Effects of tyrosine kinase inhibitor therapy on skin toxicity and skin-related quality of life in patients with lung cancer
An observational study
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Abstract
Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy is the primary treatment option for patients with non-small cell lung cancer (NSCLC). However, one of the major adverse effects associated with this therapy is skin toxicity, which impacts the patient’s quality of life. This study aimed to describe the severities and locations of skin toxicity, and to analyze their association with the quality of life in patients with advanced NSCLC who received EGFR-TKI therapy as first-line treatment.

This cross-sectional and correlation study was conducted at a tertiary medical center in northern Taiwan between July 2015 and March 2016. Skin toxicity was assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). The Skinindex-16 scale was used to measure the skin disease-related quality of life.

A total of 146 NSCLC patients who received EGFR-TKI therapy within the first 3 months of diagnosis were included in this study; 93.2% of these patients experienced skin toxicities. Approximately 70% of the patients developed xerosis and pruritus, while 50% had papulopustular eruptions and paronychia. The mean skin symptom impact score was 5.38 (standard deviation = 2.65). The skin-related quality of life varied widely among the participants but remained acceptable (mean score = 13.96, standard deviation = 16.55). Skin symptoms correlated significantly with poor quality of life ($r=0.50, P<.001$). Younger patients and those treated with afatinib were the most affected, reporting the poorest quality of life. Patients who required EGFR-TKI dose reduction had experienced more severe skin symptoms than had patients who did not require it (7.35 vs 5.01, $P<.001$).

Skin toxicity related to EGFR-TKI treatment impacts the quality of life in patients with NSCLC. During the treatment period, skin assessment and tailored management should be incorporated into the daily care plan.

Abbreviations: ECOG PS = Eastern cooperative oncology group performance status, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, NCI-CTCAE = National Cancer Institute- Common Terminology Criteria for Adverse Events, NSCLC = non-small cell lung cancer, SD = standard deviation, SRQOL = skin-related quality of life, SSI = skin symptom impact.

Keywords: advanced non-small cell lung cancer, dermatological side effects, quality of life, skin toxicity, targeted therapy

1. Introduction
Lung cancer is a highly prevalent and deadly global disease.[11–3] Approximately 70% to 75% of patients newly diagnosed with lung cancer are already at an advanced disease stage (ie, stage 3B or 4).[4] Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) including gefitinib, erlotinib, and afatinib have recently emerged as major therapeutic agents for treating advanced non-small cell lung cancer (NSCLC).[4–6] EGFR-TKIs block the activation of downstream EGFR signaling, resulting in cancer cell death. However, these agents can damage normal skin cells and cause skin toxicities such as xerosis, pruritus, acniform or papulopustular eruption, nail changes, and paronychia.[7,8] The incidence of skin toxicity has been estimated to range between 66.5% and 91%, with most classified as grade 1 or 2 toxicity.[4,9,10] Skin toxicity has been identified as the most debilitating factor in patients receiving EGFR-TKI therapy.[11]

A meta-analysis that compared patients receiving chemotherapy to those receiving EGFR-TKIs found that the latter generally experience a better quality of life,[5] but may develop severe skin rashes that can lead to poor skin-related quality of life (SRQOL).[19] The ‘symptom’ and ‘emotion’ domains of the health-
related quality of life are also impaired in patients treated with EGFR-TKIs. Therefore, it is important that patients are made aware of skin-related adverse effects before initiating EGFR-TKI therapy, and are provided with a comprehensive assessment and early treatment of any skin-related symptoms that arise.

Understanding the effects of skin toxicity on the quality of life can provide a reference for clinical professionals who manage patients receiving EGFR-TKI therapy, as well as an empirical basis for the development of guidelines to enhance the quality of life of these patients. Therefore, this study aimed to examine (1) the skin toxicity and SRQOL, (2) association between skin toxicity and SRQOL, and (3) effect of EGFR-TKI dosage reduction on skin toxicity in patients with NSCLC receiving EGFR-TKI therapy.

2. Materials and methods

2.1. Study design and patients

This was a cross-sectional study that was conducted in the outpatient clinic of the Departments of Chest Medicine and Oncology at a medical center in northern Taiwan. Patients included in the study were those who

1. were newly diagnosed with advanced NSCLC,
2. received treatment with gefitinib, erlotinib, or afatinib as the first-line therapy within the first 3 months,
3. were aged >18 years,
4. had not undergone surgical resection or chemotherapy, and
5. provided written consent.

Patients with lung cancer recurrence and those who had a second primary cancer were excluded from the study.

2.2. Procedure

Prior to the formal study, the first author and a clinical skin specialist performed a skin toxicity assessment in five patients receiving EGFR-TKI therapy, based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 skin toxicity severity grading, to confirm inter-observer reliability. These five patients were not included in the actual analysis cohort. Formal data collection was performed between July 2015 and March 2016. Patients who met the inclusion criteria were invited to participate in the study. The severity and location of their skin symptoms were graded by the first author using the NCI-CTCAE in an examination room immediately after study participants completed their questionnaires. This study was approved by the Institutional Review Board of the hospital (approval number 104-22008). Data collection commenced after obtaining written consent from the participants. Patients were guaranteed the option to withdraw from the survey at any time, and were informed that all their provided information would be kept confidential and used only for academic purposes. Data were processed anonymously to avoid the divulging of information and to protect the privacy rights of the participants.

2.3. Questionnaires

2.3.1. Skin symptoms. Skin symptoms were assessed for severity, location, and impact. Four common symptoms of skin toxicity, namely, papulopustular reaction, paronychia, xerosis (skin dryness), and pruritus (itching), were assessed using the NCI-CTCAE version 4.03 and graded with scores of 1 to 4 based on severity. For example, grade 1 pruritus included mild or localized symptoms for which topical intervention was indicated, while grade 2 was characterized by moderate or widespread pruritus that involved skin changes from scratching, required oral medication, and limited instrumental activities of daily living. Grade 3 included symptoms that were serious and constant (but not immediately life-threatening) that led to hospitalization or an extended hospital stay, resulted in limited self-care activities of daily living or sleep, and required oral corticosteroid or immunosuppressive therapy. Grade 4 symptoms were life-threatening and required emergency treatment. Skin toxicity locations were divided into 5 regions: the scalp, face, limbs (arms and legs), fingers, and trunk (back, chest and belly). The skin symptom impact (SSI) score for each patient was calculated by combining the severity grading and location of symptoms to determine the overall impact of skin toxicity. The range of the SSI score was 0 to 20, with a higher score indicating a higher impact. For example, if a patient experienced grade 2 xerosis on the limbs and 1 grade papulopustular reaction on the face, the SSI score was 7 (2 symptoms, 2 locations, and 3 grades).

2.3.2. SRQOL. The Chinese version of the Skindex-16 scale was used to measure the SRQOL. The questionnaire comprised of 16 questions covering the symptoms, emotions, and functioning domains of the quality of life. Each question was scored from 0 (never bothered) to 5 (always bothered), and the scores were subsequently converted into linear percentages with 100% indicating a full score; a higher score indicated a poorer quality of life. This scale has been validated and shown to have good reliability. In this study, the internal consistency reliability was good, with a Cronbach’s alpha value of 0.96.

2.3.3. Basic data. The collected data included sex, age, physical function (Eastern Cooperative Oncology Group performance status [ECOG PS]), EGFR-TKI regimen and dose, treatment duration (days), and whether or not the EGFR-TKI dosage had been reduced during the treatment process.

2.4. Statistical analysis

Data were analyzed using the SPSS Statistics 22.0 software (IBM, Armonk, NY). Descriptive data including mean, standard deviation (SD), frequencies, and percentages were used to estimate the distribution of the data. Group differences were evaluated using the independent sample t-test or one-way analyses of variance for continuous variables, followed by pairwise comparisons for significant results. The chi-square test was used to examine group differences between categorical variables. The statistical significance level was set at P < .05.

3. Results

The study originally included 148 patients; however, one patient who required immediate chest ultrasound-guided examination owing to breathing difficulties, and was too weak to complete the questionnaire, was excluded from the study, as was another patient who no longer wished to participate. Thus, the final analysis evaluated data from 146 patients. Most participants were women (n = 95, 65.1%) with a mean age of 65.4 years (SD: 12.1) and stage IV disease (n = 131, 89.7%). The ECOG PS score was 0 in most patients (n = 108, 74%), indicating good physical...
Table 1

| Variables                      | Mean | SD  | n  | %  |
|--------------------------------|------|-----|----|----|
| Age                            | 65.4 | 12.1| 73 | 50 |
| Treatment Duration (d)         | 59   | 28.7| 41 | 28.1|
| Sex (female)                   | 95   | 65.1| 106| 72.6|
| Marital status (married)       | 106  | 72.6| 45 | 30.8|
| Education (high school and above) | 45   | 30.8| 41 | 28.1|
| Smoker                         | 41   | 28.1| 73 | 50 |
| Employed                       | 15   | 10.3| 131| 89.7|
| Stage                          | 0    | 106 | 72.6|
| IIIB                           | 123  | 84.2|
| IV                             | 8    | 5.5 |
| ECOG PS                        | 2    | 1.4 |
| Regimen                        | 1    | 0.7 |
| Gefitinib (250 mg)             | 32   | 21.9|
| Erlotinib (150 mg)             | 30   | 20.5|
| Erlotinib (100 mg)             | 1    | 0.7 |
| Afatinib (40 mg)               | 74   | 50.7|
| Afatinib (30 mg)               | 9    | 6.2 |
| Dose Reduction                 | 123  | 84.2|
| No                             | 23   | 15.8|
| Yes                            | 3    | 2.1 |

ECOG PS = Eastern cooperative oncology group performance status, SD = standard deviation.

function status. Afatinib was the most frequently administered therapeutic agent (n = 83, 56.8%), followed by gefitinib (n = 32, 21.9%), and erlotinib (n = 31, 21.3%). The mean duration of the EGFR-TKI therapy was 59 days (SD: 28.7); 23 patients (15.8%) required dose reduction because of skin toxicity (Table 1).

Overall, 136 patients (93.2%) experienced grade ≥1 skin toxicity. The incidences of the four types of symptoms (grade ≥1) were as follows: xerosis (74.7%), pruritus (71.2%), papulopustular eruption (56.8%), and paronychia (55.5%). In terms of location, skin symptoms mostly appeared on the fingers (n = 81, 55.5%), followed by the face (n = 73, 50%), limbs (n = 60, 41.1%), trunk (n = 53, 36.3%), and scalp (n = 48, 32.9%). The SSI scores ranged from 0 to 12 with a mean score of 5.38 (SD: 2.63), while the Skindex-16 scores ranged from 0 to 82 with a mean score of 13.96 (SD: 16.55) (Table 2).

Age showed a negative correlation with both the SSI (r = -0.29, P < .001) and SRQOL (r = -0.29, P < .001) scores. Patients in the afatinib group had a higher SSI score (F = 12.29, P < .001) and poorer SRQOL score (F = 3.978, P = .021) compared to those in the gefitinib group (post-hoc Scheffe test). The SSI and SRQOL scores showed no associations with treatment duration, sex, marital status, education level, smoking, employment status, stage, or ECOG PS (Table 3).

Patients with skin toxicity symptoms other than xerosis experienced poor SRQOL. Skin symptoms appearing on the scalp (t = -2.09, P = .04), face (t = -3.95, P < .001), and fingers (t = -2.84, P = .005) were associated with poor SRQOL. The SSI score was negatively correlated with the SRQOL (r = -0.50, P < .001) (Table 4).

Skin toxicity symptoms appeared on the scalp in 56.5% of the patients in the dose reduction group, compared to 28.5% of those in the non-dose reduction group (x² = 5.70, P = .02). The SSI was significantly higher in the dose reduction group than in the non-dose reduction group (t = -4.09, P < .001), whereas the SRQOL was poorer in the former than in the latter (t = -2.88, P = .008) (Table 5). Comparisons between the dose reduction and non-dose reduction groups for each type of EGFR-TKI are shown in Table 6. In the afatinib group, patients who required dose reduction had higher SSI scores (7.61 vs 5.48) and poorer SRQOL scores (28.87 vs 13.02) than did those in whom doses were not reduced. No significant differences between patients who underwent dose reductions and those who did not were observed in the other treatment groups.

4. Discussion

In this study, 93.2% of the participants reported EGFR-TKI-induced skin toxicities; nearly 70% of these patients experienced xerosis and pruritus, while 50% had papulopustular eruptions and paronychia. Overall, the SRQOL was acceptable but varied

Table 2

| Symptoms            | Grade 1, 2, 3 | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|---------------------|--------------|---------|---------|---------|---------|
| Xerosis             | 109          | 74.7    | 37      | 25.3    | 97      | 66.4    | 12      | 8.2    | 0       | 0       |
| Pruritus            | 104          | 71.2    | 42      | 28.8    | 89      | 61      | 13      | 8.9    | 2       | 1.4     |
| Papulopustular      | 83           | 56.8    | 63      | 43.2    | 52      | 35.6    | 27      | 18.5   | 4       | 2.7     |
| Paronychia          | 81           | 55.5    | 65      | 44.5    | 54      | 37      | 24      | 16.4   | 3       | 2.1     |

Locations vs symptoms
Scalp               | 48           | 32.9    | 39      | 81.3    | 39      | 81.3    | 42      | 87.6   | -       | -       |
Face                | 73           | 50      | 57      | 78.1    | 56      | 76.7    | 65      | 89.0   | -       | -       |
Trunk               | 53           | 36.3    | 49      | 92.5    | 50      | 94.3    | 29      | 54.7   | -       | -       |
Limbs               | 60           | 41.1    | 56      | 93.3    | 50      | 83.3    | 28      | 46.7   | -       | -       |
Fingers             | 81           | 55.5    | 59      | 72.8    | 58      | 71.6    | 58      | 71.6   | 81      | 100     |

Skin symptom impact (mean/SD) | 5.38 | 2.65 |
Skindex-16 (mean/SD) | 13.96 | 16.55 |

*Skin symptom impact = symptom grade + number of locations.

all grades.
### Table 3
Relation among basic data, skin symptom impact and skin-related quality of life (N=146).

| Variables               | Skin symptom impact |            |            |            | Skin-related quality of life |            |            |            |
|-------------------------|---------------------|------------|------------|------------|-------------------------------|------------|------------|------------|
|                         | r       | Mean  | SD       | T     | P    | r       | Mean  | SD       | T     | P    |
| Age                     | −0.29   | 3.57  | 2.36     | 0.64  | .52  | 11.58  | 14.73  | −1.28    | .20  |
| Duration of treatment (d)| 0.14    | 5.27  | 2.79     |        | .09  | 15.24  | 17.39  |          |     |
| Sex                     |          |        |          |       |      |          |        |          |     |
| Male                    | 5.57    | 2.36  | 0.64     | .52   |      | 11.58  | 14.73  | −1.28    | .20  |
| Female                  | 5.27    | 2.79  |          |       |      | 15.24  | 17.39  |          |     |
| Marital status          |          |        |          |       |      |          |        |          |     |
| Married                 | 5.48    | 2.84  | 0.27     | .78   |      | 13.17  | 14.09  | −0.35    | .73  |
| Unmarried               | 5.34    | 2.58  |          |       |      | 14.25  | 17.45  |          |     |
| Education               |          |        |          |       |      |          |        |          |     |
| High school and below   | 5.32    | 2.78  | −0.41    | .68   |      | 13.71  | 16.21  | −0.27    | .79  |
| High school and above   | 5.51    | 2.34  |          |       |      | 14.51  | 17.48  |          |     |
| Smoking                 |          |        |          |       |      |          |        |          |     |
| No                      | 5.30    | 2.66  | −0.52    | .60   |      | 14.78  | 16.66  | −0.52    | .60  |
| Yes                     | 5.56    | 2.64  |          |       |      | 11.86  | 16.29  |          |     |
| Employed                |          |        |          |       |      |          |        |          |     |
| No                      | 4.96    | 2.86  | −1.92    | .06   |      | 13.61  | 18.02  | −0.25    | .80  |
| Yes                     | 5.79    | 2.37  |          |       |      | 14.31  | 15.07  |          |     |
| Stage                   |          |        |          |       |      |          |        |          |     |
| IIIB                    | 5.07    | 2.28  | −0.48    | .63   |      | 10.56  | 16.30  | −0.84    | .40  |
| IV                      | 5.41    | 2.69  |          |       |      | 14.35  | 16.66  |          |     |
| ECOG                    |          |        |          |       |      |          |        |          |     |
| 0                       | 5.35    | 2.57  | −0.19    | .85   |      | 14.16  | 16.17  | 0.24     | .81  |
| 1/2/3                   | 5.45    | 2.89  |          |       |      | 13.40  | 17.82  |          |     |
| EGFR-TKI                |          |        |          |       |      |          |        |          |     |
| Gefitinib               | 3.47    | 2.31  | 12.29    | .000  |      | 6.96   | 14.80  | 3.98     | .02  |
| Erlotinib               | 5.84    | 2.49  | (post-hoc test Afatinib > Gefitinib) | 14.48 | 14.78 | (post-hoc test Afatinib > Gefitinib) | 16.46 | 17.21 |
| Afatinib                | 5.94    | 2.51  |          |       |      |          |        |          |     |

ECOG PS = Eastern cooperative oncology group performance status, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, SD = standard deviation.

### Table 4
Association between skin toxicity and skin-related quality of life (N=146).

| Variables               | Mean  | SD       | t      | P    |
|-------------------------|-------|----------|--------|------|
| Symptoms                |       |          |        |      |
| Xerosis                 | Yes   | 15.45    | 17.22  | 1.88 | .062 |
|                         | No    | 9.57     | 13.69  |     |
| Pruritus                | Yes   | 15.75    | 17.42  | 2.08 | .039 |
|                         | No    | 9.52     | 13.37  |     |
| Papulopustular          | Yes   | 20.39    | 18.73  | 6.66 | .000 |
|                         | No    | 5.48     | 5.96   |     |
| Paronychia              | Yes   | 17.36    | 16.46  | 2.84 | .005 |
|                         | No    | 9.72     | 15.79  |     |
| Location                |       |          |        |      |
| Scalp                   | Yes   | 18.01    | 16.23  | −2.09| .038 |
|                         | No    | 11.37    | 16.43  |     |
| Face                    | Yes   | 19.12    | 17.52  | −3.95| .000 |
|                         | No    | 8.80     | 13.82  |     |
| Trunk                   | Yes   | 14.19    | 17.60  | −0.13| .90  |
|                         | No    | 13.83    | 16.02  |     |
| Limbs                   | Yes   | 12.10    | 15.18  | 1.14 | .26  |
|                         | No    | 15.26    | 17.42  |     |
| Fingers                 | Yes   | 17.36    | 16.46  | −2.84| .006 |
|                         | No    | 9.72     | 15.79  |     |
| Skin symptom impact     |       | R=0.50   | P=.000 |      |

SD = standard deviation.
greatly among the participants (ie, the SD was large). Patients who reported a greater impact on the skin experienced a worse quality of life. Specifically, younger patients and those treated with afatinib had higher SSI scores and a poorer quality of life. Moreover, the SSI score was associated with EGFR-TKI dose reduction.

The incidence rate of skin toxicity in our study was comparable to those reported previously.4,5,9,10,17 Skin-related symptoms have generally been shown to appear immediately after the initiation of treatment and to persist for the entire treatment period.6,16 Papulopustular eruptions are recognized as a clearly visible and less tolerable symptom because they usually appear on the scalp and face.7 Skin symptoms interfere with body image and social interactions, which results in additional emotional distress in young patients given that they are more socially active.18 Skin-related toxicities led to EGFR-TKI dose reductions during the 3-month treatment period. Patients who required dose reductions had been more severely impacted by skin-related symptoms than had those who did not require such dose reductions. Boone et al. noted that 30% of the patients in their study required EGFR-TKI dose delays or discontinuation owing to skin toxicity,19 while Takeda et al. reviewed 21 studies and found skin toxicity to be one of the reasons that targeted therapy was terminated.20 Notably, neither skin symptoms nor locations alone caused dose reductions in our study; rather, both factors combined were associated with dose reduction. To avoid having to reduce the dose, it is important to provide adequate information and instruct the patients to report symptoms as soon as they manifest.21 To that end, the SSI scores in this study can be used to assess the degree of impact of the skin symptoms.

Our study had some limitations. Its cross-sectional nature made it difficult to detect the changing patterns of skin symptoms. Future studies that use a longitudinal design are required to ascertain the trajectory of the symptoms. Moreover, only four

Table 5

| Variables | Reduced (n = 23) | Non-reduced (n = 123) | χ² | P |
|-----------|-----------------|----------------------|----|---|
| Symptoms  |                 |                      |    |   |
| Xerosis (yes) | 109 | 21 | 91.3 | 88 | 71.5 | 3.02 | .08 |
| Pruritus (yes) | 104 | 20 | 87.0 | 94 | 68.3 | 2.45 | .12 |
| Papulopustular (yes) | 83 | 17 | 73.9 | 66 | 53.7 | 2.47 | .12 |
| Paronychia (yes) | 81 | 16 | 69.6 | 65 | 52.8 | 1.57 | .21 |
| Location  |                 |                      |    |   |
| Scalp (yes) | 48 | 13 | 56.5 | 35 | 28.5 | 5.70 | .02 |
| Face (yes) | 73 | 16 | 69.6 | 57 | 46.3 | 3.30 | .07 |
| Trunk (yes) | 53 | 9 | 39.1 | 44 | 35.8 | 0.01 | .94 |
| Limbs (yes) | 60 | 8 | 13.3 | 52 | 42.3 | 0.19 | .66 |
| Fingers (yes) | 81 | 16 | 69.6 | 65 | 52.8 | 1.57 | .21 |
| Mean SD |                      |                      |    |   |
| Skin symptom impact | 7.35 | 1.89 | 5.01 | 2.61 | −4.09 | .000 |
| Skin-related quality of life | 26.22 | 23.51 | 11.67 | 13.87 | −2.88 | .008 |

Table 6

| EGFR-TKI | Dose | Skin symptom impact | Quality of life | Quality of life |
|----------|------|---------------------|----------------|----------------|
|          | Mean SD | t | P | Mean SD | t | p |
| Afatinib | Reduced | 7.61 | 1.72 | −3.39 | .001 | 28.87 | 22.97 | −2.79 | .01 |
|          | Non-reduced | 5.48 | 2.50 | .59 | .55 | 13.02 | 13.57 | .51 | .62 |
| Erlotinib | Reduced | 6.67 | 3.21 | −0.59 | .55 | 23.26 | 33.09 | −0.51 | .66 |
|          | Non-reduced | 5.75 | 2.45 | .11 | .11 | 13.54 | 12.34 | .02 | .98 |
| Gefitinib | Reduced | 6.00 | 1.41 | −1.64 | .11 | 6.77 | 9.57 | .02 | .98 |
|          | Non-reduced | 3.33 | 2.27 | 6.97 | 15.20 | .02 | .98 |

EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, SD = standard deviation.

*P < .05.
symptoms were assessed in this study, although these are reportedly the most obvious and noteworthy skin-related symptoms in patients with NSCLC. Lastly, the prevalence of other skin reactions such as hair disturbances ought to be further examined in future studies.

5. Conclusions

Our results demonstrated that skin toxicity has significant effects on the quality of life of patients with advanced NSCLC who receive EGFR-TKIs as first-line therapy. Healthcare professionals should educate their patients regarding skin care following treatment with EGFR-TKIs. Additionally, skin assessment and individually tailored management should be regularly provided during the treatment period.

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