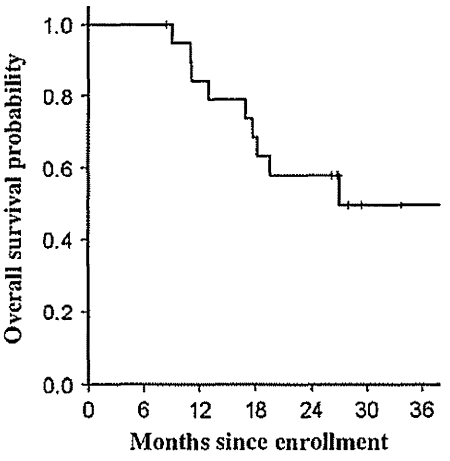

Fig. 2 Kaplan–Meier survival curve with gefitinib

Quality-of-life assessment

All 20 patients completed the FACT-LCS questionnaire at registration and after 4, 8, and 12 weeks of treatment. The adjusted mean FACT-LCS score was 22.8 ± 1.0 at baseline and 25.1 ± 0.7 at 4 weeks. The score improved

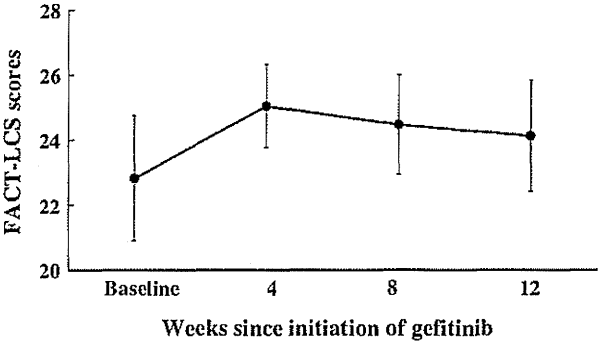

Fig. 3 FACT-LCS scores before treatment and at 4, 8, and 12 weeks after initiation of gefitinib. *Abbreviation FACT-LCS* Functional Assessment of Cancer Therapy-Lung Cancer Subscale

significantly at 4 weeks ($P = 0.037$) and maintained favorably during the 12-week assessment period (Fig. 3). FACT-LCS consisted of seven items: shortness of breath, cough, chest tightness, ease of breathing, changes in appetite, body weight loss, and disruptions to clear thinking. Among those seven items, shortness of breath and cough improved significantly after 4 weeks of treatment ($P = 0.046$ and $P = 0.008$, respectively).

Toxicity

Toxicity data for all 20 patients are listed in Table 3. Nonhematologic toxicity was the principal toxicity from gefitinib treatment and mainly consisted of liver dysfunction, skin rash, anorexia, diarrhea, and fatigue. Grade 3 or Grade 4 liver dysfunction occurred in 3 patients (15 %) but no other Grade 3 or Grade 4 toxicity was occurred. One case of Grade 1 pneumonitis developed in an 87-year-old woman. She had no specific symptoms; however, routine chest X-ray on day 14 showed an increase in density in the bilateral lower lung fields. Since subsequent chest computed tomography revealed bilateral diffuse interstitial opacities and the bronchoalveolar lavage findings were consistent

Table 3 Adverse events ($N = 20$)

	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3–4
AST/ALT	8	4	2	1	3
Rash	8	10	0	0	0
Anorexia	8	2	0	0	0
Diarrhea	6	2	0	0	0
Fatigue	6	2	0	0	0
Mucositis	1	3	0	0	0
Nausea	3	0	0	0	0
Pneumonitis	1	0	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

with pneumonitis, gefitinib was discontinued and the treatment with oral prednisolone (0.5 mg/kg/day) was started. Although the pneumonitis was stable, pulmonary and brain metastases gradually progressed and she died of progression of lung cancer 6 months after the occurrence of this adverse event. No treatment-related death was observed.

Discussion

The present study evaluated the efficacy and feasibility of first-line gefitinib treatment for elderly patients harboring EGFR mutation, achieving the response rate of 70 % and disease control rate of 90 %. After we started this phase II study, three groups reported comparable results of response rates from 45.5 to 74 %, and progression-free survival of 9.7–12.9 months for similar populations [17–19]. Efficacy of the present study is also comparable to the results obtained from non-elderly phase III studies. Two prospective studies (WJTOG3405 and NEJ002) and subset analysis of EGFR-mutated patients in the IPASS showed response rates of 62.1–73.7 % and progression-free survival of 9.2–10.8 months [11–13, 20]. From these data, gefitinib treatment for elderly EGFR-mutated patients appears to be as effective as that for the younger population. A randomized trial of EGFR-TKI focusing on efficacy is needed to further improve survival of elderly patients.

We also revealed that disease-related symptoms improved significantly with gefitinib therapy. FACT-LCS score improved more than two points, which is considered a clinically meaningful change [21]. Although superior QOL results were reported with gefitinib versus chemotherapy in the IPASS and NEJ002 studies, the QOL benefit for the elderly population has not been reported [22, 23]. Among the seven items of FACT-LCS, shortness of breath and cough improved significantly. This finding is in accordance with two previous QOL analyses during gefitinib treatment. Cella et al. [24] found that more patients showed an improvement in the pulmonary items of FACT-LCS, such as shortness of breath, cough, or chest tightness than in the non-pulmonary items in the IDEAL2 study, which evaluated two doses of gefitinib for the mutation-unselected population. Oizumi et al. [23] reported that more patients showed an improvement in pain and shortness of breath in the gefitinib arm in the NEJ002 study. With regard to the speed of symptom improvement, our data demonstrated significant improvement at the first follow-up, namely at 4 weeks of treatment. A former analysis reported that the median time to symptom improvement was as immediate as 10 days with gefitinib [24]. In light of its rapid effect, gefitinib could be a good treatment option for patients suffering from pulmonary symptoms like cough or dyspnea.

Toxicity in the present study was generally mild and well tolerated. Grade 3 or Grade 4 adverse events were only in three cases of liver dysfunction. No unpredicted toxicity or treatment-related death was observed. On the other hand, a subgroup analysis of a phase III study of erlotinib treatment indicated that elderly patients experienced significantly more toxicity and tended to discontinue treatment more than their younger counterparts [25]. This difference may be partly explained by the difference in EGFR-TKIs. Gefitinib 250 mg is about one-third of the maximum tolerated dose, and erlotinib 150 mg is just the maximum tolerated dose [26, 27]. Accordingly, gefitinib may have some safety margin, especially for the frail population. In the present study, the oldest patient, aged 90 years, was able to continue gefitinib therapy for about 7 months with side effects no more severe than Grade 2 mucositis and Grade 2 rash.

Pneumonitis is one of the most serious adverse events related to EGFR-TKI therapy. In our previous study evaluating gefitinib in mutation-unselected elderly NSCLC patients, three out of 30 patients (10 %) had pneumonitis, two of them with a Grade $\geq$3 [28]. In the present study, Grade 1 pneumonitis developed in one patient (5 %). Since risk factors of pneumonitis include smoking, preexisting interstitial lung disease, and older age, careful monitoring is desirable for elderly patients [29, 30].

In conclusion, the present study revealed that first-line therapy with gefitinib is effective and feasible for elderly patients harboring EGFR mutation, and improves disease-related symptoms.

Conflict of interest Kosuke Takahashi, Hiroshi Saito, Yoshinori Hasegawa, Yasuteru Sugino, and Joe Shindoh received honoraria from AstraZeneca. Yoshinori Hasegawa received research funding for his institute from AstraZeneca.

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