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Cost-effectiveness and safety of the molecular targeted drugs afatinib, gefitinib and erlotinib as first-line treatments for patients with advanced EGFR mutation-positive non-small-cell lung cancer

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Abstract. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib, erlotinib and afatinib are standard first-line treatments for EGFR gene mutation-positive non-small cell lung cancer. The present study aimed to compare the cost-effectiveness of using erlotinib, afatinib or gefitinib. The safety of EGFR-TKIs was also investigated. Expected costs were calculated based on data from patients with advanced EGFR mutation-positive non-small-cell lung cancer who were treated with gefitinib, erlotinib or afatinib. Literature was collected to obtain the necessary clinical information for calculating the probability and the validity of each chemotherapy. Median survival time (MST) was used to evaluate the therapeutic effect of the regimens. The cost-effectiveness ratio was calculated using expected costs and MSTs for the three regimens. The cost-effectiveness ratio per month was JPY 386,859.4/MST for afatinib, JPY 264,788.7/MST for gefitinib and JPY 397,039.9/MST for erlotinib. Significant differences were observed between the three groups ($p<0.001$). The incremental cost-effectiveness ratio (ICER) of gefitinib compared with afatinib per month was JPY 122,070.7/MST. The ICER of gefitinib compared with erlotinib was JPY -69,605.9/MST. Adverse effects of Grade 3 and higher, including diarrhoea (28.6%) and paronychia (14.3%) were observed in the afatinib treatment group. Paronychia (23.1%) was observed in the erlotinib treatment group, while none were observed in the gefitinib treatment group. These findings demonstrate that gefitinib is more cost effective in comparison with the afatinib and erlotinib regimens, although the afatinib and erlotinib regimens were well-tolerated and produce sufficient effects.

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Key words: afatinib, gefitinib, erlotinib, cost-effectiveness, adverse event, non-small-cell lung cancer

Introduction

In recent years, significant progress has been observed in non-small-cell lung cancer chemotherapies. The median survival time (MST) of patients in a phase III clinical trial that compared four platinum-based combination regimens was ~1 year (1). Meanwhile, the MST of patients with EGFR mutation-positive non-small cell lung cancer who were treated with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is ~2-3 years, and such patients show marked improvements (2-10). Following EGFR-TKI therapy, molecular targeted therapeutic agents, such as anaplastic lymphoma kinase (ALK) inhibitors, have been introduced into clinical settings and improve the prognosis of advanced non-small cell lung cancer (11). Furthermore, nivolumab, an immune checkpoint inhibitor, has been adapted and expanded to advanced non-small cell lung cancer therapies (12,13). Thus, dramatic changes have been taking place in the treatment of lung cancer.

EGFR-TKIs include gefitinib, erlotinib, and afatinib and have shown significant improvements in prolonging progression-free survival (PFS) compared to platinum drug combination therapies (2,3). Currently, according to lung cancer clinical practice guidelines (14) for patients with EGFR gene-mutated advanced non-small cell lung cancer who present performance status (PS) scores of 0-1 and are under 75 years of age, it is recommended to perform therapy with either gefitinib, erlotinib, or afatinib as primary treatment. Gefitinib and erlotinib are considered first generation treatments, and afatinib is considered a second generation medication. Meanwhile, each EGFR-TKI has characteristic adverse events (AEs), which primarily include diarrhoea, skin disorders, liver dysfunction, and other conditions. However, the frequency and severity of the AEs associated with each EGFR-TKI are different (2-10). The use of the molecular targeted drugs is expensive, and the high medical cost associated with these treatments has often been discussed (15). Therefore, it is important to use the concept of drug economics, which is popular in western countries, for reducing medical expenses. As represented by the guideline of the National Institute for Health and Clinical Excellence and the Canadian Agency for Drugs and Technologies in Health, economic evaluations have

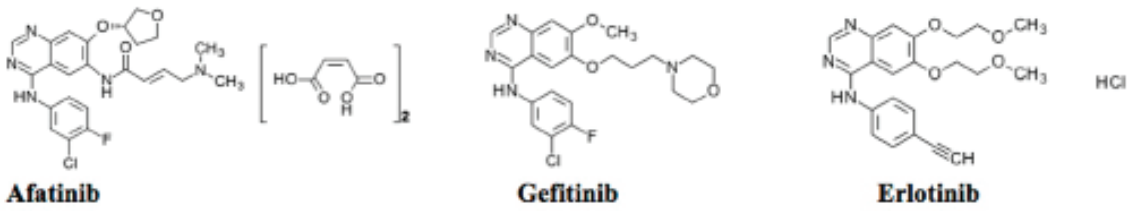

Figure 1. Chemical schemes of each epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI).

already been mandated in the US and European countries (16). However, few cost-benefit analyses of advanced EGFR mutation-positive non-small-cell lung cancer chemotherapies have been reported (17).

In this study, we evaluated the economic superiority of afatinib to gefitinib and erlotinib as treatments for patients with advanced EGFR mutation-positive non-small-cell lung cancer. In addition, we investigated the safety of each EGFR-TKI (Fig. 1).

Patients and methods

Treatment regimens. Afatinib was orally administered once a day at 40 mg on an empty stomach. Gefitinib was orally administered at 250 mg once a day. Erlotinib was administered orally, once a day 1 hour or more before a meal or 2 h after a meal.

Cost-effectiveness analysis. For non-small cell lung cancer, data from patients who received afatinib, gefitinib, or erlotinib chemotherapy between August 2014 and August 2017 (n=142) were extracted from electronic medical records. Patients who were administered the abovementioned chemotherapy after second line therapy (n=56) with a PS score of ≥2 and those aged 75 years or older (n=45) were excluded (Fig. 2). A total of 41 patients were included in the study.

Cost data. Cost data includes direct costs incurred at the time of chemotherapy. Fees for medications (including supportive care), inspections, and outpatient medical examinations were calculated. We collected information about drug prices from the Insurance Drug Encyclopedia (18) and medical fees from the Medical Fee Points Table (19) to calculate total medical expenses. The average medical cost per course was calculated from the actual patient data, and we simulated cost up to the MST.

Calculation exclusions. The diagnostic imaging (chest CT-scan) costs and the labour costs of medical staff are included for each chemotherapy treatment. We excluded these costs from the calculations in this analysis. We also excluded the running and depreciation costs of facilities because they are difficult to dispense on a per patient basis.

Data source of therapeutic effect. A literature review was performed to obtain clinical information for calculating the efficacy probability of each chemotherapy. The search was performed as of October 2017, using PubMed as a document retrieval system. The search used keywords including, 'afatinib',

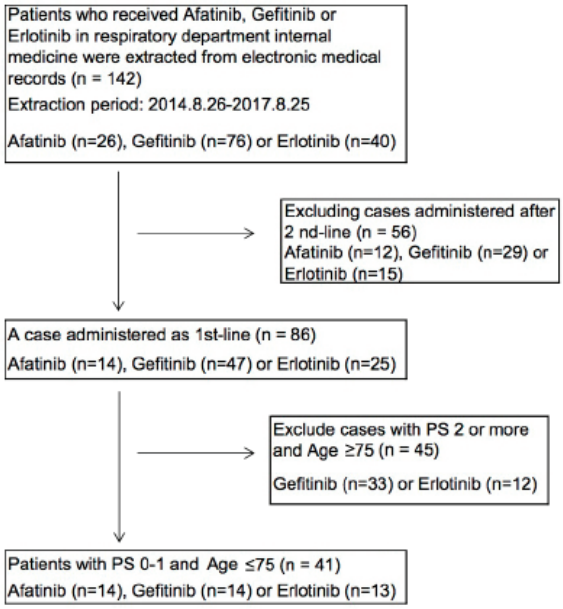

Figure 2. Subject selection and the number of subjects analysed. Exclusion was based on lung cancer clinical practice guidelines.

'gefitinib', 'erlotinib', and 'non-small-cell lung cancer', and was narrowed down to include randomized controlled trials. Cost-effectiveness: The cost-effectiveness analysis was conducted by examining the cost and effectiveness data of each chemotherapy identified through the above methods. The cost-effectiveness ratio of each chemotherapy was calculated by dividing the expected cost by the MST. In addition, the incremental cost-effectiveness ratio (ICER) was used to examine the superiority of the gefitinib versus the afatinib or erlotinib using the following equation: i) ICER (JPY/MST) = (expected cost of afatinib-expected cost of gefitinib)/(MST of afatinib-MST of gefitinib); ii) ICER (JPY/MST) = (expected cost of erlotinib-expected cost of gefitinib)/(MST of erlotinib-MST of gefitinib)

AE analysis. AEs were retrospectively investigated for each patient. The date for each AE was identified using electronic charts and pharmacy service records. The severities of AEs were classified according to the Common Terminology Criteria for Adverse Events (20).

Statistical analysis. One-way ANOVA was used to analyse the patient characteristics shown in Table I. One-way ANOVA and Fisher's protected least significant difference (Fisher's PLSD) was used to analyse the variables shown in Tables II and III.

Table I. Patient characteristics

Variable	Afatinib	Gefitinib	Erlotinib	P-value
Number	14	14	13	
Age, years				
Median (range)	64 (52-75)	71 (44-75)	69 (59-74)	0.212[a]
Sex, n				
Male/female	6/8	6/8	8/5	0.173[b]
ECOG performance status				
0	7	8	9	0.155[b]
1	7	6	4	
Alb, g/dl				
Median (range)	3.9 (3.4-4.7)	4.1 (3.3-4.8)	4.1 (3.2-4.7)	0.908[c]
Body surface area, m^2				
Median (range)	1.65 (1.44-1.92)	1.49 (1.20-1.77)	1.53 (1.29-1.72)	0.015[a]
CrCl, ml/min				
Median (range)	76.3 (46.4-151.1)	59.4 (43.3-131.2)	61.6 (22.3-93.3)	0.073[a]
Disease status				
Unresectable	15	9	10	0.293[b]
Recurrent	0	5	3	
Metastatic site				
Lymph node	8	8	5	0.397[b]
Pleural dissemination	3	5	2	
Liver	4	1	2	
Bone	6	5	6	
Brain	5	0	8	
Others	2	0	1	

[a]One-factor ANOVA, [b]Chi-square for independence test and [c]Fisher's PLSD (afatinib vs. gefitinib; p=0.005; afatinib vs. erlotinib; p=0.051, gefitinib vs. erlotinib; p=0.354). Fisher's PLSD,Fisher's protected least significant difference; CrCl, creatinine clearance; Alb, serum albumin value.

Table II. Cost data (JPY).

Variable	Afatinib	Gefitinib	Erlotinib	P-value
Medication fee				
Anticancer drugs	302,898.3	197,246.2	294,893.1	<0.001[a]
Supportive care drugs	16,998.9	8,631.9	24,554.9	0.110
Inspection fee	4,965.2	5,499.2	6,376.8	0.539
Outpatient medical examination fee	8,523.8	5,021.0	7,737.1	0.012[b]
Hospitalization expense	52,294.7	43,221.7	52,294.7	0.004[c]
Others	6,151.9	5,168.7	11,183.3	0.368
Total	391,832.8	264,788.7	397,039.9	<0.001[d]

Each cost in one course is shown. Other costs include drug information providing fees, outpatient prescription fees, dispensing technology basic fees, oncology patient service fee. [a]Afatinib vs. gefitinib; p<0.001, afatinib vs. erlotinib; p=0.560, gefitinib vs. erlotinib; p<0.001. [b]Afatinib vs. gefitinib; p=0.005, afatinib vs. erlotinib; p=0.512, gefitinib vs. erlotinib; p=0.028. [c]Afatinib vs. gefitinib; p=0.004, afatinib vs. erlotinib; p=0.998, gefitinib vs. erlotinib; p=0.004. [d]Afatinib vs. gefitinib; p<0.001, afatinib vs. erlotinib; p=0.510, gefitinib vs. erlotinib; p<0.001.

In all significance tests, p-values<0.05 were considered to indicate statistical significance. All statistical analyses were performed with EZR (v1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (21).

Table III. Cost-effectiveness ratios.

Variable	Expected cost (JPY/person)	Cost-effectiveness ratio[a] (JPY/MST)	MST (months)
Afatinib	9,942,286.8	386,859.4	25.7
Gefitinib	6,540,280.3	264,788.7	24.7
Erlotinib	9,052,508.9	397,039.9	22.8
P-value	<0.001[b]	<0.001[c]	0.892

[a]Cost-effectiveness ratio is defined as the expected cost per person/the effectiveness determined by the MST. [b]Fisher's PLSD (afatinib vs. gefitinib; p<0.001, afatinib vs. erlotinib; p=0.027, gefitinib vs. erlotinib; p<0.001). [c]Fisher's PLSD (afatinib vs. gefitinib; p<0.001, afatinib vs. erlotinib; p=0.510, gefitinib vs. erlotinib; p<0.001). MST, median survival time; PLSD, Protected Least Significant Difference.

Ethical considerations. Personal information was protected in the aggregated data. This study was approved by the Institutional Review Board of Ogaki Municipal Hospital, Ogaki, Japan.

Results

Patient characteristics. The patient characteristics are summarized in Table I. The median age of patients who received afatinib, gefitinib, and erlotinib was 64 years (range, 52-76), 71 years (range, 44-75), and 69 years (range, 59-74), respectively, and body surface areas were 1.65 (1.44-1.92), 1.49 (1.20-1.77) and 1.53 (1.29-1.72), respectively.

Cost data. For afatinib, the calculated direct medical costs included medication fees (anticancer drugs = JPY 302,898.3, supportive care drugs = JPY 16,998.9), inspection fees of JPY 4,965.2, outpatient medical examination fees of JPY 8,523.8, and hospitalization fees of JPY 52,294.7. For gefitinib, the calculated direct medical costs included medication fees (anticancer drugs = JPY 197,246.2 supportive care drugs = JPY 8,631.9), inspection fees of JPY 5,499.2, outpatient fees of JPY 5,021.0, and hospitalization fees of JPY 43,221.7. For erlotinib, the calculated direct medical costs included medication fees (anticancer drugs = JPY 294,893.1, supportive care drugs = JPY 24,554.9), inspection fees of JPY 6,376.8, outpatient medical examination fees of JPY 7,737.1, and hospitalization fees of JPY 52,294.7. We found that gefitinib were more inexpensive than other regimens, with respect to each medical expense (Table II).

Cost-effectiveness analysis. The cost-effectiveness ratio per month was JPY 386,859.4/MST for afatinib, JPY 264,788.7/MST for gefitinib, and JPY 397,039.9/MST for erlotinib. We found significant differences between the three groups (Table III; p<0.001). The ICER ratio per month of gefitinib to afatinib was JPY 122,070.7/MST. The ICER of gefitinib to erlotinib was JPY -69,605.9/MST.

AE analysis. The major AEs are summarized in Table IV. For afatinib, AEs included diarrhoea (92.9%), rash (71.4%), oral mucositis (71.4%), and increased alanine aminotransferase (ALT) levels (50.0%). For gefitinib, rash (64.3%), aspartate aminotransferase/ALT increases (57.1%), anaemia (42.9%), and diarrhoea (35.7%) were observed. For erlotinib, anorexia (84.6%), nausea (84.6%), rash (76.9%), and leucopenia (53.8%) occurred.

Discussion

In this study, we conducted a drug-economic analysis to compare afatinib, gefitinib, and erlotinib for first-line treatment of patients with advanced EGFR mutation-positive non-small-cell lung cancer. In addition, we investigated the safety of afatinib, gefitinib, and erlotinib.

We found that the cost-effectiveness of gefitinib achieved better results than both afatinib and erlotinib. In implementing gefitinib, total expenses such as anticancer drug costs, outpatient fees, and hospitalization fees were lower than for afatinib and erlotinib. Notably, we found that the cost of anticancer drugs greatly affects the total cost. However, the cost data in this study are based on the patient population of a single facility. In the future, if cost data are collected from several facilities, the data can be applied more widely. In terms of therapeutic effects, there are no direct comparison tests of the three EGFR-TKIs. In the current data, there is a possibility that the therapeutic effects of afatinib, gefitinib, and erlotinib may be expected in order (2-10). In this study, the effect of EGFR-TKIs is not different between the three therapeutics (afatinib, erlotinib, and gefitinib), as defined by MST in various phase III trials.

According to a survey conducted by Shiroiwa *et al* (22). and Ohkusa *et al* (23), <500-6 million yen per quality-adjusted life year (QALY) is considered cost effective. As this study does not consider patient quality of life, it is impossible to accurately determine cost-effectiveness. However, since the ICER of gefitinib versus afatinib or erlotinib were JPY 122,070.7/MST and JPY -69,605.9/MST, respectively, gefitinib are relatively lower cost than afatinib and erlotinib in terms of medical expenses, and we assumed that this is within a good range in terms of cost effectiveness. Through comparing the cost-effectiveness of erlotinib, afatinib, and cisplatin plus pemetrexed, we observed that both TKIs were more cost-effective than cisplatin-pemetrexed (17). Erlotinib had an ICER of $61,809/QALY compared with afatinib. Ting *et al* reported that erlotinib is the preferred first-line treatment for advanced epithelial growth factor receptor mutation-positive non-small-cell lung cancer (17). Meanwhile, in this study, there was no difference between erlotinib and afatinib.

Table IV. Adverse events for each drug regimen.

	Afatinib (n=14)				Gefitinib (n=14)				Erlotinib (n=13)			
	Grade				Grade				Grade			
Adverse event	1	2	≤3	All grades (%)	1	2	≤3	All grades (%)	1	2	≤3	All grades (%)
Leucopenia	2	0	0	2 (14.3)	2	1	1	4 (28.6)	3	4	0	7 (53.8)
Neutropenia	0	0	0	0 (0)	2	0	1	3 (21.4)	4	0	0	4 (30.8)
Platelet count decreased	0	0	0	0 (0)	1	0	0	1 (7.1)	2	0	0	2 (15.4)
Anaemia	0	0	0	0 (0)	3	2	1	6 (42.9)	3	1	0	4 (30.8)
AST increased	3	2	0	5 (35.7)	6	1	1	8 (57.1)	2	1	0	3 (23.1)
ALT increased	3	2	1	6 (42.9)	6	1	1	8 (57.1)	3	1	1	5 (38.5)
Blood bilirubin increased	0	0	0	0 (0)	1	0	0	1 (7.1)	3	1	0	4 (30.8)
Creatinine increased	0	4	0	4 (28.6)	3	1	0	4 (28.6)	1	3	0	4 (30.8)
Fatigue	3	0	0	3 (21.4)	2	0	0	2 (14.3)	3	0	0	3 (23.1)
Anorexia	3	0	0	3 (21.4)	2	1	0	3 (21.4)	9	1	1	11 (84.6)
Nausea	5	1	0	6 (42.9)	1	0	0	1 (7.1)	9	1	1	11 (84.6)
Vomiting	2	0	0	2 (14.3)	0	0	0	0 (0)	0	0	0	0 (0)
Mucositis oral	7	3	0	10 (71.4)	4	0	0	4 (28.6)	7	1	0	8 (61.5)
Diarrhoea	6	3	4	13 (92.9)	4	1	0	5 (35.7)	9	0	0	9 (69.2)
Constipation	0	0	0	0 (0)	2	0	0	2 (14.3)	0	0	0	0 (0)
Rash	7	3	0	10 (71.4)	6	2	1	9 (64.3)	7	2	1	10 (76.9)
Paronychia	3	1	2	6 (42.9)	0	0	0	0 (0)	1	3	3	7 (53.8)
Palmar-plantar erythrodysesthesia syndrome	0	3	0	3 (21.4)	1	0	0	1 (7.1)	0	0	0	0 (0)
Fever	1	0	0	1 (7.1)	2	0	0	2 (14.3)	0	0	0	0 (0)
Dysgeusia	0	0	0	0 (0)	1	0	-	1 (7.1)	0	0	0	0 (0)
Neuralgia	1	0	0	1 (7.1)	1	0	0	1 (7.1)	1	0	0	1 (7.7)
Others	5	0	0	5 (35.7)	4	0	0	4 (28.6)	2	0	0	2 (15.4)

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

The development of AEs varies according to the type of TKI. Each adverse event profile was similar to those observed in previous reports (2-10). Rash toxicity is a common adverse event, but hepatic injury is observed more frequently for gefitinib, anorexia and nausea is more frequent for erlotinib, and diarrhoea is more common for afatinib. Interstitial lung disease (ILD), which is a type of pulmonary toxicity, was not observed in this study. Although the frequency of ILD occurrence is small, it is reported that ~4-5% cases occur in any TKI therapy and in slightly <1%, it is lethal (24). Adverse effects of Grade 3 and higher were found in afatinib therapy, including diarrhoea and paronychia, and in erlotinib therapy, including paronychia, but not for gefitinib. Therefore, it can be predicted that AEs are intensified in the order of gefitinib, erlotinib, and afatinib. From the above observations, we consider that the choice of TKI should be determined based on the balance between beneficial effects and AEs.

This study is the first to analyse the cost-effectiveness of three types of molecular targeted drugs for first-line treatment of patients with advanced EGFR mutation-positive non-small-cell lung cancer. Gefitinib is cost effective compared to afatinib and erlotinib, although afatinib and erlotinib are well-tolerated with sufficient effects.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MK, FY, EU, SK, MI, MG YI and TY conceived and designed the study. MK and FY acquired the data. MK, FY, EU, SK, MI, MG, YI and TY drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Ogaki Municipal Hospital, Ogaki, Japan.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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