A Correlational Study of Skin Toxicity and Quality of Life in Patients With Advanced Lung Cancer Receiving Targeted Therapy

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ABSTRACT

Background: Oral targeted therapy is increasingly used worldwide to treat patients with advanced lung cancer. The adverse skin toxicity that is associated with treatment with epidermal growth factor receptor inhibitors often results in acniform rash, dry skin (xerosis), pruritus, and paronychia, which may cause discomfort in patients and affect their quality of life.

Purpose: This study was designed to explore changes in skin toxicity and quality of life (measured overall by three subscales) as well as the correlation between skin toxicity and overall quality of life over a 3-month period for patients with advanced lung cancer receiving oral targeted therapy.

Methods: This study used a longitudinal research design. Baseline data were collected before initiating targeted therapy. Data for the effects of targeted therapy on skin toxicity and quality of life were collected at 2, 4, 8, and 12 weeks after therapy initiation. Data on skin toxicity were collected using the Common Terminology Criteria for Adverse Events Version 4.03, and quality of life was measured using the Chinese version of the Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18 questionnaire. Demographic and clinical data were analyzed using descriptive statistics, and Spearman’s rank correlation coefficient was used to measure the correlation between skin toxicity and quality of life.

Results: Thirty-two patients participated in this study. The symptoms of skin toxicity that increased over the 3-month study period included xerosis and paronychia, whereas acniform rash and pruritus fluctuated during this period. Over the study period, more than 70% of the participants exhibited symptoms of skin toxicity. Skin toxicity was the greatest and quality of life was the lowest, respectively, at the end of the study. All of the symptoms of skin toxicity were significantly correlated with quality of life, although each varied over time ($r = .36–.61$, $p < .05$).

Conclusions/Implications for Practice: The results of this study indicate that healthcare providers should consider the impact of skin toxicity on quality of life in patients with advanced lung cancer who are receiving oral targeted therapy. These findings may be used to design interventional measures for skin and medical care to improve quality of life in patients with advanced lung cancer.

KEY WORDS:
lung cancer, skin toxicity, targeted therapy, quality of life.

Introduction

According to official statistics, the proportion of patients in Taiwan in 2016 who had advanced non-small-cell lung cancers such as Stage IIIB or IV and were receiving oral targeted therapy exceeded the proportion of those receiving traditional chemotherapy (29.6% vs. 17.4%, respectively; Health Promotion Administration, Ministry of Health and Welfare, Taiwan, ROC, 2018). Oral targeted therapy for the treatment of advanced lung cancer uses epidermal growth factor receptor (EGFR) inhibitors (Tischer, Huber, Kraemer, & Lacouture, 2017), which include drugs such as Iressa, Tarceva, and Giotrif (National Health Insurance Administration [NHIA], Taiwan, ROC, 2019). Oral targeted therapy has been shown to offer a longer median time of progression-free survival, a better tumor response rate (Langer, 2013), and fewer serious side effects (Rosell et al., 2012; Wu et al., 2014) than chemotherapy.

Unfortunately, 80% of patients treated with targeted therapy experience skin toxicities such as acniform rash, xerosis, pruritus, and paronychia (Tischer et al., 2017), which occur repeatedly within 3 months of treatment at varying levels of

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severity. Consequently, patients may experience considerable discomfort that affects work and everyday activities and may reduce quality of life (Clabbers et al., 2016; Lacouture, 2013; Lacouture et al., 2011). Because quality of life is regarded as one of the most important indicators for tracking the effectiveness of cancer treatment (Dai, Yang, Chen, & Tang, 2017; Jacobsen, Davis, & Cella, 2002), monitoring the impact of skin toxicity on the quality of life of patients receiving targeted therapy is crucial.

The number of long-term follow-up studies on patients with advanced lung cancer receiving targeted therapy at different times in the literature is limited. One cross-sectional study found a significant correlation between skin toxicities of rash and pruritus and the Skindex-29 measure of quality of life (Lin, 2009), although no longitudinal data were collected. A short-term, 6-week follow-up study by Clabbers et al. (2016) found that acneiform rash, xerosis, and pruritus had a significant association with a reduction in quality of life during treatment with targeted therapy, although the study population included multiple cancers and patients were treated with several different drugs. Lung cancer is the leading cause of death in Taiwan among both men and women (Ministry of Health and Welfare, Taiwan, ROC, 2018). Thus, understanding the specifics of the impact of targeted therapy and of the care provided to this population is critical. Lacouture (2013) found that symptoms of skin toxicity occurred within 3 months of treatment, although the empirical data from the longitudinal research design were insufficient. Therefore, this study was a long-term, 3-month investigation to monitor changes in skin toxicity and quality of life at different times. The purpose of this study was twofold: (a) to measure changes in skin toxicity and assess quality of life in patients with advanced lung cancer after treatment with targeted therapy for a period of 3 consecutive months and (b) to assess correlations between skin toxicity and overall quality of life as well as changes over time in these correlational relationships. The findings may facilitate the design of skin or clinical care interventions and improve quality of life in patients during targeted therapy.

**Literature Review**

Since 2004, Taiwan has added Iressa, Tarceva, and Giotrif as targeted drugs to the NHIA plan as the first line of treatment for patients with advanced lung adenocarcinoma. Patients with the genetic mutation of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) are candidates for using Iressa and Giotrif as first-line therapies, whereas Tarceva may be used as the second- or third-line therapy (NHIA, Taiwan, ROC, 2019). The EGFR-TKIs use small molecules to block the ligand of the EGFR (genetic receptor: ErbB1–ErbB4), which induces the inactivation and phosphorylation of the tyrosine kinase in cells, thus blocking the transmission of EGFR signals and restricting the growth and proliferation of cancerous cells to alleviate the tumor (Li & Perez-Soler, 2009; Raymond, Faivre, & Armand, 2000).

Patients with lung cancer who receive EGFR targeted therapy often experience skin toxicity in the form of acneiform rash (the most common), followed by xerosis, pruritus, or paronychia (Lacouture, 2013; Lacouture et al., 2011; Tischer et al., 2017). Studies that employed Common Terminology Criteria for Adverse Events (CTCAE) v3.0 to determine posttreatment skin conditions after use of the three previously discussed drugs in Phase 3 clinical trials for first-line lung cancer therapy have reported the following results: 66.2%–80.8% of patients experienced rash or acneiform rash, 23.9% experienced dry skin, 10.9%–19.4% experienced pruritus, and 4%–32.6% experienced paronychia. Among these patients, only 2.1% of those who received Giotrif developed skin toxicity of a severity great enough (≥ Grade 3) to require suspension of treatment or a change in dosage (Mok et al., 2009; Wu et al., 2014; Zhou et al., 2011). Of the three target drugs, Giotrif had the highest incidence of severe skin toxicity, followed by Tarceva and then Iressa, which had the lowest incidence (Passaro, Di Maio, Del Signore, Gori, & de Marinis, 2014). Symptoms often begin to appear several days after completion of the therapy. The temporal order of these symptoms is acneiform rash, which appears within 2–4 weeks after the initiation of treatment and is typically at its most serious during the fourth week; xerosis and pruritus, which both appear about 4–6 weeks after the initiation of treatment and, in most cases, lasts for more than 6 months; and, finally, paronychia, which appears from about 20 days to 6 months after the initiation of treatment (Lacouture, 2013; Lacouture et al., 2011). Although all skin toxicities are reversible and not life-threatening (Jatoi & Nguyen, 2008; Ricciardi, Tomao, & de Marinis, 2009), the lesions are uncomfortable, often appear over the entire body, and occur repeatedly during therapy. One study identified changes in skin-related symptoms during the first 2 weeks of targeted therapy as having the most significant impact on quality of life in this patient population (Tischer et al., 2017). Thus, the side effects of skin toxicity cause chronic discomfort and affect quality of life (Lacouture, 2013; Ricciardi et al., 2009).

In their study of patients with cancer across the first 6-week period of treatment, Clabbers et al. (2016) found that the ratio of patients experiencing acneiform rash, xerosis, and pruritus rose steadily from pretreatment through the second week of treatment and then fluctuated afterward, whereas quality of life gradually declined over the entire 6-week period. When the level of skin toxicity and the Skindex-29 quality-of-life scale were examined, a significant correlation was found between acneiform rash and pruritus and the subscales of symptoms, emotions, and functioning (p < .05; Lin, 2009). However, as Clabbers et al. included patients with multiple forms of cancer, specific inferences about patients with advanced lung cancer and quality of life are not possible. Therefore, clinically assessing how skin toxicity affects quality of life is necessary. Previous systematic studies have reviewed subjective assessment instruments that are appropriate for routine evaluation and application, including Skindex-16/29, Dermatology Life Quality Index, and Functional Assessment of Cancer Therapy-Epidermal Growth.
Factor Receptor Inhibitor-18 (FACT-EGFRI-18), to identify the impact of drug-induced skin toxicity on quality of life (Chan et al., 2015). However, empirical data on the use of these instruments are lacking. Because the lack of relevant empirical data for patients with advanced lung cancer, this study was designed to assess the long-term (3-month) changes in skin toxicity and quality of life in patients with advanced lung cancer and to examine the relationship between skin toxicity and quality of life at different time points.

Methods

This study used a longitudinal research design to measure skin toxicity and quality of life in patients with advanced lung cancer undergoing targeted therapy.

Sampling

Patients were recruited from the thoracic and oncology outpatient departments or wards of two medical centers in northern Taiwan. The inclusion criteria were as follows: older than 20 years, fluent in Mandarin or Taiwanese, diagnosed with Stage IIIIB or IV advanced non-small-cell lung cancer and informed of the disease by a physician, and currently scheduled to receive therapy using the single targeted drugs (Tarceva and Giotrif) for the first time (including first-line or above second-line). Otherwise-qualified patients were excluded if they were unconscious or had an intellectual disability. After approval from the institutional review board of the hospitals (IRB 16MMHIS037 and 104-8048B), the researcher described the study purposes and the procedures to the patients. Patients were required to provide written informed consent before participating in the one-to-one interviews.

Measures

The measures for this study included demographic and clinical characteristics. A Chinese version of a structured questionnaire was adopted to collect data.

Demographic and clinical characteristics

Demographic data included gender, age, occupation, educational level, and marital status. Clinical characteristics included treatment-related information such as lung cancer stage, pathology, and type of EGFR-TKI treatment (Tarceva or Giotrif).

Severity of skin toxicity

Severity of skin toxicity was assessed using a Chinese version of the CTCAE v4.03 (National Cancer Institute, 2010). This translated Chinese version, which has been used in previous studies, summarizes the common skin toxicities related to the oral targeted drugs for lung cancer, including acneiform rash, xerosis, pruritus, and paronychia (Chan, Liao, Lee, & Lai, 2014; Chang et al., 2015). Acneiform rash is characterized by an eruption of papules and pustules, which typically appear on the face, scalp, upper chest, and back. Pruritus is characterized by an intense itching sensation. Xerosis, or dry skin, is characterized by flaky, dull skin with a papery thin texture. Paronychia, which involves the soft tissues around the nail, is characterized by discharge or nail plate separation. The grades of severity of acneiform rash, pruritus, xerosis, and paronychia are well defined in the CTCAE v4.03, with acneiform rash graded on a scale of 1–5 and xerosis, pruritus, and paronychia, respectively, graded on a scale of 1–3 (National Cancer Institute, 2010) and with higher scores indicating greater skin toxicity. Good validities for these grading metrics have been established for these four skin toxicities (Chan & Tan, 2011).

Chinese version of the Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18

This is the first study conducted in Taiwan to use the Chinese version of the FACT-EGFRI-18 developed by Wagner et al. (2010) to explore quality of life in patients with lung cancer after targeted therapy. The scale includes 18 items and the three subscales of physical (seven items), social/emotional (six items), and functional (five items). Scale items are scored using a 5-point Likert scale (from 0 to 4); total possible subscale scores range from 0 to 28 (physical), 0 to 24 (social/emotional), and 0 to 20 (functional); and the total possible scale score ranges from 0 to 72. Higher scores suggest poorer quality of life because of skin toxicity (Wagner et al., 2013). Scores in this study showed good internal consistency at the different time points (Cronbach’s alpha of .83–.95). This study used the overall score to analyze the relevant factors at each time point.

Data Collection

Participants were recruited and data were collected from February 2016 to December 2016. To increase the likelihood of patient participation, data were collected during scheduled return visits. The health insurance system in Taiwan requires regular follow-up visits once therapy begins. Baseline data regarding demographic and clinical characteristics and quality of life were collected before initiating targeted therapy (T0). Data for the effects of targeted therapy on skin toxicity and quality of life were collected at 2 weeks (T1), 4 weeks (T2), 8 weeks (T3), and 12 weeks (T4) after the initiation of therapy.

Statistical Analysis

In this study, data were analyzed using IBM SPSS Statistics Version 20.0 (IBM, Inc., Armonk, NY, USA). Demographic and clinical data employed descriptive statistics (M ± SD), frequency, and percentage. Frequency, percentage, mean and standard deviation were used to analyze dermatologic adverse events and the changes in quality of life across the different time points. Inferential statistics were used because of the small number of participants, and Spearman’s correlation analysis was used to analyze the correlation between the dermatologic adverse events and overall quality of life.
Results

Thirty-four patients with lung cancer met the inclusion criteria and provided a signed informed consent. Two of these were subsequently excluded because their original targeted therapy was modified at T1. Thus, the data from 32 participants were available for analysis. The participant numbers over the course of the study was as follows: baseline (before beginning therapy; T0), \( n = 32 \); after 2 weeks of therapy (T1), \( n = 32 \); at the end of the fourth week (T2), \( n = 29 \); at the end of the eighth week (T3), \( n = 29 \); and at the end of 12 weeks (T4), \( n = 27 \). A diagram of the participants over the course of the 12-week period is shown in Figure 1. Three participants were lost between T1 and T2 because of death (\( n = 1 \)) and deterioration of health (\( n = 2 \)); two participants were lost between T3 and T4 because of loss of consciousness and an Eastern Cooperative Oncology Group Performance Status of \( \geq 3 \). None of the participants refused to continue with the study at any time.

Patient Characteristics

Demographic and clinical data for the participants at baseline are shown in Table 1. The mean age of participants was 63 years (SD = 11.5); men and women were nearly equally represented (47% and 53%, respectively); the mean number of years of education was 9.2 ± 3.7; and most participants were married (75%), unemployed (75%), and considered themselves religious (84%). Most participants (97%) had Stage IV lung cancer with adenocarcinoma (97%) as the pathology. Targeted therapy employed Giotrif for 63% of the participants and Tarceva for 37%. Slightly more than three quarters (78%) of participants were receiving first-line treatment.

![Figure 1. Flow chart of participant sampling for patients with lung cancer undergoing treatment.](https://example.com/figure1.png)

**TABLE 1.**

| Characteristic                  | \( n \) | %  |
|---------------------------------|--------|----|
| Gender                          |        |    |
| Male                            | 15     | 47 |
| Female                          | 17     | 53 |
| Age (years; \( M \) and SD)     | 63.0   | 11.5|
| Education (years; \( M \) and SD)| 9.2    | 3.7 |
| Occupational status             |        |    |
| Unemployed                      | 24     | 75 |
| Employed                        | 8      | 25 |
| Marital status                  |        |    |
| Married                         | 24     | 75 |
| Single/divorced/separated or widowed | 8     | 25 |
| Religious                       |        |    |
| Yes                             | 27     | 84 |
| No                              | 5      | 16 |
| Stage of lung cancer            |        |    |
| IIIIB                           | 1      | 3  |
| IV                              | 31     | 97 |
| Pathology of cancer             |        |    |
| Adenocarcinoma                  | 31     | 97 |
| SqCC                            | 1      | 3  |
| Targeted therapy                |        |    |
| Giotrif                         | 20     | 63 |
| Tarceva                         | 12     | 37 |
| EGFR-TKI                        |        |    |
| First line\(^a\)                | 25     | 78 |
| \( \geq \) Second line          | 7      | 22 |

*Note. SqCC = squamous cell carcinoma; EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor.

\(^a\) First-line patients never received any therapy or received chemotherapy before targeted therapy.
**Dermatologic Adverse Events and Quality of Life**

The levels of severity for skin toxicities were graded over time from baseline (T0) to 12 weeks (T4; Table 2). Two weeks after therapy was initiated (T1), more than half of the participants exhibited some level of severity of acneiform rash (71.9%), whereas xerosis and pruritus were observed in 53.1% and 46.9% of the participants, respectively. Over the 3 months of therapy, the number of participants with xerosis and paronychia steadily increased, resulting in 88.9% exhibiting xerosis during the study period and 81.5% exhibiting paronychia at T4. The number of participants with acneiform rash peaked at 4 weeks (T2, with none of the participants exhibiting a severity ≥ 3), whereas the number with pruritus peaked at 8 weeks (T3). However, symptoms for all skin toxicities occurred in more than 70% of patients at T4.

Total scores for the FACT-EGFRI-18 gradually increased over the study period and peaked at T4, suggesting that overall quality of life continued to decline with therapy. In addition, the physical subscale score earned the highest average score of all three subscales at all five time points. During the fourth and eighth weeks (T2 and T3), the mean score for the functional subscale (2.2 ± 3.4 vs. 3.0 ± 3.9, respectively) was similar to the score for the social/emotional subscale (2.1 ± 3.0 vs. 2.4 ± 3.1, respectively), as is shown in Figure 2.

**Correlation Between Dermatologic Adverse Events and Quality of Life**

The Kolmogorov–Smirnov test indicated a nonnormal distribution for the quality-of-life scores. Therefore, Spearman’s rank order correlation was used to analyze the correlation between skin toxicity symptoms and overall quality of life for the participants, with findings showing a significant correlation between acneiform rash and quality of life during the second week (T1), eighth week (T3), and 12th week (T4; \( r = .36–.60, p < .05 \)). Both xerosis and pruritus showed a significant correlation with quality of life at T1 and T4 (\( r = .60–.61, p < .01; r = .40–.37, p < .05 \), respectively). However, only pruritus was correlated with quality of life at baseline (T0; \( r = .57, p < .01 \)). There was also a significant correlation between paronychia and quality of life at T2 and T3 (\( r = .41–.55, p < .05 \)). Although these findings show a weak or intermittent correlation between symptoms of skin toxicity and quality of life at different time points after therapy, none of these symptoms was found to significantly correlate with overall quality of life at every time point (Table 3).

**Discussion**

This was the first long-term follow-up study of changes in skin toxicity and quality of life in patients with advanced lung cancer during the first 12 weeks of targeted therapy. Acneiform rash, xerosis, pruritus, and paronychia were the most common symptoms of skin toxicity, of which the earliest and latest to appear were acneiform rash (second week) and paronychia (fourth week), respectively. Overall, the number of participants with xerosis and paronychia increased steadily, whereas the number of those with acneiform rash and pruritus fluctuated. The FACT-EGFRI-18 scores indicated a decline in quality of life over time; the most significant correlation was found between quality of life and skin toxicity at T1 (second week) and T4 (12th week). In particular, acneiform rash, pruritus, and xerosis showed a moderate correlation \( (r = .36–.61, p < .05) \), with a higher correlation coefficient at T4 than at T1. This may be because the considerable

**TABLE 2.**  
**Skin Toxicities and Symptom Severity Grades for Participants at Baseline and Over the 12 Weeks of Targeted Therapy**

| Skin Toxicity | T0 (n = 32) | T1 (n = 32) | T2 (n = 29) | T3 (n = 29) | T4 (n = 27) |
|---------------|-------------|-------------|-------------|-------------|-------------|
|               | Severity Grade, \( n (%) \) | Severity Grade, \( n (%) \) | Severity Grade, \( n (%) \) | Severity Grade, \( n (%) \) | Severity Grade, \( n (%) \) |
| Acneiform rash | 1 2 3 All | 1 2 3 All | 1 2 3 All | 1 2 3 All | 1 2 3 All |
|               | 16 3 4 23 | 18 6 24 | 12 9 22 | 10 10 1 21 | (50.0) (9.4) (12.5) (71.9) |
|               | (62.1) (20.7) | (82.8) (41.4) (31.0) (3.4) (75.9) | (37.0) (37.0) (3.7) (77.8) | (37.0) (37.0) (3.7) (77.8) | (37.0) (37.0) (3.7) (77.8) |
| Pruritus       | 4 4 12 3 | 15 | 22 | 25 | 12 8 20 |
|               | (12.5) | (12.5) (37.5) | (9.4) | (46.9) | (65.5) (10.3) | (75.9) (72.4) (13.8) | (86.2) (44.4) (29.6) | (74.1) |
| Xerosis        | 3 3 14 3 | 17 | 18 | 19 6 25 | 13 11 24 |
|               | (9.4) | (9.4) (43.8) (9.4) | (53.1) (62.1) | (62.1) (65.5) (20.7) | (86.2) (48.1) (40.7) | (88.9) |
| Paronychia     | 1 4 4 2 | 9 2 11 | 9 11 | 20 11 11 22 |
|               | (3.1) | (3.7) | (12.5) | (12.5) | (31.0) | (6.9) | (37.9) (31.0) (37.9) | (69.0) | (40.7) | (40.7) | (81.5) |

Note. T0 = baseline; T1 = 2 weeks of therapy; T2 = 4 weeks of therapy; T3 = 8 weeks of therapy; T4 = 12 weeks of therapy.

*Although severity grading ranges from 1 to 5 for acneiform rash, none of the participants exhibited a severity ≥ 4.*
discomfort of all three symptoms at T1 (second week) encouraged physicians to either immediately perform dermatological treatment or refer the patients to the dermatology department for further treatment. This further treatment would have alleviated the skin toxicity symptoms and mitigated their effect on quality of life, explaining why the correlation was less significant at T2 (fourth week) and T3 (eighth week). However, the clinical evidence suggests that, once discomfort is relieved through dermatological treatment, patients often spontaneously stop taking their medication or do not report back to the dermatology department as instructed. Thus, this may explain the recurrence of symptoms at T4 (12th week), when a significant correlation between skin toxicity and quality of life was found again.

No published studies on targeted therapy have investigated paronychia. In this study, the onset of paronychia was relatively late (at the fourth week) and regional (in fingers or toes) in comparison with other common skin toxicity symptoms (i.e., acneiform rash, xerosis, and pruritus). Furthermore, the correlation between paronychia and quality of life was most significant at T2 (fourth week) and T3 (eighth week) and much less significant at T4 (12th week). This is likely because the 20% silver nitrate solution that physicians applied to regions affected by paronychia would require several weeks to reduce granulation tissues and alleviate discomfort (Chang et al., 2015). Because the symptoms of paronychia had eased by T4 (12th week), the effect of paronychia on quality of life was less prominent at this time point.

**TABLE 3.** Correlation Between Dermatologic Adverse Events and Overall Quality of Life During Targeted Therapy

| Skin Toxicity     | Time of Assessment of Quality of Life |
|-------------------|--------------------------------------|
|                   | T0 (n = 32)  | T1 (n = 32)  | T2 (n = 29)  | T3 (n = 29)  | T4 (n = 27)  |
| Acneiform rash    | NA          | .36**       | .30          | .40*         | .60**        |
| Pruritus          | .57**       | .60**       | .26          | .26          | .61**        |
| Xerosis           | .07         | .40*        | .36          | .23          | .37*         |
| Paronychia        | .14         | .05         | .55**        | .41*         | .31          |

*Note. Correlations determined by Spearman’s rank-correlation coefficient analysis. T0 = baseline; T1 = 2 weeks of therapy; T2 = 4 weeks of therapy; T3 = 8 weeks of therapy; T4 = 12 weeks of therapy; NA = no patients experienced symptoms.*

*p < .05 (two-tailed). **p < .01 (two-tailed).
Given the increasing number of patients with advanced lung cancer receiving targeted therapy, this study identified the temporal sequence of skin toxicity symptoms as acneiform rash, pruritus, xerosis, and paronychia. In clinical practice, case managers and nurses are required to familiarize patients who are receiving targeted therapy with skin toxicity. However, in practice, patients typically receive only a rudimentary introduction to possible skin toxicity symptoms and few are expressly informed of the expected timing and severity of these symptoms. In this regard, the findings of this study provide medical personnel with greater insights into the timing of skin toxicity symptoms and their effects on quality of life. These findings should be incorporated into on-the-job training for relevant medical staff to improve their understanding of targeted therapy, skin toxicity symptoms, and the temporal sequence and severity of such symptoms, thereby increasing their training effectiveness. Because prior research suggests that skin toxicity is an indicator of favorable targeted therapy results (Petrelli, Borgonovo, Cabiddu, Lonati, & Barni, 2012), patients often brave the discomfort of the symptoms of skin toxicity (Tischer et al., 2017). Thus, medical staff who provide timely instructions on skin toxicity prevention and on effective strategies for delaying the onset of skin toxicity or alleviating its symptoms may positively affect the quality of life and treatment compliance of their patients.

Furthermore, the findings of this study are similar to those of Clabbers et al. (2016), who used the FACT-EGFRI-18 to track the effects of targeted therapy over a 6-week period. First, the number of patients who developed skin toxicity symptoms such as acneiform rash, xerosis, and pruritus increased between pretreatment and the second week of treatment. This study observed that the number of participants with paronychia began to increase significantly at T2 (fourth week). A correlation between symptoms (i.e., acneiform rash, xerosis, pruritus, and paronychia) and quality of life at different time points was established. However, although Clabbers et al. monitored changes in skin toxicity and quality of life over a 6-week period of targeted therapy, their study did not establish a correlation between these two variables at different time points. Second, in Clabbers et al., the scores for the FACT-EGFRI-18 and its subscales deteriorated continuously over the 6-week period, with the physical subscale achieving the highest (i.e., poorest) score. This is consistent with the findings of this study, suggesting that the physical aspect has the greatest impact on quality of life in patients receiving targeted therapy for advanced lung cancer and further conforms to the notion of skin toxicity becoming increasingly pronounced as targeted therapy progresses.

Because quality of life is a key indicator of cancer treatment effectiveness, many related measurement instruments have been developed. However, despite using multiple instruments (FACT-EGFRI-18, FACT-General, 36-Item Short Form Health Survey, and Skindex-16), Clabbers et al. (2016) did not examine the correlation between them at different time points, thus rendering evaluation of convergent validity impossible. Considering the physical and mental conditions of patients with advanced lung cancer and the principles of ethical research, researchers who intend to use multiple instruments are advised to select and use those that both are brief and have strong validity and reliability to avoid overburdening patients and compromising the research results. Whereas Clabbers et al. performed a 6-week follow-up on the effects of targeted therapy for various types of cancer, this study focused on these effects for a single type of cancer (advanced lung cancer) over 3 months. According to Langer (2013), the median progression-free survival of patients with advanced lung cancer receiving first-line targeted therapy is 8–13 months, indicating that a follow-up period of 3 months is insufficient. Therefore, prospective researchers should extend the follow-up period to gain a fuller understanding of changes in skin toxicity and quality of life in patients with lung cancer. Furthermore, according to the theory of unpleasant symptoms developed by Lenz, Pugh, Milligan, Gift, and Suppe (1997), assessment of such symptoms should cover intensity, timing, distress, and quality. However, this study was unable to address all four aspects when examining skin toxicity symptoms induced by targeted therapy because the instruments used (CTCAE and FACT-EGFRI-18) addressed only two aspects (intensity and quality). The research team intends to revise the questionnaire to include assessments of the timing and distress aspects, which should provide a more comprehensive investigation of targeted-therapy-induced skin toxicity, further assist in understanding which aspect(s) most affects quality of life, and provide important references for designing related interventions.

**Limitations**

This study was affected by several limitations. First, the FACT-EGFRI-18 is currently the only measurement tool that is designed to measure quality of life specifically for patients affected by targeted-therapy-related skin toxicity (Chan et al., 2015). Therefore, it cannot completely represent the impact of other influences on the general quality of life for patients receiving targeted therapy. Second, the targeted drugs that are currently being used for the clinical treatment of advanced lung cancer in Taiwan include Iressa, Tarceva, and Giotrif (NHIA, Taiwan, ROC, 2019). Few patients in the institution where this study was conducted were being treated with Iressa; and none was included in this study. Therefore, it may be difficult to generalize these findings to all targeted drug therapies in Taiwan. In addition, limited information is available regarding the factors related to the three subscales of quality of life in patients during targeted therapy. Therefore, future studies should investigate this issue further. Finally, future studies should extend the follow-up period to 6 or even 12 months to more fully explore the changes in different aspects of quality of life and skin toxicity during treatment.

**Conclusions**

Although the use of oral targeted drugs in patients with advanced lung cancer has become widespread in recent years and the effects of drug-induced skin toxicity on quality of life...
have received much attention, little empirical data regarding long-term follow-up are currently available. It is hoped that the results of this study will help healthcare providers better understand the long-term changes in skin toxicity severity and quality of life in patients undergoing oral targeted therapy and identify the important time points correlated with skin toxicities and quality of life. These findings should assist healthcare providers to treat patients proactively by providing treatment regimens that are tailored to patient symptom patterns, referring patients to appropriate specialists at different stages of treatment, and providing personalized skin care and support resources. Furthermore, treatment strategies may allow the provision of interventional measures that are tailored to the unique needs of patients based on their current targeted drug regimen.

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