ORIGINAL REPORT

Skin Toxicities Induced by Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors and their Influence on Treatment Adjustments in Lung Cancer Patients

Ji Su LEE[1–3#], Jimin WOO[4#], Tae Min KIM[1,4], Namkyu KIM[4], Bhumsuk KEAM[5,6] and Seong Jin JO[1–4]

[1]Department of Dermatology, Seoul National University Hospital, Seoul, [2]Laboratory of Cutaneous Aging and Hair Research, Clinical Research Institute, Seoul National University Hospital, Seoul, [3]Institute of Human–Environmental Interface Biology, Medical Research Center, Seoul National University, Seoul, [4]Department of Dermatology, Seoul National University College of Medicine, Seoul, [5]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, and [6]Cancer Research Institute, Seoul National University, Seoul, Republic of Korea
[#]Equal contribution.

Skin toxicities caused by epidermal growth factor receptor tyrosine kinase inhibitors can affect patient quality of life and lead to treatment adjustments, including dose reduction or discontinuation. This retrospective study aimed to profile skin toxicities and their impact on treatment adjustments. A total of 288 non-small cell lung cancer patients treated with first-, second-, or third-generation epidermal growth factor receptor tyrosine kinase inhibitors were included. Skin toxicities, including papulopustular rash, xerosis, paronychia, and pruritus, were assessed based on medical records, and their severity was evaluated based on the required dermatological intervention. Papulopustular rash was the most common toxicity (74.3%), followed by pruritus (61.1%), xerosis (52.4%), and paronychia (39.6%). Papulopustular rash was more common in males and more severe in younger patients. Papulopustular rash was more prevalent in patients treated with first- and second-generation epidermal growth factor receptor tyrosine kinase inhibitors, while paronychia was notably frequent for the second-generation epidermal growth factor receptor tyrosine kinase inhibitors. Second-generation epidermal growth factor receptor tyrosine kinase inhibitors frequently caused multiple skin toxicities. Importantly, skin toxicities led to epidermal growth factor receptor tyrosine kinase inhibitor treatment adjustments in 26.7% of cases, with second-generation epidermal growth factor receptor tyrosine kinase inhibitors demonstrating higher adjustment rates. Papulopustular rash and paronychia were the main causes of treatment adjustments, with even mild paronychia being linked to treatment adjustments. Effective management of skin toxicities is essential for optimizing treatment outcomes in patients receiving epidermal growth factor receptor tyrosine kinase inhibitors.

Key words: epidermal growth factor receptor tyrosine kinase inhibitors; skin toxicities; dermatological adverse events; papulopustular rash; xerosis; paronychia; pruritus.

Submitted Apr 11, 2024. Accepted after revision Aug 5, 2024

Published Aug 28, 2024. DOI: 10.2340/actadv.v104.40555

Acta Derm Venereol 2024; 104: adv40555.

SIGNIFICANCE

Epidermal growth factor receptor tyrosine kinase inhibitors, commonly used anti-cancer drugs, frequently cause skin problems that can lead to epidermal growth factor receptor tyrosine kinase inhibitor treatment adjustments. This study reveals how these skin toxicities vary with different epidermal growth factor receptor tyrosine kinase inhibitors, age, and gender. Specifically, the study highlights the significant impact of certain skin toxicities, such as papulopustular rash (a rash with red bumps) and paronychia (inflammation around the nails), on the adjustments of epidermal growth factor receptor tyrosine kinase inhibitor treatments. Understanding these skin toxicities is crucial for effective management and ensuring continuous epidermal growth factor receptor tyrosine kinase inhibitor treatment.

Corr: Seong Jin Jo, MD, PhD, Department of Dermatology, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea. E-mail: sj.jo@snu.ac.kr

Epidermal growth factor receptor (EGFR) is widely distributed in normal skin, including skin keratinocytes, dendritic cells, pilosebaceous units, and the capillary system (1–5). EGFR normally plays a role in proper skin functioning and maintaining its integrity, including regulation of cell survival, proliferation, differentiation and migration, wound healing, inhibition of inflammation, and capillary constriction (1, 3, 6, 7). However, pathologic overexpression of EGFR promotes cell proliferation, adhesion, metastasis, and angiogenesis and inhibits apoptosis, all of which can induce tumorigenesis (3, 8). EGFR tyrosine kinase inhibitors (TKIs) have been widely used to treat several cancers, including lung cancer, breast cancer, human glioblastoma, gastric carcinoma, rectal cancer, and head and neck cancer (3).

EGFR-TKIs are classified into 3 generations based on their interaction with EGFR (9). First-generation EGFR-TKIs (e.g., gefitinib, erlotinib) bind to the protein tyrosine kinase domain of EGFR reversibly through non-covalent interactions. Second-generation EGFR-TKIs (e.g., afatinib, dacomitinib) bind to EGFR covalently and irreversibly inhibits EGFR (10). Third-generation

EGFR-TKIs (e.g., osimertinib) have great efficacy in patients with the *EGFR T790M* mutation, a leading cause of drug resistance to first- and second-generation EGFR-TKIs (9, 11).

Although typical adverse events of conventional chemotherapy are less frequent with the use of EGFR-TKIs, they commonly cause skin toxicities (1). The most prevalent skin toxicities are papulopustular rash, xerosis, paronychia, and pruritus (12, 13). Papulopustular rash, also known as papulopustular eruption or acneiform rash, typically manifests as red papules and/or pustules without comedones on the face, scalp, chest, back, abdomen, or thighs (14, 15). Xerosis, also known as xeroderma or dry skin, is characterized by dryness, roughness, and scaling of the skin (14, 15). Paronychia is characterized by an inflammatory process involving the soft tissues around the nail. Paronychia manifests as painful erythema, swelling, granulation, bleeding, or exudation around the nails (14, 15). Itchiness is a sensation provoking a desire to scratch. Pruritus is a disorder characterized by an intense itching sensation (14, 15). Skin toxicities negatively affect patient quality of life and even cause EGFR-TKI treatment adjustments, including dose reduction or treatment discontinuation in severe cases (13). Therefore, understanding skin toxicity profiles of EGFR-TKIs and identifying factors related to treatment adjustments due to skin toxicities are essential for planning individualized administration strategies and providing appropriate management. Previous studies have investigated skin toxicities of EGFR-TKIs in meta-analyses using separate clinical trials of each EGFR-TKI (1, 16). However, the results mainly provided descriptive findings and lacked real-world data analysing factors associated with skin toxicities leading to treatment adjustments. In this study, we aimed to investigate the profiles of the 4 most common skin toxicities induced by each generation of EGFR-TKIs and their influence on treatment adjustments of EGFR-TKIs.

MATERIALS AND METHODS

Study population

This retrospective, single-centre study included patients who met the following criteria: (*i*) diagnosis of non-small cell lung cancer (NSCLC); (*ii*) treatment with EGFR-TKIs (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib) without other concurrent chemotherapy; and (*iii*) visit to the Department of Dermatology or Chemotherapy Skin Care Center at a single tertiary hospital between 1 January 2015, and 31 December 2021, due to skin toxicities caused by specific EGFR-TKIs. For statistical analysis, we focused on the 4 most common skin toxicities (papulopustular rash, xerosis, paronychia, pruritus), excluding less common skin problems (12, 13). The following patients were excluded: (*i*) those who visited because of skin problems other than the 4 most common skin toxicities; (*ii*) those who visited the dermatology clinic before the EGFR-TKI treatment started or after the EGFR-TKI treatment was terminated; and (*iii*) those for whom detailed data on the skin toxicities were missing. This study was approved by the Institutional Review Board of Seoul National University Hospital (No. H-2209-085-1359).

Data collection

Demographic and clinical data regarding EGFR-TKI treatment and skin toxicities were collected from electronic medical records. Patients were followed up until the last visit or the end of coverage (30 September 2022), whichever came first. Anticancer treatment data were collected from the medical records of the Department of Oncology. The cancer stages of the patients at the start of EGFR-TKI treatment were determined based on the eighth tumour-node-metastasis staging system for lung cancer approved by the American Joint Committee on Cancer. Prior cytotoxic agent use was determined based on whether the patient had received conventional chemotherapy before EGFR-TKI treatment. The line of treatment was determined based on the prior use of other EGFR-TKIs before the specific EGFR-TKI treatment. Treatment adjustments were defined as a dose reduction or discontinuation of EGFR-TKIs due to toxicities.

Severity grade of skin toxicities

The Common Terminology Criteria for Adverse Events (CTCAE) provides definitions and grading for common skin toxicities related to chemotherapy (Table SI) (14). According to CTCAE, a papulopustular rash covering less than 10% of the body surface area (BSA) without pruritus or tenderness is grade 1, 10–30% BSA is grade 2, and more than 30% BSA is grade 3. Xerosis covering less than 10% BSA without pruritus is grade 1, 10–30% BSA is grade 2, and more than 30% BSA is grade 3. Grade 1 paronychia involves nail-fold oedema or erythema and disruption of the cuticle, grade 2 paronychia involves pain, discharge, or nail plate separation, and grade 3 paronychia requires surgical intervention and systemic treatments. Localized pruritus is grade 1, intense or widespread pruritus is grade 2, and more severe pruritus, which limits activities of daily living or sleep, is grade 3. CTCAE grades are commonly employed to assess skin toxicities related to chemotherapy (14). However, CTCAE grades lack specificity for each skin toxicity because they are primarily based on patient discomfort. Furthermore, they predominantly reflect the perspective of oncologists and cannot offer dermatological guidelines for managing skin toxicities (17–19). Therefore, we developed a new severity grading system based on the grade of dermatological intervention to treat skin toxicities into "mild", "moderate", and "severe" (Table SI). This grading system was made according to the recommended management of skin toxicities from previous studies (Table SII). Previous studies recommended topical agents (antibiotics, corticosteroids, or calcineurin inhibitors) for grade 1 papulopustular rash, oral antibiotics for grade 2, and oral isotretinoin or corticosteroids for grade 3 or more severe cases. Similarly, in our new grading system, topical agents were categorized as mild, oral antibiotics as moderate, and oral isotretinoin or corticosteroids as severe. For xerosis, previous studies recommended applying moisturizers and topical corticosteroids for cases with eczematous lesions. In our new grading system, the severity of xerosis was scored according to the potency of prescribed topical corticosteroids. For paronychia, previous studies recommended topical agents (corticosteroids, antibiotics, or anti-inflammatory agents) for grade 1, oral antibiotics for grade 2, and consideration of surgical intervention for grade 3. Similarly, in our new grading system, topical agents were categorized as mild, oral antibiotics as moderate, and the need for surgical intervention as severe. For pruritus, previous studies recommended topical steroids and oral antihistamines for grade 1 or 2, and increasing the dose of antihistamines or adding corticosteroids for grade 3. In our new grading system, the severity of pruritus was scored according to

the number of oral antihistamines and whether oral corticosteroids were prescribed.

To validate the new grading system, we evaluated the correlation between the CTCAE grades and severity grades based on dermatological intervention using the Jonckheere–Terpstra test for each skin toxicity. The analysis revealed a significant correlation between the 2 grading methods for papulopustular rash ($p<0.001$), xerosis ($p=0.008$), and paronychia ($p<0.001$) (Table SIII), indicating a strong association between the severity grades based on dermatological intervention and CTCAE grading. In this study, we employed the dermatological intervention-based grade as a severity index because it better aligned with physician-assessed clinical severity compared with the CTCAE grading system, which primarily assessed the impact on the quality of life of patients.

Statistical analyses

The results are presented as *n* (%) or mean±standard deviations, unless stated otherwise. To compare the clinical characteristics among different generations of EGFR-TKIs, the χ^2 or Fisher's exact test for numerical variables and one-way analysis of variance or Kruskal–Wallis test for continuous variables were used. The Jonckheere–Terpstra test was used to analyse the correlation between CTCAE and severity grades based on dermatological intervention. Logistic regression was used to assess the association between skin toxicities and treatment adjustments, adjusted for age, sex, chronic skin disorders, prior cytotoxic agent usage, cancer stage, and EGFR-TKI treatment duration. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 19 (IBM Corp, Armonk, NY, USA).

RESULTS

Demographics and clinical characteristics

A total of 288 patients treated with first- ($n=248$), second- ($n=19$), or third- ($n=21$) generation EGFR-TKIs for NSCLC were included (**Fig. 1**). A comparison of the demographic and clinical characteristics according to the generation of EGFR-TKIs is given in **Table I**. There were no significant differences in age or sex among the 3 generations. Third-generation EGFR-TKIs were primarily utilized in second- (66.7%) or third- (19%) line treatments following the failure of first- or second-generation EGFR-TKIs. A majority of patients receiving first- (45.2%) and second-generation (63.2%) EGFR-TKIs experienced 3 or more skin toxicities, while 95.2% of those treated with third-generation EGFR-TKI exhibited only 1 or 2 skin toxicities ($p=0.002$). Second-generation EGFR-TKI resulted in more frequent treatment adjustments (dose reduction or discontinuation) due to skin toxicities than those in the other 2 groups (second-generation, 89.5%; first-generation, 24.2%; third-generation, 14.3%; $p<0.001$). Treatment adjustments due to toxicities other than skin toxicity did not differ among the 3 groups ($p=1.000$).

Patterns of skin toxicities due to epidermal growth factor receptor tyrosine kinase inhibitors

To identify the factors associated with skin toxicities of EGFR-TKIs, logistic regression was performed between various clinical factors and skin toxicity (Table SIV). Papulopustular rash was the most common (74.3%), followed by pruritus (61.1%), xerosis (52.4%), and paronychia (39.6%). Papulopustular rash was common in male patients (odds ratio [OR], 2.05; 95% confidence interval [CI], 1.08–3.89; $p=0.028$), had longer EGFR-TKI treatment duration (OR, 1.02; 95% CI, 1.01–1.04; $p=0.011$), and was common in first- (OR, 23.47; 95% CI, 6.57–83.82; $p<0.001$) and second-generation EGFR-

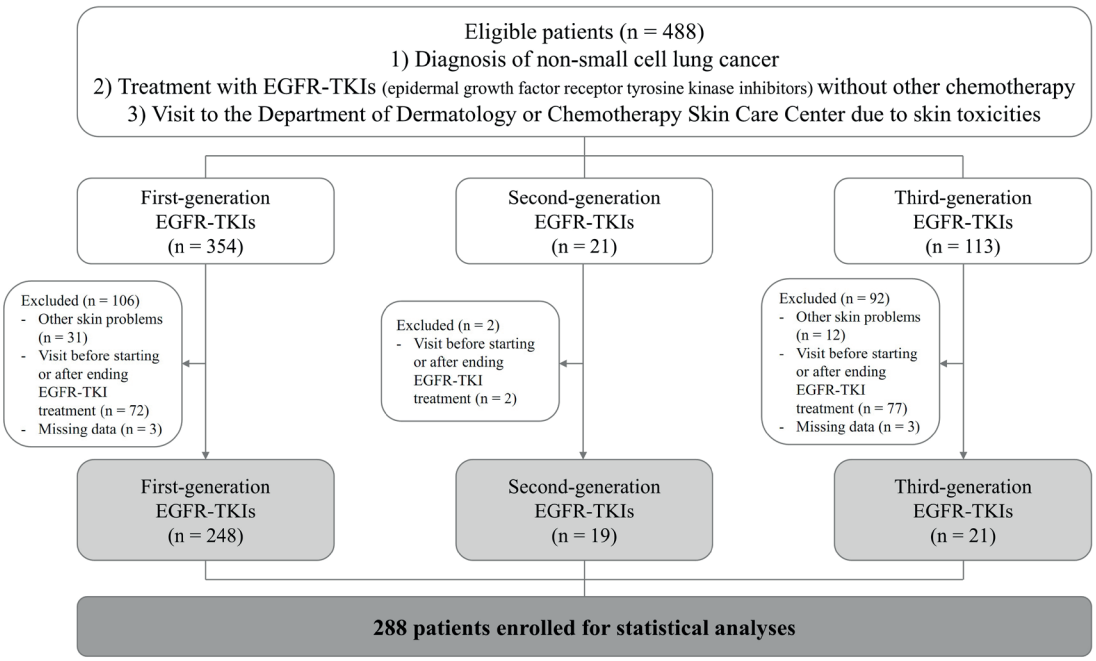

Fig. 1. Flowchart of patient enrolment.

Table I. Demographics and clinical characteristics according to different generations of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)

Factor	First-generation (*n* = 248)	Second-generation (*n* = 19)	Third-generation (*n* = 21)	*p*-value
Age, years, mean±SD	64.1±10.8	60.7±10.1	64.6±8.4	0.423
Sex, *n* (%)				0.527
Male	97 (39.1)	6 (31.6)	6 (28.6)	
Female	151 (60.9)	13 (68.4)	15 (71.4)	
Chronic skin disorder, *n* (%)				1.000
Yes	8 (3.2)	0 (0)	0 (0)	
No	240 (96.8)	19 (100)	21 (100)	
Prior cytotoxic agent usage, *n* (%)				0.054
Yes	84 (33.9)	3 (15.8)	3 (14.3)	
No	164 (66.1)	16 (84.2)	18 (85.7)	
Cancer stage, *n* (%)				0.225
II or III	9 (3.6)	1 (5.3)	2 (9.5)	
IV	238 (96.4)	18 (94.7)	19 (90.5)	
Line of anti-cancer treatment, *n* (%)				<0.001***
1	226 (91.1)	18 (94.7)	3 (14.3)	
2	22 (8.9)	1 (5.3)	14 (66.7)	
3	0.0	0.0	4 (19)	
EGFR-TKI treatment duration, months, mean±SD	26.7±29.5	35.2±27.6	21.9±14.1	0.249
Number of skin toxicities, *n* (%)				0.002**
1	67 (27.0)	3 (15.8)	10 (47.6)	
2	69 (27.8)	4 (21.1)	10 (47.6)	
≥3	112 (45.2)	12 (63.2)	1 (4.8)	
EGFR-TKI treatment adjustments, *n* (%)				
Due to skin toxicities	60 (24.2)	16 (84.2)	1 (4.8)	<0.001***
Due to other toxicities	22 (8.9)	1 (5.3)	2 (9.5)	1.000

SD: standard deviation. ***$p < 0.001$, **$p < 0.01$

TKIs (OR, 10.542; 95% CI, 2.15–51.63; $p = 0.004$) (Table SIV). The severity of papulopustular rash was increased at a younger age (OR, 0.96; 95% CI, 0.94–0.99; $p = 0.002$) (Table SV). The frequency of xerosis increased with longer EGFR-TKI treatment duration (OR, 1.010; 95% CI, 1.00–1.02; $p = 0.045$) (Table SIV). Paronychia was significantly common in second-generation EGFR-TKIs (OR, 24.00; 95% CI, 2.68–214.73; $p = 0.004$) (Table SIV).

Skin toxicities and treatment adjustments of epidermal growth factor receptor tyrosine kinase inhibitors

Approximately 26.7% (77/288) of the patients underwent EGFR-TKI treatment adjustments due to skin toxicities. Among the 77 patients, 5 patients (1.7%) completely discontinued EGFR-TKI treatment due to skin toxicities. The others maintained EGFR-TKI treatment after dose reduction. Among these, 54 patients discontinued EGFR-TKI due to poor response, 13 patients continued EGFR-TKI during the observation period, 1 patient died due to complications from lung cancer, and 4 patients were lost to follow-up. The treatment adjustments were significantly correlated with the number of skin toxicities (OR, 1.96; 95% CI, 1.38–2.87; $p < 0.001$) and the presence of each toxicity: papulopustular rash (OR, 2.55; 95% CI, 1.26–5.16; $p = 0.009$), paronychia (OR, 2.00; 95% CI, 1.18–3.30; $p = 0.010$), and pruritus (OR, 1.86; 95% CI, 1.06–3.27; $p = 0.031$) (**Table II**). Number of skin toxicities (OR, 1.91; 95% CI, 1.33–2.73, $p < 0.001$), papulopustular rash (OR, 2.49; 95% CI, 1.21–5.14; $p = 0.014$), and paronychia (OR, 2.07; 95% CI, 1.20–3.56; $p = 0.009$) remained statistically significant after multivariate analysis (Table II). More severe papulopustular rash (OR, 3.34; 95% CI, 1.90–5.85; $p < 0.001$) or pruritus (OR, 1.55; 95% CI, 1.06–2.27; $p = 0.023$) was more likely to cause EGFR-TKI treatment adjustments (**Table III**). The severity of papulopustular rash showed a stronger correlation to treatment adjustments in multivariate analysis (OR, 4.43; 95% CI, 2.35–8.35; $p < 0.001$) (Table III). Notably, even mild paronychia caused treatment adjustments as frequently as moderate and severe cases (OR, 0.93; 95% CI, 0.53–1.64; $p = 0.793$) (Table III).

Regarding the relationship between the severity of skin toxicities and the response of cancer to EGFR-TKIs, we observed a positive correlation between the severity of papulopustular rash and the response of cancer to EGFR-TKIs, but not with the severity of xerosis, paronychia, and pruritus. As the severity of papulopustular rash increased, there was a higher likelihood of cancer responding to EGFR-TKIs (OR, 2.29; 95% CI, 1.18–4.45; $p = 0.015$) (Table SVI). This correlation was significant only for first-generation EGFR-TKIs and not for second- or third-generation EGFR-TKIs.

DISCUSSION

The exact pathophysiology of skin toxicities associated with EGFR-TKIs remains unclear; however, it is thought that skin toxicities are caused by the direct inhibition of EGFR in the skin and subsequent destruction of the physical barrier, damage to hair follicles, and destruction of skin homeostasis, inflammation, and host immune activation (1–3). Because EGFR is widely distributed in the normal skin, skin toxicities are one of the most common adverse events associated with EGFR-TKI treatment (3).

Table II. Association between skin toxicities and treatment adjustments (dose reduction or discontinuation) of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)

Factor	EGFR-TKI treatment adjustments		OR (95% CI)	aOR (95% CI)
	Adjusted ($n=77$)	Not adjusted ($n=211$)		
Age, years, mean±SD	65.5±8.7	63.4±11.2	1.02 (0.99–1.05)	
Sex, *n* (%)			0.85 (0.49–1.46)	
Male	27 (35.1)	82 (38.9)		
Female	50 (64.9)	129 (61.1)		
Chronic skin disorder, *n* (%)			0.38 (0.05–3.17)	
Yes	1 (1.3)	7 (3.3)		
No	76 (98.7)	204 (96.7)		
Prior cytotoxic agent usage, *n* (%)			0.79 (0.45–1.37)	
Yes	27 (35.1)	63 (29.9)		
No	50 (64.9)	148 (70.1)		
Cancer stage, *n* (%)			1.88 (0.40–8.76)	
II or III	2 (2.6)	10 (4.8)		
IV	75 (97.4)	200 (95.2)		
EGFR-TKI treatment duration, months, mean±SD	30.1±25.0	25.7±29.7	1.01 (1.00–1.01)	
Number of skin toxicities, *n* (%)			1.96 (1.38–2.78)***	1.91 (1.33–2.73)***
1	11 (14.3)	69 (32.7)		
2	19 (24.7)	64 (30.3)		
≥3	47 (61.0)	78 (37.0)		
Skin toxicities, *n* (%)				
Papulopustular rash	66 (85.7)	148 (70.1)	2.55 (1.26–5.16)**	2.49 (1.20–5.14)*
Xerosis	44 (57.1)	107 (50.7)	0.77 (0.46–1.31)	1.22 (0.71–2.09)
Paronychia	40 (51.9)	74 (35.1)	2.00 (1.18–3.30)*	2.07 (1.20–3.56)**
Pruritus	55 (71.4)	121 (57.3)	1.86 (1.06–3.27)*	1.78 (1.00–3.17)

***$p<0.001$, **$p<0.01$, *$p<0.05$.
SD: standard deviation; aOR: adjusted odds ratio; CI: confidence interval; OR: crude odds ratio.

In this study, among the skin toxicities, papulopustular rash was most common, followed by pruritus, xerosis, and paronychia. Papulopustular rash was more frequent in males and more severe in younger patients, which might be associated with higher androgen and sebum levels in men and younger individuals (20, 21). Moreover, decreased expression of EGFR in older individuals may make some contribution to this phenomenon (22). Jatoi et al. demonstrated that younger patients with colon cancer treated with cetuximab, a monoclonal EGFR antibody, developed a more severe skin rash, which was similar to our findings (23). These findings indicate the potential benefit of encouraging male young patients to use a light emollient to prevent or alleviate papulopustular rash (24). Xerosis increased with prolonged treatment duration of EGFR-TKIs; therefore, as EGFR-TKI treatment duration increases, it is beneficial to prioritize the use of emollients and avoid habits that exacerbate skin dryness, such as hot baths, showers, and saunas (24).

Regarding the 3 different generations of EGFR-TKIs, patients receiving first- and second-generation EGFR-TKIs experienced multiple skin toxicities, whereas patients treated with third-generation EGFR-TKIs experienced only 1 or 2 skin toxicities. Papulopustular rash was frequent in first- and second-generation EGFR-TKIs, while paronychia was frequent in second-generation EGFR-TKIs. This finding was consistent with that of a previous meta-analysis of clinical trials that reported

Table III. Association between severity of skin toxicities and treatment adjustments (dose reduction or discontinuation) of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)

Factor	EGFR-TKI treatment adjustments		OR (95% CI)	aOR (95% CI)
	Adjusted	Not adjusted		
Papulopustular rash			3.34 (1.90–5.85)***	4.43 (2.35–8.35)***
Mild	7 (10.6)	40 (27.0)		
Moderate	39 (59.1)	97 (65.6)		
Severe	20 (30.3)	11 (7.4)		
Xerosis			1.59 (0.89–2.86)	1.49 (0.82–2.68)
Mild	8 (18.2)	33 (30.8)		
Moderate	29 (65.9)	62 (60.0)		
Severe	7 (15.9)	12 (11.2)		
Paronychia			0.93 (0.53–1.64)	0.84 (0.46–1.55)
Mild	20 (50.0)	36 (48.6)		
Moderate	16 (40.0)	29 (39.2)		
Severe	4 (10.0)	9 (12.2)		
Pruritus			1.55 (1.06–2.27)*	1.50 (1.02–2.22)*
Mild	34 (61.8)	95 (78.5)		
Moderate	5 (9.1)	7 (5.8)		
Severe	16 (29.1)	19 (15.7)		

***$p<0.001$, *$p<0.05$.
aOR: adjusted odds ratio; CI: confidence interval; OR: crude odds ratio.

a higher risk of rash, dry skin, paronychia, and pruritus with dacomitinib and afatinib (second-generation EGFR-TKIs), whereas osimertinib (third-generation EGFR-TKI) has the lowest risk of rash (16). The different affinities to EGFR and abilities to spare wild-type EGFR among different generations of EGFR-TKIs likely contribute to the variations in skin toxicities (1, 16). Third-generation EGFR-TKIs are designed to selectively target EGFR mutations, including *T790M*; thus, normal function of the wild-type EGFR remains unaffected (25, 26).

Our study underscores the impact of skin toxicities on the risk of EGFR-TKI treatment adjustments. A total of 26.7% patients experienced treatment adjustments. The majority of these adjustments were dose reductions, while only 1.7% were discontinuations. As complete discontinuation of EGFR-TKI could negatively impact lung cancer status, oncologists usually attempt dose reduction first. Patients who have more skin toxicities have a higher risk of experiencing treatment adjustments. Notably, papulopustular rash and paronychia were the main causes of EGFR-TKI treatment adjustments. We found a strong correlation between the severity of papulopustular rash and treatment adjustments, emphasizing the importance of implementing appropriate dermatological interventions to mitigate its severity. Conversely, the severity of paronychia was not correlated with treatment adjustments, indicating that even mild paronychia can cause significant discomfort to patients. Therefore, early and meticulous management of paronychia is imperative to sustain EGFR-TKI treatment in its initial stages. Aligned with previous studies, we found a positive correlation between the severity of papulopustular rash and the response of lung cancer to EGFR-TKIs (3, 27). This correlation was observed specifically in first-generation EGFR-TKIs, but not in second- and third-generation EGFR-TKIs (28, 29). The papulopustular rash may serve as an indicator of the efficacy of first-generation EGFR-TKI in treating lung cancer (27).

Limitations

Our study has some limitations. Owing to the retrospective nature of this study, a relatively small number of patients treated with second- and third-generation EGFR-TKIs were enrolled. Additionally, by focusing on common skin toxicities, severe but less common skin toxicities such as erosive pustular dermatosis were not included. Furthermore, this was a tertiary-level, single-centre study; as such, further prospective studies including patients from multiple centres are required. Nevertheless, the strength of the present study is that this is the largest retrospective study using real-world data on the skin toxicities of EGFR-TKIs. Notably, our data included patients treated by well-trained dermatologists in a single tertiary centre with a significant number of EGFR-mutant lung cancers. Moreover, this is the first study to elucidate the impact of individual skin toxicity on the adjustments of EGFR-TKI treatment.

Conclusion

In summary, our study reveals the profile of skin toxicities induced by EGFR-TKIs varies according to EGFR-TKI generation, age, and sex. Specifically, our study highlights the significant impact of skin toxicities, particularly papulopustular rash and paronychia, on the EGFR-TKI treatment adjustments. Understanding the profile of skin toxicities caused by EGFR-TKIs is crucial for implementing tailored dermatological interventions and ensuring continuous EGFR-TKI treatment.

The authors have no conflicts of interest to declare.

REFERENCES

1. Sun W, Li J. Skin toxicities with epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients: a meta-analysis of randomized controlled trials. Cancer Invest 2019; 37: 253–264. https://doi.org/10.1080/07357907.2019.1634089
2. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol 2005; 16: 1425–1433. https://doi.org/10.1093/annonc/mdi279
3. Li Y, Fu R, Jiang T, Duan D, Wu Y, Li C, et al. Mechanism of lethal skin toxicities induced by epidermal growth factor receptor inhibitors and related treatment strategies. Front Oncol 2022; 12: 804212. https://doi.org/10.3389/fonc.2022.804212
4. Joly-Tonetti N, Ondet T, Monshouwer M, Stamatas GN. EGFR inhibitors switch keratinocytes from a proliferative to a differentiative phenotype affecting epidermal development and barrier function. BMC Cancer 2021; 21: 5. https://doi.org/10.1186/s12885-020-07685-5
5. Annunziata MC, De Stefano A, Fabbrocini G, Leo S, Marchetti P, Romano MC, et al. Current recommendations and novel strategies for the management of skin toxicities related to anti-EGFR therapies in patients with metastatic colorectal cancer. Clin Drug Investig 2019; 39: 825–834. https://doi.org/10.1007/s40261-019-00811-7
6. Jost M, Kari C, Rodeck U. The EGF receptor – an essential regulator of multiple epidermal functions. Eur J Dermatol 2000; 10: 505–510.
7. Mitchell EP, Perez-Soler R, Van Cutsem E, Lacouture ME. Clinical presentation and pathophysiology of EGFRI dermatologic toxicities. Oncology (Williston Park, NY), 2007; 21: 4–9.
8. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016; 17: 367–377. https://doi.org/10.1016/S1470-2045(15)00551-3
9. Abourehab MAS, Alqahtani AM, Youssif BGM, Gouda AM. Globally approved EGFR inhibitors: insights into their syntheses, target kinases, biological activities, receptor interactions, and metabolism. Molecules (Basel, Switzerland), 2021; 26. https://doi.org/10.3390/molecules26216677
10. He J, Huang Z, Han L, Gong Y, Xie C. Mechanisms and management of 3rdgeneration EGFRTKI resistance in advanced nonsmall cell lung cancer (Review). Int J Oncol 2021; 59: 90. https://doi.org/10.3892/ijo.2021.5270
11. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol 2018; 29: i10–i19. https://doi.org/10.1093/annonc/mdx703

12. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies, Part I: Inhibitors of the cellular membrane. J Am Acad Dermatol 2015; 72: 203–218; quiz 219–220. https://doi.org/10.1016/j.jaad.2014.07.032
13. Chu CY, Choi J, Eaby-Sandy B, Langer CJ, Lacouture ME. Osimertinib: a novel dermatologic adverse event profile in patients with lung cancer. Oncologist 2018; 23: 891–899. https://doi.org/10.1634/theoncologist.2017-0582
14. Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Washington, DC: US Department of Health and Human Services, 2017.
15. Chu C-Y, Chen K-Y, Wen-Cheng Chang J, Wei Y-F, Lee C-H, Wang W-M. Taiwanese Dermatological Association consensus for the prevention and management of epidermal growth factor receptor tyrosine kinase inhibitor-related skin toxicities. J Formos Med Assoc 2017; 116: 413–423. https://doi.org/10.1016/j.jfma.2017.03.001
16. Zhao Y, Cheng B, Chen Z, Li J, Liang H, Chen Y, et al. Toxicity profile of epidermal growth factor receptor tyrosine kinase inhibitors for patients with lung cancer: a systematic review and network meta-analysis. Crit Rev Oncol Hematol 2021; 160: 103305. https://doi.org/10.1016/j.critrevonc.2021.103305
17. Chan A, Tan EH. How well does the MESTT correlate with CTCAE scale for the grading of dermatological toxicities associated with oral tyrosine kinase inhibitors? Supportive Care Cancer 2011; 19: 1667–1674. https://doi.org/10.1007/s00520-010-0999-2
18. Wollenberg A, Moosmann N, Klein E, Katzer K. A tool for scoring of acneiform skin eruptions induced by EGF receptor inhibition. Exp Dermatol 2008; 17: 790–792. https://doi.org/10.1111/j.1600-0625.2008.00715.x
19. Beech J, Germetaki T, Judge M, Paton N, Collins J, Garbutt A, et al. Management and grading of EGFR inhibitor-induced cutaneous toxicity. Future Oncol 2018; 14: 2531–2541. https://doi.org/10.2217/fon-2018-0187
20. Le-Rademacher JG, Rowland K, Atherton PJ, Dakhil C, Sun Z, Tan A, et al. Androgen mediation – and antiandrogens mitigation – of the epidermal growth factor receptor (EGFR) inhibitor-induced rash: results from a pilot randomized trial and small translational case series. Am J Hosp Palliat Care 2019; 36: 519–525. https://doi.org/10.1177/1049909118819820
21. Nakahara T, Moroi Y, Takayama K, Itoh E, Kido-Nakahara M, Nakanishi Y, et al. Changes in sebum levels and the development of acneiform rash in patients with non-small cell lung cancer after treatment with EGFR inhibitors. Onco Targets Ther 2015; 8: 259–263. https://doi.org/10.2147/OTT.S76860
22. Reenstra WR, Yaar M, Gilchrest BA. Aging affects epidermal growth factor receptor phosphorylation and traffic kinetics. Exp Cell Res 1996; 227: 252–255. https://doi.org/10.1006/excr.1996.0274
23. Jatoi A, Green EM, Rowland KM, Jr., Sargent DJ, Alberts SR. Clinical predictors of severe cetuximab-induced rash: observations from 933 patients enrolled in north central cancer treatment group study N0147. Oncology 2009; 77: 120–123. https://doi.org/10.1159/000229751
24. Beech J, Germetaki T, Judge M, Paton N, Collins J, Garbutt A, et al. Management and grading of EGFR inhibitor-induced cutaneous toxicity. Future Oncology 2018; 14: 2531–2541. https://doi.org/10.2217/fon-2018-0187
25. Finlay MRV, Anderton M, Ashton S, Ballard P, Bethel PA, Box MR, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. J Med Chem, 2014; 57: 8249–8267. https://doi.org/10.1021/jm500973a
26. Russo A, Franchina T, Ricciardi GRR, Smiroldo V, Picciotto M, Zanghì M, et al. Third generation EGFR TKIs in EGFR-mutated NSCLC: where are we now and where are we going. Crit Rev Oncol Hematol 2017; 117: 38–47. https://doi.org/10.1016/j.critrevonc.2017.07.003
27. Shah DR, Shah RR, Morganroth J. Tyrosine kinase inhibitors: their on-target toxicities as potential indicators of efficacy. Drug Safety 2013; 36: 413–426. https://doi.org/10.1007/s40264-013-0050-x
28. Bollinger MK, Agnew AS, Mascara GP. Osimertinib: a third-generation tyrosine kinase inhibitor for treatment of epidermal growth factor receptor-mutated non-small cell lung cancer with the acquired Thr790Met mutation. J Oncol Pharm Pract 2018; 24: 379–388. https://doi.org/10.1177/1078155217712401
29. Chen P, Chen F, Lei J, Zhou B. Curative effectiveness and safety of osimertinib in the treatment for non-small-cell lung cancer: a meta-analysis of the experimental evidence. Onco Targets Ther 2018; 11: 9033–9047. https://doi.org/10.2147/OTT.S182077