ORIGINAL

Relationship between Epidermal Growth Factor Receptor Mutations and Adverse Events in Non-Small Cell Lung Cancer Patients treated with Afatinib

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Abstract : Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors such as afatinib are used for non-small cell lung cancer (NSCLC) and show varying efficacy depending on EGFR gene mutation. Few studies have examined the relationship between EGFR gene mutations and the adverse events of afatinib in NSCLC. This retrospective study included 32 Japanese patients with NSCLC with EGFR gene mutation who were treated with afatinib between May 2014 and August 2018 at Kagawa University Hospital. Among the 32 Japanese patients with NSCLC treated with afatinib, 19 patients were positive for exon 19 deletion mutation (Del 19) and 13 patients were negative for Del 19. The incidence of grade ≥ 2 skin rash was slightly higher in patients positive for Del 19 (42.1% vs. 7.7%, $P = 0.050$). No significant differences were detected in other adverse events between the two patient groups. Patients positive for Del 19 also showed significantly longer median progression-free survival (288 vs. 84 days, $P = 0.049$). Our study indicates a higher incidence of skin rash associated with afatinib treatment in Japanese patients with NSCLC positive for Del 19 compared with patients without Del 19. The Del 19 positive patient group also showed better progression-free survival. J. Med. Invest. 68 : 125-128, February, 2021

Keywords **:** *non-small cell lung cancer, skin rash, exon 19 deletion mutation, afatinib*

INTRODUCTION

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), i.e., gefitinib, erlotinib, afatinib, osimertinib, and dacomitinib, are administered for non-small cell lung cancer (NSCLC) positive for EGFR gene mutations. EGFR gene mutations in NSCLC are frequently detected in the intracellular tyrosine kinase domain. Exon 19 deletion (Del 19) and exon 21 point mutation (L858R) account for 44.8% and 39.8%, respectively (85% in total) (1, 2). Both mutations indicate high susceptibility to EGFR-TKIs. However, the therapeutic effects of EGFR-TKIs on NSCLCs vary depending on the EGFR gene mutation. For example, the LUX-Lung 3/6 study demonstrated that afatinib prolonged progression free-survival (PFS) in Del 19 patients (3).

Although the effects of afatinib as first-line treatment may not necessarily be compared with first-generation TKIs, a meta-analysis revealed that afatinib was more effective as a second-line treatment for advanced squamous cell carcinoma than erlotinib (4). However, afatinib treatment should be started at a low dose in Del 19 patients at risk of malnourishment, sarcopenia, and low body surface area because of the higher incidence of adverse events, such as skin rash, diarrhoea, and mucositis (5).

EGFR is widely expressed in normal skin tissues and cells, such as the epidermis, sebaceous glands, glands, eccrine glands, and dendritic cells, and plays an important role in the normal development and physiology of the epidermis. The epidermis mainly originates from keratinocytes, and keratinocyte differentiation and migration to the skin surface are regulated by the EGFR signalling pathway. EGFR-TKIs have been associated with the development of numerous adverse events, such as skin rash, diarrhoea, and mucositis, through their effects on inhibiting EGFR signal transduction (6).

Several studies have reported the relationships between the adverse events and therapeutic effects of anticancer drugs, such as skin rash due to erlotinib in NSCLC patients (7), hand-foot syndrome due to capecitabine in breast cancer patients (8), and hypertension and proteinuria due to bevacizumab in colorectal and breast cancer patients (9, 10). However, few reports have been published on the relationship between EGFR gene mutations and the adverse events of EGFR-TKIs in NSCLC. We previously reported that Del 19 patients were less likely to develop skin rash than L858R patients, although no significant difference was found on comparison of each drug (11). In one study in Japan, the therapeutic effects of afatinib were more significant with skin rash of grade 2 or higher at 1 week of treatment, although no significant difference was found because it was a small-scale study (12). In this study, we retrospectively investigated the relationship between EGFR gene mutations and the incidence of adverse events in NSCLC patients receiving afatinib.

PATIENTS AND METHODS

Data collection and assessment

We retrospectively analysed the electronic medical records of inpatients with NSCLC who started afatinib between May 2014 and August 2018. We excluded patients who received afatinib beyond the standard dose. We collected data on genetic mutation type, age, gender, body surface area (BSA), performance status (PS), liver and renal function before administration, number of EGFR-TKIs used as prior treatment, and maximum grade of adverse events (skin rash, diarrhoea, stomatitis, and liver

Received for publication August 21, 2020 ; accepted December 15, 2020.

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dysfunction). Grades of adverse effects were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Observation periods were up to 2 weeks from starting therapy, and patients were divided into those with adverse events of grade 0–1 and those with adverse events of grade 2.

Assessment of treatment effectiveness

The best antitumour responses during the treatment period were assessed with response evaluations (complete response : CR, partial response : PR, stable disease : SD, progressive disease : PD) by physicians according to the Response Evaluation Criteria in Solid Tumors (RECIST). Between-group PFS comparisons were also performed.

Statistical analysis

We used IBM® SPSS® Statistics 24.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. Baseline patient characteristics were analysed using the Mann–Whitney U test and Fisher's exact test. We used Fisher's exact test for between-group adverse events and antitumour effect comparisons, with $P < 0.05$ indicating a significant difference. The Kaplan–Meier method was used in the PFS analysis and the log-rank test was employed for comparisons between groups, with $P < 0.05$ indicating a significant difference.

Ethics statement

This study was approved by the Kagawa University Ethical Research Committee (2018-201) and was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare of Japan. Japanese law does not require individual informed consent from participants in non-invasive observational trials such as this study. Therefore, we used our clinical research support centre website as an opt-out method rather than acquiring written or verbal informed consent from patients.

RESULTS

This study included 32 Japanese patients with NSCLC, including 19 patients positive for Del 19 and 13 patients negative for Del 19. All patients were treated with afatinib at the standard dose. The patient characteristics in the Del 19 positive and negative groups are listed in Table 1. No significant difference was found in age, gender, BSA, PS, liver and renal function before administration, and number of EGFR-TKIs used as prior treatment between groups.

In the comparison between the two groups for the incidence of grade ≥ 2 adverse events, skin rash was slightly higher in the Del 19 group than in the non-Del 19 group, but the difference was not significant ($P = 0.050$) (Table 2). No significant difference was observed for the other grade ≥ 2 adverse events.

Comparison of the objective response and disease control rates between the groups is shown in Table 3. The Del 19 group had a higher response rate (CR+PR) and disease control rate (CR+PR+SD), but the difference was not significant ($P = 0.437$

Table 1. Patient characteristics

	Del19 mutation		*P* value
	positive ($n = 19$)	negative ($n = 13$)	
Age (years)	72 (48-84)	71 (42-80)	0.762
Gender (M/F)	5/14	6/7	0.283
BSA (m^2)	1.49 (1.02-1.74)	1.49 (1.22-1.86)	0.623
PS	0 (0-3)	0 (0-4)	0.520
AST (U/L)	23 (14-58)	19 (13-32)	0.404
ALT (U/L)	13 (6-66)	13 (8-20)	0.850
T-Bil (mg/dL)[a]	0.5 (0.4-1.0)	0.5 (0.4-0.9)	1.000
LDH (U/L)	263 (186-907)	225 (185-573)	0.195
ALP (U/L)[b]	250 (94-2808)	300 (132-582)	0.258
Scr (mg/dL)	0.6 (0.40-0.98)	0.69 (0.44-1.07)	0.287
Ccr (ml/min)[c]	85.0 (44.8-154.7)	66.8 (47.7-134.8)	0.940
eGFR (ml/min/1.73m^2)	85.7 (42.8-115.4)	65.8 (52.7-125.4)	0.343
Previous treatment history with EGFR-TKIs			0.287
None	13	8	
Previously treated with 1 EGFR-TKI	6	3	
Previously treated with 2 EGFR-TKIs	0	2	

Data are expressed as the median (range)
BSA, body surface area ; PS, performance status ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; T-Bil, total bilirubin ; LDH, lactate dehydrogenase ; ALP, alkaline phosphatase ; Scr, serum creatinine ; Ccr, creatinine clearance ; eGFR, estimated glemerular filtration rate.
[a]Missing values for 3 patients.
[b]Missing value for 1 patient.
[c]Ccr was estimated by Cockcroft-Gault equation.

and 0.552, respectively).

The comparison of PFS between the groups is shown in Figure 1. The median PFS for patients with and without Del 19 was 288 and 84 days, respectively. The median PFS was significantly longer in patients with Del 19 ($P = 0.049$).

Table 2. Incidence of grade ≥ 2 adverse events according to Del 19 mutation status

	Del19 mutation		*P* value
	positive ($n = 19$)	negative ($n = 13$)	
skin rash	8 (42.1%)	1 (7.7%)	0.050
diarrhea	7 (36.8%)	5 (38.5%)	1.000
mucositis	5 (26.3%)	1 (7.7%)	0.361
liver dysfunction	0 (0%)	1 (7.7%)	0.520

Table 3. Objective Response Rate and Disease Control rate for Each Group

Response	Del 19 mutation positive group ($n = 19$)	Del 19 mutation negative group ($n = 13$)	*P* value
	No. of patients (%)	No. of patients (%)	
CR	1 (5.3)	0 (0)	
PR	10 (52.6)	5 (38.5)	
SD	7 (36.8)	6 (46.2)	
PD	1 (5.3)	2 (15.4)	
Objective Response (CR+PR)	11 (57.9)	5 (38.5)	0.437
Disease Control (CR+PR+SD)	18 (94.7)	11 (84.6)	0.552

CR : complete response. PR : partial response. SD : stable disease. PD : progressive disease.
Fisher's exact test was used for comparisons.

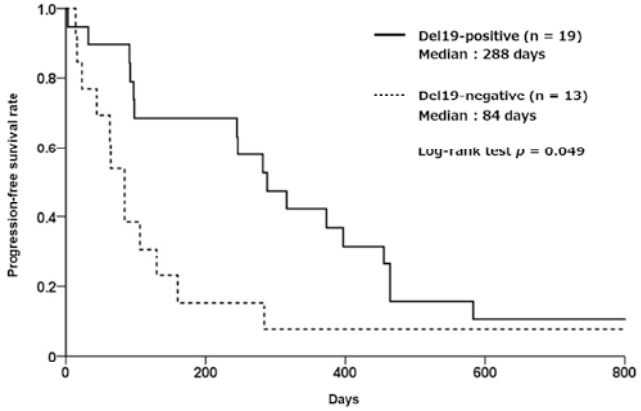

Fig 1. Comparison of progression free survival between groups. Kaplan-Meier method was used for survival analysis.

DISCUSSION

This study compared the adverse events in NSCLC patients with and without Del 19 treated with afatinib. Our results suggested a higher incidence of skin rash due to afatinib treatment in patients with Del 19 compared with patients without Del 19. The most common EGFR gene mutations found in daily clinical practice in NSCLC patients are Del 19 and L858R. Of the 32 patients included in the study, 19 and 13 patients carried Del 19 and L858R, respectively. To examine the association of EGFR gene mutation with adverse events in response to afatinib, grade 2 or higher adverse events that prevented patient daily activities were set as the cut-off value. As no difference was found in the patient background between the Del 19 positive and negative groups, the difference in the incidence of skin rash may not be because of a relative overdose. Because there was no difference in BSA, renal and hepatic function between the two groups. However, no significant difference was noted in the other adverse events. This may be explained by the development of skin rash as early as at 2 weeks in the observation period or the involvement of different factors. The preventive use of moisturizers and skin care procedures for skin rash were similarly performed among all patients, as all patients received the same formulation and instructions at the first prescription. Patients with poor PS were also able to perform uniform skin care by nurses during the hospitalization. Notably, the overall incidence of skin rash in our study was approximately 30% compared with 41.9% in the LUX-Lung 3 global phase III clinical study. However, this study cannot be simply compared with the LUX-Lung 3 study due to the observation period of only 2 weeks, age group, and racial differences. That is 229 patients in the LUX-Lung 3 study, only 54 were Japanese. Therefore, different methods of skin care and racial differences may explain the inconsistent results.

Previous studies have reported relationships between gene mutations and therapeutic effects. One report showed that treatment outcomes, i.e., PFS and response rates, in response to afatinib were generally more satisfactory in Del 19 patients (3).

Our study was limited in that it was a small-scale single-site study. In addition, the reason underlying the relatively high incidence of diarrhoea regardless of gene mutation is not clear. To address this issue, a larger-scale study should be conducted.

CONCLUSIONS

Our study suggests that the incidence of skin rash and therapeutic effects of afatinib in NSCLC patients vary according to gene mutations. This finding suggests the ability to predict the risk of skin rash before the start of treatment and may be useful for patient treatment. Furthermore, skin care instructions will be more important for such patients because more significant therapeutic effects can be expected. Thus, our study should facilitate the reduction of patients who discontinue treatment for adverse events.

CONFLICT OF INTEREST

None of the authors have any potential conflicts of interest associated with this research.

ACKNOWLEDGEMENTS

We thank all patients and medical staff at Kagawa University Hospital who were involved in this study.

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