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Efficacy of erlotinib and its effects on the quality of life of older patients with epidermal growth factor receptor-mutant non-small cell lung cancer: A prospective, multicenter, dose-modification study

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Aim: Gefitinib and erlotinib are efficacious and safe for older patients with epidermal growth factor receptor-mutant non-small cell lung cancer. However, prolonged use of epidermal growth factor receptor-tyrosine kinase inhibitors in older patients is difficult, owing to potential adverse events. Hence, dose reduction or treatment discontinuation is often required. We investigated the efficacy of low-dose first-line erlotinib and its effects on the quality of life of older patients with lung cancer.

Methods: A prospective, multicenter, phase II clinical trial was carried out in patients aged ≥75 years with epidermal growth factor receptor-mutant non-small cell lung cancer. Initially, 100 mg/day erlotinib was administered orally; if well tolerated, it was increased to 150 mg/day. The primary end-point was progression-free survival, and secondary end-points were the response rate, overall survival and change in quality of life ("Care Notebook" questionnaire).

Results: The median progression-free survival was 17.8 months, response rate was 63.6% and median overall survival was 27.8 months. The change in the quality of life after 6 weeks was assessed in 72.7% of the patients. Fatigue, pain, anxiety and deterioration in daily activities were found in at least 40% of the patients. Despite the therapeutic effect of 100 mg/day erlotinib, many patients required dose reduction, and in some, the quality of life could not be maintained.

Conclusions: Many older patients with epidermal growth factor receptor-mutant non-small cell lung cancer might require treatment dose reduction. Further studies are required to develop individualized treatments for older patients with lung cancer. **Geriatr Gerontol Int 2021; 21: 881–886**.

Keywords: epidermal growth factor receptor tyrosine kinase inhibitor, non-small cell lung cancer, older patients, quality of life.

Introduction

With aging populations, the prevalence of lung cancer and the associated mortality will increase. According to data from the Cancer Information Service of the National Cancer Center, Japan, in 2015, 79% of the lung cancer cases involved male patients aged ≥65 years, and 48% involved those aged ≥75 years, whereas among women, 78% were aged ≥65 years, and 50% were aged ≥75 years.[1] Studies have shown that, of the currently available epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), gefitinib and erlotinib are the most efficacious and safe first-line therapies for EGFR-mutant non-small cell lung cancer (NSCLC) in older patients.[2–5]

Erlotinib is a first-generation EGFR-TKI that significantly prolongs the overall survival (OS) in patients with EGFR-mutant

NSCLC compared with chemotherapy. Hence, it has been approved for insurance coverage in the treatment of EGFR-mutant NSCLC in several countries worldwide.[6,7] Phase III clinical trials comparing first-line chemotherapy and erlotinib have reported a favorable safety profile of erlotinib, and common terminology criteria for adverse events (CTCAE) grade ≥3 adverse events, such as rashes (2–13%), fatigue (0–6%) and diarrhea (1–5%), have been reported only in some cases.[6,8] A previous Japanese phase II clinical trial that compared the efficacy of erlotinib and chemotherapy, without age restrictions, reported no differences in the efficacy of erlotinib between patients aged <75 years and those aged ≥75 years,[3] although erlotinib is associated with a high rate of dose reduction, owing to adverse events in older patients (56.3%).[4] A phase I trial showed that the maximum tolerated dose of erlotinib is 200 mg/day, resulting in an approved dose of 150 mg/day.[9] This is significantly different from the dose of gefitinib, a similar drug with an approved dose of 250 mg/day and dose-limiting toxicity observed at 1000 mg/day.[10] Despite this difference, phase II trials of erlotinib and gefitinib have reported similar response rates (RRs) of 10–20%,[11,12] and 18%[13] for erlotinib and gefitinib, respectively, indicating that erlotinib might show clinical efficacy at a low dose. Furthermore, although the doses of cytotoxic chemotherapy are shown on the package insert for each drug, to be calculated based on the bodyweight of the patient, EGFR-TKI doses are fixed and independent of bodyweight. Circulating drug concentrations tend to be high in older patients due to reduced metabolism, and interactions with other drugs can further increase the circulating concentration of EGFR-TKIs.[14] Thus, both OS and quality of life (QOL) are important end-points that should be considered in the treatment of older patients with lung cancer, and avoiding adverse event-induced dose reduction or suspension is important for continuing treatment.

Thus, here, we planned a multicenter phase II clinical trial to investigate the dose of erlotinib in older patients with untreated EGFR-mutant lung cancer. We studied the efficacy and safety of low-dose erlotinib, and investigated how this low starting dose affected the continuation of treatment and changes in the QOL of older patients.

Methods

Patient selection

The main eligibility criteria for patients were as follows: (i) histological or cytological diagnosis of NSCLC; (ii) no indication for radical radiation or radical surgery, or postoperative recurrence; (iii) *EGFR* gene mutation-positive (mutant; exons 18, 19 and 21); (iv) no previous use of EGFR-TKI; (v) performance status (Eastern Cooperative Oncology Group): 0–3; (vi) lesion assessable by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (http://www.jcog.jp/doctor/tool/C_150_0010.pdf); (vii) age: ≥75 years; (viii) sufficient bone marrow function (neutrophil count ≥1500/mm^3, platelet count ≥75 000/mm^3, hemoglobin ≥9.0 g/dL), renal function, liver function and cardiopulmonary function were retained in the patient; and (ix) hemoglobin saturation (SpO_2, room air): ≥94% or partial pressure of oxygen (PaO_2) of oxygen: ≥65 mmHg.

The main exclusion criteria were as follows: (i) presence of *EGFR* exon 20 (Ex20) T790M mutation; (ii) uncontrollable ascites or pericardial effusion; (iii) interstitial pneumonitis or pulmonary fibrosis evident in CT scan images; and (iv) active double cancer.

All patients provided written informed consent to participate in the study.

Study design and treatment

This was a multicenter, single-arm, phase II clinical trial (UMIN ID: UMIN000012056) to investigate the efficacy of low-dose first-line erlotinib and its effects on the QOL in older patients with EGFR-mutant lung cancer. A total of 33 patients from four participating institutions (Hiroshima University Hospital, Hiroshima Prefectural Hospital, Hiroshima Red Cross Hospital, and Atomic-bomb Survivors Hospital and Shimane University Faculty of Medicine) in Japan were enrolled in the present study between October 2013 and June 2018. The follow-up time was 2 years, and the data cut-off point was 31 May 2020. The primary end-point was progression-free survival (PFS) and the secondary end-points were RR, OS, disease control rate and changes in the QOL based on the Care Notebook questionnaire.

Patients with confirmed EGFR-mutant lung cancer received 100 mg oral erlotinib once daily (Fig. S1). Treatment was suspended if any adverse events of CTCAE grade ≥3 were observed owing to non-hematological toxicity (including skin disorders, diarrhea and liver dysfunction), and restarted at a dose 25 mg/day lower than the initial dose when the adverse event improved to grade 2 (i.e. a patient receiving 100 mg/day was restarted the drug at 75 mg/day). The dose of erlotinib was also reduced if any adverse events of CTCAE grade ≤2 were observed, at the discretion of the patient. The treatment was discontinued when treatment suspension of ≥4 weeks was required or when any drug-induced lung disease developed in the patient. After the starting treatment with 100 mg/day erlotinib, a response evaluation of stable disease was carried out, and the dose was increased to 150 mg/day if tolerability was established. Treatment was generally discontinued after response evaluation of progressive disease (PD); however, in some patients, treatment was continued after increasing the dose to 150 mg/day at the discretion of the patient. Patients continued to receive treatment until PD, unacceptable toxicity or consent withdrawal. Computed tomography imaging to confirm the efficacy of erlotinib was carried out 4 weeks after starting the treatment, and confirmation was carried out again 4 weeks later in patients where CR or PR was confirmed. Treatment efficacy was assessed using RECIST version 1.1.[15] Adverse events were evaluated using CTCAE version 4.0.

Care Notebook is a QOL questionnaire with 24 questions validated against EORTC-QLQ-C30 and FACT-Sp-12.[16] The clinicians handed each patient a care notebook before the start of erlotinib and requested they fill it at home once a week. The patients were requested to bring the care notebook to each outpatient visit, so that the clinician could confirm the information recorded. Based on the analysis manual, changes in the QOL were assessed by comparing baseline QOL with QOL 6 weeks later.[17]

Statistical analysis

Among older patients or patients with poor PS and EGFR-mutant NSCLC treated with gefitinib and erlotinib, the PFS has been reported to be 6.5 months[18] and 9.7 months,[6] respectively. This was an equivalence study. For reference, a clinical study comparing first-line chemotherapy and first-line gefitinib reported a PFS of 10.8 months in patients on gefitinib.[19] Thus, assuming participant enrollment for 3 years, observation for 2 years, a PFS threshold of 6 months, expected PFS of 10 months, $\alpha = 0.1$ and $\beta = 0.9$, the present study required 33 participants. Considering that approximately 10% of the patients would be ineligible, we intended to enroll 38 patients.

PFS was defined as the interval between the start of the treatment and the date of the first observation of disease progression

or death from any cause. Patients who were alive without disease progression at the data cut-off point were examined at the last point, and the patients were assessed to be progression-free. PFS and OS were estimated using the Kaplan–Meier method. Statistical analyses were carried out using Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The present study was carried out in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol is based on the Clinical Trials Act (Japan), approved by Shimane University Certified Review Board, and published on UMIN (UMIN ID: UMIN000012056).

Results

Patient characteristics

The target sample size was 38; however, in August 2018, the third-generation EGFR-TKI, osimertinib, received an indication expansion and was approved for insurance repayments as a first-line treatment for EGFR-mutant lung cancer in Japan. Thus, further enrollment was difficult, and 33 patients were finally included. All patients met the eligibility criteria, and there were no dropouts.

The median age of the enrolled patients was 82 years (range 75–91 years), with a large number of patients aged >85 years. Women accounted for approximately 70% of the patients. The PS was good (0–1) in approximately 80% of patients, and the tumor type was adenocarcinoma in all patients. The proportion of enrolled patients harboring the Ex21 L858R mutation was high (approximately 60%; Table 1).

Table 1 Patient demographics and clinical characteristics at baseline

No. patients	33
Median age, years (range)	82 (75–91)
Sex male/female (%)	10 (30.3)/23 (69.7)
PS (%) 0	6 (18.2)
1	20 (60.6)
2	6 (18.2)
Unknown	1 (3.0)
Histology (%) adenocarcinoma	33 (100)
Staging (%) II–IIIB	4 (12.1)
IVA	8 (24.2)
IVB	16 (48.5)
Postoperative recurrence	5 (15.2)
EGFR mutation (%) Ex19 del	11 (33.3)
Ex21 L858R	20 (60.6)
Ex18 G719A	2 (6.1)

EGFR, epidermal growth factor receptor; Ex, exon; PS, performance status.

Efficacy

The primary end-point median PFS was 17.8 months (95% confidence interval [CI] 15.3–20.3; Fig. 1a), which was equivalent to the PFS observed after starting treatment at the standard dose of 150 mg/day. The median OS was 26.5 months (95% CI 7.8–45.2; Fig. 1b), and nine out of 33 patients received osimertinib as the subsequent therapy. There were no differences in the PFS and OS by *EGFR* mutation (Ex19 del *vs* Ex21 L858R).

The results for both RR and disease control rate were extremely favorable (63.6% and 96.9%, respectively; Table 2). Furthermore, both patients with the Ex18 G719A mutation were evaluated as SD.

Safety

The most common adverse event of any grade was acne-like eruption (72.7%); however, no events of an acne-like eruption of grade ≥3 were reported. The most common grade ≥3 adverse event was respiratory tract infection, observed in 6.1% of the patients. Grade 2 interstitial lung disease was reported in one patient (3.0%; Table 3).

Treatment was discontinued due to adverse events in 15.2% of the patients, and the dose was reduced due to adverse events in 51.5% of the patients. This shows that adverse events caused a dose reduction or discontinuation of treatment in 66.7% of the patients despite starting erlotinib at a dose of 100 mg/day (Table 4). The dose was increased to 150 mg/day in three patients; however, it had to be reduced to 100 mg/day within 7–14 days in all three patients, owing to adverse events.

QOL

Patients completed the Care Notebook questionnaires every week and brought it to each visit; however, after 6 weeks, just 66.7% of the patients completed all the QOL questionnaires. Of the 12 items in the Care Notebook, QOL was maintained (improved

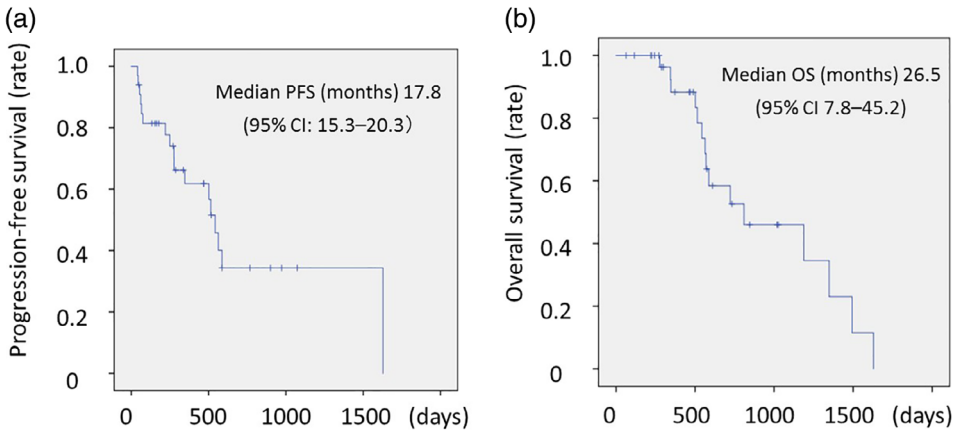

Figure 1 Kaplan–Meier curves for (a) progression-free survival (PFS) and (b) overall survival (OS). CI, confidence interval.

Table 2 Response rates and disease control rates

Response	Overall $n = 33$ (%)	Ex21 L858R $n = 20$ (%)	Ex19 del $n = 11$ (%)
CR	3 (9.1)	2 (10.0)	1 (9.1)
PR	18 (54.5)	10 (50.0)	8 (72.7)
SD	11 (33.3)	8 (40.0)	1 (9.1)
PD	1 (3.0)	0	1 (9.1)
Overall RR (CR + PR)	63.6	60.0	81.8
Disease control rate (CR + PR + SD)	96.9	100	90.9

CR, complete response; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

Table 3 Adverse events

$n = 33$	All grades (%)	Grade 1	Grade 2	Grade 3–4
Hematotoxicity				
Anemia	3 (9.1)	1 (3.0)	2 (6.1)	–
Non-hematotoxicity				
Acne-like eruption	24 (72.7)	7 (21.1)	17 (51.5)	–
Diarrhea	10 (30.3)	7 (21.1)	3 (9.1)	–
Paronychia	6 (18.2)	1 (3.0)	5 (15.2)	–
AST/ALT increased	6 (18.2)	3 (9.1)	2 (6.1)	1 (3.0)
Anorexia	4 (12.1)	–	3 (9.1)	1 (3.0)
Respiratory tract infection	4 (12.1)	–	2 (6.1)	2 (6.1)
Stomatitis	3 (9.1)	3 (9.1)	–	–
Constipation	2 (6.1)	–	2 (6.1)	–
Serum bilirubin increase	2 (6.1)	–	2 (6.1)	–
Heart failure	1 (3.0)	–	–	1 (3.0)
Depression	1 (3.0)	–	1 (3.0)	–
Interstitial lung disease	1 (3.0)	–	1 (3.0)	–
Nausea	1 (3.0)	–	1 (3.0)	–
Biliary tract infection	1 (3.0)	–	1 (3.0)	–
Autoimmune disorder	1 (3.0)	–	1 (3.0)	–

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Adverse events caused a dose reduction or discontinuation of treatment

$n = 33$	Proportion	Reason
Treatment discontinued owing to adverse events	5 patients (15.2%)	Eruption, heart failure, autoimmune disorder, anorexia, interstitial lung disease (each in one patient)
Dose reduced owing to adverse events	17 patients (51.5%)	Eruption (nine patients), anorexia (two patients), serum bilirubin increase (two patients), stomatitis, biliary tract infection, nausea, respiratory tract infection (each in one patient)

or unchanged) after 6 weeks of treatment in ≥70% patients in terms anorexia, constipation, shortness of breath, sleep disorder, depression, social life and subjective quality of life (seven items). However, fatigue, pain, anxiety and activities of daily living deteriorated in at least 40% of the patients (Fig. 2).

Discussion

Treatments for older patients with EGFR-mutant lung cancer (including molecularly targeted drugs) must be efficacious, should not require dose reduction and treatment discontinuation due to adverse events, and should maintain the QOL of the patients. Here, we show that erlotinib displays sufficient efficacy in older patients (aged ≥75 years) with lung cancer when administered at a dose of 100 mg/day, which is two-thirds the standard dose.

First-line therapy with a first- or second-generation EGFR-TKI further transitioning to the third-generation EGFR-TKI, osimertinib, after confirming the *EGFR* Ex20 T790M mutation is being considered as a potential means to prolong OS in older patients with EGFR-mutant lung cancer. However, treatment cessation before transitioning to osimertinib might be required when adverse events during first-line therapy cause treatment suspension or reduce QOL. Hence, appropriate dose selection for first-line EGFR-TKIs is extremely important. In the present study, we achieved a median PFS (primary end-point) of 17.8 months at low erlotinib starting dose of 100 mg/day, which is better than that reported in previous studies using erlotinib at the standard dose (PFS 11.8–15.5 months).[3,4] It was also better than that of a 50-mg dose study comprising older or poor PS patients (range 7.2–11.4 months).[5] In a clinical trial on afatinib carried out in patients aged ≥75 years, the starting dose was the standard dose, but the PFS in the present trial

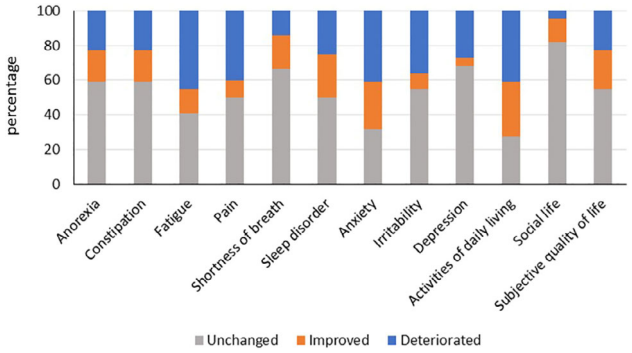

Figure 2 Changes in the quality of life.

was better than that in the previous trial.[20] Furthermore, we found that the median OS was 26.5 months, which is significantly longer for a subject group with a large number of very older patients. This might be one of the reasons why 27.3% of the patients transitioned to osimertinib after PD.

A previous prospective clinical study has reported that 23.7% of patients received osimertinib after disease progression on EGFR-TKIs in Japan.[21] In the present study, 27.3% of patients received osimertinib, thus showing that even older patients can be transitioned to osimertinib if appropriate consideration is given to rebiopsy.

In the present study, we obtained remarkable results for the secondary end-points, RR and disease control rate, when the treatment was started at 100 mg/day. This finding provides sufficient grounds to consider that this is a potential starting dose for older patients, as it showed almost the same efficacy as that in a previous clinical trial on the efficacy of erlotinib at 150 mg/day in older patients.[4] Nevertheless, two-thirds of the patients started at this low dose required dose reduction or treatment discontinuation due to adverse events, such as grade ≤2 acne-like eruption and anorexia. We believe that the QOL data from the present study are extremely valuable, because studies on the QOL of older people taking EGFR-TKI are extremely limited. Multiple QOL items also deteriorated 6 weeks after starting treatment. Given that QOL is of higher priority in older patients, identifying factors that affect the QOL is essential to develop and tailor cancer treatments accordingly for this patient group. Adverse events of seemingly low severity based on their CTCAE grading can easily reduce QOL and result in dose reduction or treatment discontinuation in older patients. Hence, these patients might require a dedicated method to assess adverse events.

The present study had some limitations. First, although individualized treatment requires a detailed assessment based on mutation type, the relatively small number of patients enrolled in the present study prevented the subset analysis. Second, although osimertinib can now be used as first-line therapy for EGFR-mutant lung cancer, no study has compared first-line therapy with osimertinib against first- or second-generation EGFR-TKIs with the dose adjusted, as in the present study, and then investigated the drug sequence once EGFR T790M is confirmed at PD. Third, as the appropriate sample size was 33 based on the formula described in the Methods section, we set a 10% margin as a buffer for potential disqualification and set 38 cases as the target sample size. The number of cases enrolled was 33. Given that a 10% margin had been set as a buffer to account for ineligibility, we consider that the criterion was met. As data on older individuals are scarce, we believe that the results of clinical trials that meet the initial sample size criterion are valid and should be shared. The present study is important, because it highlights the effect of low-dose first-line erlotinib on the QOL of patients with EGFR-positive lung cancer.

In conclusion, first-line erlotinib shows sufficient efficacy in older patients with EGFR-mutant NSCLC, even when started at 100 mg/day. The results of the present study also suggest the need to build systems that support greater individualization of care in terms of early detection of adverse events and maintaining QOL. Older patients require dedicated methods to assess adverse events. Thus, it would be desirable to establish a new assessment method for improving QOL. However, further research regarding the maintenance of QOL at this starting dose is required.

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Disclosure statement

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Study schema. CTCAE, common terminology criteria for adverse events; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD, progressive disease; PS, performance status; SD, stable disease.

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