

Update review of skin adverse events during treatment of lung cancer and colorectal carcinoma with epidermal growth receptor factor inhibitors

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Summary

The past decades have witnessed a rapid increase in the use of molecularly targeted therapies. One class of agents includes the epidermal growth factor receptor inhibitors (EGFRIs), which afford patients longer progression-free survival (PFS) times, especially among non-small cell lung cancer (NSCLC) and metastatic colorectal carcinoma (mCRC). Certain adverse effects, particularly skin toxicity, are mainly manifested as rash, xerosis, pruritus, nails changes, hair changes and mucositis. Previous studies reported the adverse events occurred based on the cutaneous inflammation reaction. Treatment recommended glucocorticoids and antibiotics. It is suggested that skin toxicity is an important issue because it usually affects patients' quality of life (QoL) and still causes dose reduction or discontinuation of targeted therapies. For these reasons, more and more oncologists and dermatologists recognize the importance of recognition and management of skin toxicities with the expansion in availability of EGFRIs. In this review, we conducted a systematic review of recent data to examine the types and frequencies of dermatologic toxicities associated with anti-epidermal growth factor receptor (EGFR) therapies in NSCLC and mCRC. In addition, we would like to explore the management and treatment options currently used by clinicians based on the possible mechanism.

Keywords: EGFRIs, skin toxicities, non-small cell lung cancer, colorectal carcinoma, review

1. Introduction

Epidermal growth factor receptor (EGFR) is often over-expressed or overactivated in human cancer, which makes EGFR a key therapeutic target. Frequently administered inhibiting EGFR have different mechanisms of action that are specific for the intracellular tyrosine kinase inhibitors (TKIs) erlotinib gefitinib, icotinib, osimertinib, dacomitinib and the monoclonal antibodies (mAbs) cetuximab and panitumumab binding the extracellular domain of the

EGFR. TKIs have been recommended as the first-line treatment for non-small cell lung cancer (NSCLC) with EGFR mutation. In the IPASS study, the first-line therapy with gefitinib significantly prolonged progression-free survival compared with paclitaxel plus carboplatin in pulmonary adenocarcinoma patients (1). The mAbs have been recommended for patients with wild-type RAS metastatic colorectal carcinoma (mCRC) by the National Comprehensive Cancer Network (NCCN) at the first line (2).

The adverse events of these targeted drugs are usually minimal in terms of frequency and severity. However, epidermal growth factor receptor inhibitors (EGFRIs) are commonly associated with dermatological toxicities that may less be seen with conventional chemotherapy or radiotherapy. They are usually manifested as acneiform rash, xerosis, pruritus, paronychia, hair changes and mucositis. The overall incidence was skin rash 47-100% (grade 3/4 1-10%), xerosis 10-49% (grade 3/4 0-7%),

Released online in J-STAGE as advance publication December 17, 2018.

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pruritus 8-57% (grade 3/4 0-2%), paronychia 3-25% (grade 3/4 0-2%), hair abnormalities 0-13% (grade 3/4 0-12%), mucositis 0-44% (grade 3/4 0-1%), while skin reactions occur more frequently in mAbs than in TKIs (3). EGFRIs-related skin toxicities usually lead to infection, pain, discomfort and greatly affect quality of life, causing depression, sleep interruptions and feel self-abasement. Most importantly, skin toxicities influence anti-cancer therapies adherence of patients. Gefitinib induced skin toxicity led to drug interruption of 6.9% patients (4). Herein, skin adverse events perhaps present the greatest concern with EGFRIs use. Prevention and treatment are recommended by experts and constitutions, mostly using topical or systematic glucocorticoids and antibiotics. But these recommendations rarely are supported by large clinical trials (5).

The use of EGFRIs in cancer therapy is very likely to expand, and oncologists should be familiar with the incidence, manifestation, possible mechanism and appropriate management of their associated a constellation of adverse effects. Here, we summarize the characteristics of commonly encountered skin toxicities associated with EGFR-inhibiting mAbs and TKIs among lung cancer and colorectal carcinoma patients, and provide recommendations for prophylaxis and treatment. When reviewed clinical study articles, priority was granted to the randomized clinical trials (RCT).

2. The common dermatological adverse events (dAEs) occurred in TKIs and mAbs

The main safety profiles of current clinical used EGFRIs are comparable between TKIs and mAbs, while the difference in incidence of each drug is observed. Evidence in EURTAC and CTONG0806 may further demonstrate the rash is more likely to occur in Eastern patients (all grades 80%, grade 3/4 13%) compared to western patients (all grades 42%, grade 3/4 0) (6,7).

2.1. TKIs

There are inherent differences in active and skin toxicities of the first-generation reversible TKIs, gefitinib, erlotinib and icotinib, the second-generation irreversible TKI, afatinib, and the third-generation TKI, osimertinib, who has activity in patients with T790M-negative acquired resistance (8). Dacomitinib is a novel second-generation, irreversible TKI, which showed potent EGFR signaling inhibition in experimental models, including first-generation TKI-resistant NSCLC cell lines (9).

In Table S1 (<http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (1,11,44,48,101-116), the review of gefitinib showed rash and pruritus were prominent, while Wo HM *et al.* reported dry skin, grade 3/4 rash, pruritus was significantly prominent in gefitinib groups than in other agent-based regimens (10). As for erlotinib, the skin toxicity occurred in more patients.

The TITAN study not included in the table demonstrated erlotinib associated skin toxicity was in 52% patients, and grade 3/4 5% (11). In this review, icotinib involved significant CONVINCE and BRAIN study and the most dAEs were in mild grade. However, a cohort study of first-line icotinib treatment in 152 advanced NSCLC patients with mutated EGFR reported the main safety profiles that 43.4% and 5.9% patients appeared rash and paronychia (12). Rash (36.0%) was one of the most common afatinib-related dAEs, while only 0.3% rates of discontinuation due to rash provided the expanded access program (13). In LUX-Lung series trials, afatinib-related dAEs had higher rates in patients (14). Investigator assessed the osimertinib associated adverse events in the AURA Study Phase II Extension Component, showing rash was also predominant (8). Future safety analyses from AURA extension and AURA2 included clustered terms of rash (41%), dry skin (31%), and nail toxicity (25%) (15). The result of AURA3 presented that osimertinib did not share more incidence of skin toxicity than first-generation and second-generation TKI. In the phase 2 trial of dacomitinib, the most common all-grade treatment-related adverse events of dacomitinib were dermatitis acneiform in 78% patients, dry skin in 44% patients, and stomatitis in 40% patients (16). The phase 3 NCIC CTG BR.26 study in this review had similar results.

In Table S2 (<http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (25,117-134), the third-generation TKI seemed to induce less skin toxicity than other TKIs, while the second-generation TKI showed predominant incidence of dAEs and dose modification among TKIs (17). Grade 3/4 adverse events rate of afatinib was comparable to that of erlotinib but higher than that of gefitinib (18). As for first-generation TKI, skin toxicity most commonly occurred in erlotinib, followed by gefitinib, icotinib in terms of incidence and severity (19).

2.2. EGFR-mAbs

Panitumumab and cetuximab have been approved by the US Food and Drug Administration for the treatment of certain patients with mCRC to treat patients with wild-type RAS mCRC. Necitumumab is a second-generation recombinant human EGFR mAb to blocks ligand-induced receptor phosphorylation and downstream signaling.

The adverse events most frequently associated with EGFR TKIs are skin conditions, notably rash, pruritus, and as with the EGFR mAbs, it appeared to be associated with an increased risk of some forms of mucosal inflammation, notably stomatitis, when used in combination with chemotherapy except for rash (20). In Table S3 (<http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (25,125-134), the review also illustrated the skin toxicity profile: cetuximab

and panitumumab have comparable skin disorders, and necitumumab seem to induce less skin disorders. Rash is likely to occur, while pruritus and mucositis are less likely to be observed (21). Few patients had grade 3 skin-related toxicities (22). In phase I/II study of necitumumab, rash (70.5%), dry skin (18.2-67%), pruritus (11.4-60%), paronychia (36.4%) and grade ≥ 3 events, rash (20.5%) were observed (23,24). In SQUIRE study, rash (1.1%) led to necitumumab interruption (25).

Evidences showed that the overall incidence of skin toxicities for EGFR-MoAbs was 77.1% and high-grade (\geq grade 3) occurred in 24.6%. Longer treatment with EGFR-MoAbs (≥ 5 months) was more likely to cause skin toxicity and rash than in the shorter duration (< 5 months) (26).

Compared with cetuximab, panitumumab was associated with less incidence of rash, pruritus, mucositis, while overall skin toxicity has a higher rate. However, a meta-analysis of different toxicity of cetuximab and panitumumab in mCRC treatment showed cetuximab was associated with fewer grade 3/4 skin toxicities, slightly more frequent grade 3/4 acne-like rash, and paronychia, but fewer cases of skin fissures and pruritus than panitumumab (27).

2.3. Other EGFRIs under study

Pozotinib, a second-generation EGFR-TKI in patients with lung adenocarcinoma with EGFR mutation was reported the most frequent grade 3 adverse events were rash (59%), mucosal inflammation (26%), and stomatitis (18%) in a phase II study (28). AC0010, a mutation-selective third-generation TKI, reported the incidence of skin rash was 48% in the treatment-emergent adverse events and grade 3 or higher was 4% in the first-in-human phase I trial (29). In BLOOM study of AZD3759 in EGFR-mutant NSCLC, grade 3 skin disorders occurred in 17% patients at a dose of 200 mg twice a day, and in 40% patients at a dose of 300 mg twice a day (30). The EGFR-MoAbs against the EGFR T790M resistance mutation under study, HM61713 and EGF816, also reported the skin toxicities (31).

3. The appearance of dAEs occurred in TKIs and mAbs

3.1. Grading algorithm of skin toxicity

The Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) is a widely used classification system (32). The Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group conducted a new grading system, which is specially proposed for EGFRIs-induced dAEs and maintains consistency with the grading principles CTCAE system. Moreover, MASCC grading algorithm includes relevant patient-reported

health-related quality of life factors and is commonly used as well (33).

There have been concerted efforts to develop more precise and clinically relevant tools to quantify and monitor EGFRi-related skin toxicities, including the MASCC EGFRi Skin Toxicity Tool (MESTT) (34) and the EGFRi related Skin Toxicity Index (EGFRISTI) (35). However, the MESTT requires individual pustules to be counted, which is impractical in a busy clinic, and the EGFRISTI is again based on the surface area affected, whose score ranged from 6.0 to 64.5 (36). In addition, Wollenberg A *et al.* presented a new scoring tool for acneiform skin eruptions by calculating from body involvement, facial involvement and clinical grading of the skin items erythema, papulation, pustulation and scaling/crusts (37).

3.2. The distribution and typical time course of skin appearance

Rash is the earliest and most common cutaneous reaction. Braden RL *et al.* conducted a retrospective chart review on 157 patients with EGFRi-induced skin reactions. Papulopustular eruption was observed at the average duration of 9.4 weeks, and eruption mostly involved in face with 97 % of patients affected, followed by the chest (75%) and back (61%). The abdomen (8%), upper extremity (8%), and lower extremity (4%) were less frequently observed. Bacterial skin infection accounted for 21% patients, in which the upper extremity (64%), lower extremity (52%), and abdomen (33%) were the most common infectious locations. The mean time to onset of the acneiform rash was 1.5 weeks after initiation of EGFRi, while the mean time to onset of bacterial superinfection was 28.6 weeks (38). Xerosis generally occurs late, after the patient has been on anti-EGFR treatment for at least 30-60 days. This condition usually follows or accompanies by acneiform eruption and itch. Dry skin is also a cause of increased susceptibility to injuries and fissures, whose secondary causes include bacterial and viral infections. Deep painful fissures are most often seen in the area of fingertips, heels, periungual skin and dorsal surface of the interphalangeal joints (39). Pruritus often coexists with xerosis (50%) and papulopustular rash (62%), and also commonly accompanies rash at onset (40). Similarly, paronychia frequently accompanies papulopustular rash. It develops later on, usually 4-8 weeks after starting treatment (41). The lesions develop 2-5 months after the onset of treatment.

3.3. Common appearances involved in anti-EGFR treatment

Rash, xerosis, pruritus, nail changes, hair changes, mucositis are common skin toxicities involved in TKIs and mAbs, and in some extreme cases, severe cutaneous



Grade 1

Grade 2

Grade 3

Grade 1: Papular and/or pustular lesions covering < 10% BSA, not associated with itching or pain.

Grade 2: Papular and/or pustular lesions covering 10-30% BSA; may cause pruritus, pain, and adverse psychosocial effects.

Grade 3: Papular and/or pustular lesions covering > 30% BSA; may cause pruritus, pain, and adverse psychosocial effects, secondary infection requiring oral antibiotic therapy, limiting self-care.

Figure 1. The different degrees of severity of the rash according to CTCAE v4.03. In grade 1, the rash only occurred on head and face dispersedly. In grade 2, papular lesions occurred on the patient's face and all his back with pain and pruritus. In grade 3, the head of the patient suffered secondary infection, and the face was swelling and red, which effected his daily life obviously. *Note:* No patients with grade 4/5 rash were observed. BSA = body surface area. The pictures were taken from 2014 to 2018.

adverse reactions (SCARs) may occur, while they specifically have some differences.

3.3.1. Rash

The eruption generally evolves through four distinct phases. The skin rash lesions can be manifested as 24% rash, 16% dermatitis acneiform, 7% rash maculopapular, 11% acne (42). At the first 1-2 weeks from initial treatment, rash occurred with dysesthesia, erythema and edema, then erythematous papules and pustules. Until 3-6 weeks purulent crusts appear, progressing to telangiectasias with pain and pruritus. Symptoms typically resolved within 4 weeks after EGFR TKI is ceased; but there could be partial or even complete resolution despite continued EGFR TKI therapy. The duration and severity of symptoms depend on the dose and kinds of EGFRs, if properly managed, the symptoms may also self-relieve to some extent, even disappear. Complete disappearance of lesions but hyperpigmentation left is observed about one month after discontinuity of treatment. Sibaud V reported 4 patients presented an unusual presentation of acneiform rash, characterized by late development after several months of EGFRs treatment, localization to the limbs with sparing of the face, and association with severe pruritus and *Staphylococcus aureus* superinfection in all cases (43). Seriously, skin exfoliation and toxic epidermal necrolysis are diagnosed (44,45). The different degrees of severity of the papulopustular rash

are illustrated in Figure 1.

3.3.2. Xerosis

EGFRs impair the epidermal barrier based on keratinocyte differentiation, causing shortage of water and abnormal oil production in the epidermis. Skin secondary infection may contribute to xerosis. The risk of skin dryness during treatment increases with age, pre-eczema, and prior cytotoxic use. Evidence showed patients who received gefitinib experienced xerosis cutis, acneiform have mean Transepidermal Water Loss values higher than normal (46). The different degrees of severity of the xerosis are illustrated in Figure 2.

3.3.3. Pruritus

Pruritus is an uncomfortable sensation leading to intensive scratching. Your skin looks dry and scaly. During treatment, generalized or localized itching is observed in arms, legs or body, ranging in strength from mild to severe pruritus. The severe condition shows the skin on the fingertips and heels crack. Dry mouth, eyes and nose also can be observed in the late. The different degrees of severity of the pruritus are illustrated in Figure 3.

3.3.4. Nail changes

Paronychia is the typical appearance of nail changes



Grade 1 **Grade 2** **Grade 3**
Grade 1: Covering < 10% BSA and no associated erythema or pruritus.
Grade 2: Covering 10-30% BSA and associated with erythema or pruritus; limiting instrumental ADL.
Grade 3: Covering > 30% BSA and associated with pruritus; limiting self-care ADL.

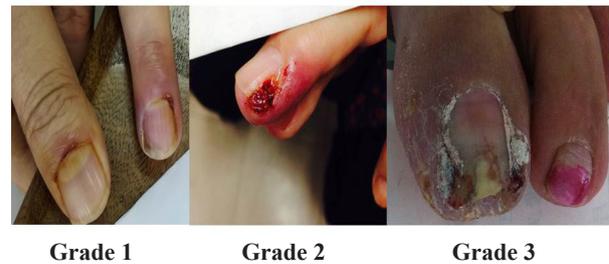
Figure 2. The different degrees of severity of the xerosis according to CTCAE v4.03. In grade 1, the calf of patient was exposed to xerosis without erythema or pruritus. When progressed to grade 2, all the limbs suffered from xerosis with rhagades and pruritus. In grade 3, the patient suffered from a wide range of xerosis and pruritus with obvious scratch. *Note:* ADL = activities of daily living; BSA = body surface area. The tags with words and time in the pictures represented as code names from their name acronyms and the time of collection.



Grade 1 **Grade 2** **Grade 3**
Grade 1: Moderately intensive, limited to a particular part of the body, requires topical treatment.
Grade 2: Increased local or periodically generalized, present lesions resulting from scratching, impairment of basic patient activity, requires systemic treatment.
Grade 3: Increased local or permanently generalized, significant limitation of self-care activity or impairment of sleep, requires oral corticosteroids or immunosuppressive therapy.

Figure 3. The different degrees of severity of the pruritus according to CTCAE v4.03. In grade 1, pruritus only occurred in regional area of the leg with erythema. In grade 2, pruritus induced obvious scratch with hemorrhagic spot and hyperpigmentation. In grade 3, the scratch because of skin itch caused secondary infection and need systematic therapy. *Note:* The tags with words and time in the pictures represented as code names from their name acronyms and the time of collection.

usually with secondary inflammation, characterized by edema, redness, nail fold and severe pain in the area around the nail plate, even progression to onycholysis or onychodystrophy. The big toe is commonly the first area to be affected, and eventually one or more fingers and toes were involved (47). The different degrees of severity of the paronychia are illustrated in Figure 4.



Grade 1 **Grade 2** **Grade 3**
Grade 1: Nail fold edema or erythema; disruption of the cuticle.
Grade 2: Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL.
Grade 3: Surgical intervention or intravenous antibiotics indicated; limiting self-care ADL.

Figure 4. The different degrees of severity of the paronychia according to CTCAE v4.03. In grade 1, the first picture showed mild edema and erythema of fingernails without limiting daily life. In grade 2, the edema erythema and bleeding occurred with intervention of antibiotic. In grade 3, the inflammation occurred around the fingernails and need surgery treatment. *Note:* The pictures were taken from 2014 to 2018.

3.3.5. Hair changes

Hair changes are characterized as the alterations in the hair structure, accompanied by curly hair, and thin, as well as a change in color. The typical manifestation is alopecia, reported in 1.9-4.9% of patients (48). Non-scarring hair loss is reversible, slow, and usually does not lead to complete baldness. Alopecia is not the only described changes to hair during EGFRIs use. A five-year review of spectrum of ocular toxicities from EGFRIs showed eyelash changes (trichomegaly and trichiasis) were also the commonly observed appearances



Figure 5. The appearance of eyelash changes. In these two pictures, the patients suffered from trichomegaly and trichiasis. The eyelash grew irregular and disturbed their sight. *Note:* The pictures were taken from 2014 to 2018. The tags with words and time in the pictures represented as code names from their name acronyms and the time of collection.

(49). Excessive hypertrichosis also included of the face (50). The appearance of eyelash change is presented in Figure 5.

3.3.6. Mucositis

EGFRIs result in a range of alterations in visible mucosal tissues, mainly in oral cavity. Patients may suffer from mild red and swollen to severe ulceration and pain, which lead to discomfort and influence eating and drinking (34).

3.3.7. SCARs

There have been a substantial number of reports concerning life-threatening SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms, drug-induced hypersensitivity syndrome, and acute generalized exanthematous pustulosis. Literature review showed a total of 12 patients suffered from SCAR episodes: two SJS caused by afatinib, one SJS, one SJS/TEN and two TEN (one death) caused by cetuximab, one SJS caused by erlotinib, two TEN (one death) and two acute generalized exanthematous pustulosis caused by gefitinib, one SJS caused by panitumumab (51).

4. The possible mechanism of dAEs

The skin toxicity due to EGFRi is not yet fully understood. Evidences demonstrated the skin reactions may be illustrated from point of pathogenesis, signal molecule, polymorphism, and pharmacokinetics.

4.1. Pathogenesis and molecular biomarkers

Biomarkers of skin toxicity induced by anti-EGFR treatment mainly include three major signalling outputs, namely RAS/RAF/MEK/ERK with the function of

cell proliferation, cell cycle and cell migration and on the expression of inflammatory mediators, JAK/STAT pathway reaction to proliferative response, protection from apoptosis and PI3K/Akt pathway governing survival responses (52). Lacouture ME firstly systematically reviewed the underlying pathobiological mechanism of EGFRIs-associated skin reactions based on previous experimental and clinical data (53). Then Paul *et al.* explored the changes of signal molecules among cancer patients (54). The chemokine expression in keratinocytes further illustrated skin inflammation mechanism when treated with EGFRIs (55).

In general, the molecular mechanism is the following aspects: a. EGFRIs inhibit the PI3K-Akt and MAPK pathways, contributing to the inhibition of keratinocyte growth and survival; b. EGFRIs has an inhibitory effect on differentiation of keratinocyte by interfering in the expression of signal molecular, such as keratin 1 (KRT1), KRT10, ASK1, STAT3 BCL2 and BCL-XL; c. EGFRIs change the function of attachment and migration by the up-regulation or down-regulation of related proteins. d. EGFRIs induced the release of chemokines and cytokines, CCL2, CCL5, CXCL10, CCL18, XCL1, CXCL9 (CXC chemokine ligand 9), CCL3, NFκB, IL6, IL7, and IFN regulatory factor 5, which developed inflammation. e. EGFRIs damage the protection function of skin from ultraviolet radiation. Consequently, the effects of proinflammatory chemokines in the epidermis lead to inflammation.

The abnormal signal processes accordingly lead to pathological changes. The EGFR is known to be expressed in skin keratinocytes, the sebaceous glands, hair follicle epithelium, and periungual tissue (56). EGFR inhibition leads to dysfunction of keratinocyte migration, maturation, and proliferation, resulting in inflammatory cell recruitment and cutaneous injury (53). Release of pro-inflammatory cytokines contributes to subsequent tissue damage and apoptosis (55). EGFRIs associated skin lesions are formed owing to secondary bacterial infections and other complications as well (57). The possible pathogenesis of pruritus may involve cutaneous nerve endings, unmyelinated C-fibers, and neurotransmitters or regulation of various receptors, included serotonin, neurokinin (NK)-1 receptor, opioid receptors, and gammaaminobutyric acid (GABA). Mast cell degranulation and maturation may be the important activation way (58).

4.2. Gene polymorphisms

Pharmacogenomic analyses of EGFR polymorphisms and several genomic mutations have been undertaken to determine their predictive value in the development of skin toxicity after anti-EGFR treatment (Table S4, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (135-141)). From the literatures review, molecular markers of EGFR polymorphisms can

predict skin toxicity, and also has association with the efficacy of the anti-cancer. Unfortunately, these studies are sporadic and have not been validated by larger and further research to reveal the occurrence mechanism and clinical biomarkers.

4.3. Pharmacokinetics

Concentration of HGF might be significantly inversely correlated with severity of rash. Increased HGF/MET signaling might compensate the inhibitory effect of EGFRs in skin as well as tumor cells, leading to less severe skin rash and decreased efficacy of the anti-tumor therapy (59). Kimura K *et al.* used the average binding occupancies (Phi ss) of EGFR-TKIs, gefitinib and erlotinib to evaluate frequency of rash (60). Vasavda C *et al.* found gefitinib, erlotinib, osimertinib had responsible proteins by reverse phase protein arrays among 301 proteins associated with EGFR signaling. These three EGFRs equally suppressed phosphorylation of 12 proteins, while they respectively regulated phosphorylation of 13 other proteins, such as 4E-BP1 and eIF4E. Gefitinib most potently inhibited the 13 proteins, whereas osimertinib blocked fewer, and erlotinib even fewer. Osimertinib also independently resulted in phosphorylation of histone H2AX, suggesting that osimertinib may promote double-strand DNA breaks. These differences may explain why patients treated with different inhibitors experience differing dermatologic effects (61). Erlotinib concentration was also associated with occurrence and severity of skin rash (62). Accordingly, the proteins identified as differentially regulated by these inhibitors may be candidates for evaluating the mechanisms underlying their dermatologic toxicities.

Raman spectroscopy is novel method to distinguish the patients with or without skin toxicity by correlating the skin patients Raman signature and the drugs concentration into patient's blood. Raman spectroscopy can be a pharmacodynamic biomarker for EGFRs-related adverse reactions (63).

5. Management

EGFRs treatment associated dAEs has caused a substantial economic burden and lower quality of life (64). Hence, it is essential to establish appropriate strategies, including prophylactic treatment, reactive treatment, dose reductions and drug discontinuance, to deal with skin toxicity, especially the management does not compromise anti-cancer efficacy. At present, recommendations are almost based on expert opinion and consensus, which large randomized clinical trials are insufficient. The existing guidelines include CTCAEv4.0 suggestions for interventions (65), MASCC Skin Toxicity Study Group Clinical Practice Guidelines (66), NCCN dermatologic toxicities management guidelines

(5), disciplinary therapeutic algorithm from various areas (67-70). The management treatment options for dAEs mainly consist of topical moisturizers or corticosteroid creams for mild reactions or systemic treatments of antibiotics and corticosteroids. Supportive care, such as prevention from sun exposure, comfortable clothes and shoes, non-irritating bath products are recommended. (Table S5, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (142-159))

5.1. Patient education

Patient and doctor education are fundamental to treatment. The explanation of the care strategies and symptoms management are especially important. The oncologists and dermatologists should provide patients with specific instructions on when to ask for medical attention to manage the skin reactions and give appropriate advice on basic dermatologic care, such as maintaining cleanliness, moisturisation, and prevention from stimuli. In general, patients should recognize and early evaluate the signs and symptoms of EGFRs-associated dAEs. They should be instructed to realize the risk of skin infection, avoid scratching and sun, protect arms and legs from extreme heat or cold, and wear loose cotton clothing and shoes (71).

5.2. Rash

Lacouture *et al.* recommended topical and systemic treatment for EGFRs-induced rash according to the severity of rash (66). Dose modification is unnecessary for grade one. Apply low to mid potency topical steroids such as hydrocortisone, betamethasone dipropionate and antibiotics such as clindamycin, gentamicin externally daily until rash resolution. As for grade two, oral antibiotics, for example doxycycline or minocycline 100 mg twice a day, are applied until rash eases except for recommendations of grade one. Dose reduction is essential for grade three, as well as the recommendations of grade two. The grade four rash would lead to treatment discontinuity and be managed refer to grade three.

Prophylactic treatment of EGFRs-related rashes, oral antibiotics and steroid creams, is more effective than reactive treatment, which does not compromise survival (72). Doxycycline and tetracycline appear to be a favorable option in rash with safety profile either prophylactic treatment or reactive treatment (70). Case reports of topical recombinant human EGF or topical vitamin K cream resulting in a reduction of rash grade within a few weeks are very promising. Vitamin K3 (menadione), a synthetic pro-drug of vitamin K, has been suggested to be able to re-phosphorylate EGFR-even during treatment with EGFR-inhibitors (73) (Table S5, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (142-159)).

5.3. Pruritus

Pruritus intervention can be challenging. The prevention of scratching is the first management strategy for patient, which may induce secondary infections. The mechanism of EGFRIs-associated pruritus has not yet been explained. In general, the classical mediators, such as histamine and neurotransmitters, are chosen as the target to provide symptom relief (74). Emollients or moisturizing creams are recommended if pruritus is caused by skin xerosis. Topical and systematic glucocorticosteroids are recommended for moderate and severe pruritus. Besides, gabapentin and pregabalin, doxepin also reported as candidates (65). Recently, aprepitant, a neurokinin-1 receptor antagonist was demonstrated to reduce pruritus caused by erlotinib, which may imply substance P is one of key itch-induced neurotransmitters (75).

5.4. Xerosis

Staying hydrated is the key to preventing xerosis. Xerosis rarely lead to dose changes of EGFRIs. Patients should be encouraged to adopt emollients without irritants. If hyperkeratotic skin appeared, exfoliants and urea cream can be used. Other management includes steroid creams, salicylic acid, zinc oxide (76).

5.5. Nail changes

Paronychia is the most commonly appearance of nail changes. Lacouture *et al.* recommend prevention of paronychia by comfortable footwear, avoiding irritants and treatment of topical corticosteroids or calcineurin inhibitors, systemic tetracyclines if diagnosed infection (76). A series of cases of nail changes from cetuximab, panitumumab, erlotinib showed the topical povidone-iodine/dimethyl sulfoxide solution described is very effective in alleviating the signs and symptoms. There was a total of 25 nails affected in the case series, and 21/25 (84%) resolved overall. The culture results suggested the microorganisms included *Staphylococcus aureus*, *Pseudomonas*, *T. mentagrophytes*, *Streptococcus pyogenes*, *Trichophyton mentagrophytes* (77).

5.6. Hair changes

The EGFRIs-associated hair changes mainly manifest as trichomegaly and alopecia. Abnormal trichomegaly may be treated with temporary or permanent hair removal (66). Alopecia generally resolves after target drugs discontinuation.

5.7. Mucositis

Oral mucositis is the prominent factor that affects the daily life of patient. The principles of treating stomatitis

are oral care, pain management, maintaining oral function, oral complications control, and the quality of life improvement (78). The prevention approaches include soft tooth brushing, frequent mouth and teeth clean and avoiding alcohol and tobacco products (79). The treatment recommendations of EGFRIs-associated mucositis in expert consensus and ESMO guideline are as follows (76,80).

5.8. Traditional Chinese medicines (TCM) and Japanese kampo for skin toxicity

There is only one study, none for TCM, on the effects of Japanese kampo on EGFRIs-related rash in English. Still, a few reports are designed to observe proved prescriptions on EGFRIs-associated dAEs in China (Table S6, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=32>) (82-87)). We conducted a meta-analysis to evaluate the effect of TCM on EGFRIs-induced rash, suggesting that TCM could significantly relieve EGFRIs induced rash and symptoms and improve patients' quality of life (81).

5.8.1. Japanese kampo

Ichiki M (82) studied Japanese kampo on afatinib-induced rash, diarrhea, and oral mucositis with prophylactic use of minocycline and TJ-14 in Japan. The result showed TJ-14 mainly reduced the risk of diarrhea rather than skin toxicity compared with minocycline. Therefore, the effect of Japanese kampo for EGFRIs-associated dAEs seems to be absence of evidence.

5.8.2. TCM herbs

TCM herbs are used on the foundation of TCM theory. The EGFRIs-associated dAEs belongs to the category of "drug toxicity". The pathogenesis is that wind, dampness and heat invade lung on the foundation of deficiency. The basic principle of treatment is dispelling wind and dampness to promote eruption and itch, clearing heat-toxin and cooling blood, nourishing yin and blood and moistening dryness. In TCM, couplet medicines are the commonly used prescribing method, which was also applied for the skin toxicity. Herba Schizonepetae (Jing jie) and Radix Saposhnikovia (Fang feng) are combined to dispel wind to promote eruption. Flos Lonicerae (Jin yin hua) and Fructus Forsythiae (Lian qiao) are combined to clear heat-toxin. Cortex Moutan Radicis (Mu dan pi) and Radix Paeoniae Rubra (Chi shao) are combined to clear heat and cool blood. Herba Taraxaci (Pu gong ying) is also used to remove toxin for detumescence in the condition of secondary infection. Cortex Dictamni (Bai xian pi), and Radix Sophorae Flavescentis (Ku shen) are adopted to promote diuresis and itch if pruritus is the cardinal symptom.

5.8.3. TCM formula

TCM formula mainly included external or oral decoction, and another study involving the combination of auricular acupuncture. The basic formulas included Xiaofeng powder (from Waikē Zhengzong), Jingfang Baidu powder (from Shesheng Zhong miao Fang), Siwu decoction (from Xianshou Lishang Xuduan Mifang), Wuwei Xiaodu drink (from Yizong Jinjian). The auricular acupuncture chosen was to regulate qi and blood, balance yin and yang, improve immunity and defense against tumor.

Xu JX *et al.* studied oral and external Jingfang Baidu San Jiawei combined with auricular acupuncture on EGFRIs-related dAEs, which confirmed that TCM could lower the incidence and grade of skin toxicity, improve quality of life (QoL) as well (83). Zhao ZW *et al.* recommended oral Siwu Xiaofeng San to treat gefitinib-related rash. All the patients treated with TCM had therapeutic effect and the rash discontinuation rate in treatment group was lower than the control group (84). Similarly, the efficacy of Xiaozhen San was also verified by Zhang PY *et al.* (85). In Sun T *et al.* researched the efficacy of oral Yangfei Xiaozhen Tang, suggesting that TCM had an advantage in effective rate, recovery rate of TCM syndromes and QoL improvement (86). Peng YM *et al.* conducted a trial to confirm the effect of external Zhiyang Pingfu Lotion. The result showed that the effective rates of TCM in the treatment of rash, cutaneous pruritus, xerosis cutis and nail changes were higher than that of the standard treatment group (87).

However, the efficacy of TCM and Japanese kampo for skin toxicity based on present studies may not draw a definitive conclusion because of the poor methodological quality and further large clinical trials are needed to confirm results (88).

6. Skin toxicity, clinical outcomes, QoL

Series of studies have confirmed that the occurrence and the severity of dAEs are related to better anti-cancer efficacy and survival benefits (89), however, the dAEs are also involved in with lower QoL and higher financial burden (90), especially for serious skin reactions. The identical standard of tools used to measure QoL of patients with EGFRIs treatment is actually unclear.

6.1. The association of dAEs and response rates

As we known, numerous studies have varied the association between skin toxicity caused by EGFRIs and clinical outcomes. Recently, retrospective analyses further showed that skin toxicity might be a positive indicative of EGFRIs for lung cancer and mCRC. Grade 2 or higher skin rash of afatinib might be a useful marker for long-term efficacy (91). Erlotinib-associated rash may be a valuable biomarker for the prediction of clinical

response and overall survival (OS) in advanced NSCLC patients (92). Patients treated with cetuximab also showed that early skin toxicity suggested significantly longer OS and higher skin toxicity grades indicated longer PFS (93).

6.2. QoL evaluation algorithm

The Dermatologic toxicity of EGFRIs may affect the physical, emotional, and social well-being, which suggests the potential to severely influence patients' QoL (94). No uniform evaluation standard for QoL is provided and researchers recommend some useful tools, such as dermatology-specific quality-of-life questionnaire (Skindex-16) (95) and the EGFRi-specific Functional Assessment of Cancer Therapy Questionnaire-EGFRi (FACT-EGFRi-18) (96).

Skindex-16 is a general instrument to be used in skin disorders, including acne and psoriasis. Although it is not specific for EGFRIs-associated skin toxicity, its item content focused on multidimensional evaluation of skin disorders and related ease of management, making it a feasible measure. In a subsequent study using Skindex-16 to evaluate the QoL of EGFRIs-associated skin toxicity found that the rash grade in CTCAE system was significantly connected with Skindex-16 scores (97). Using Skindex-16 to evaluate patients' QoL with EGFRIs therapy including symptoms, emotion, and function, Rosen *et al.* found higher scores across all 3 domains in patients who experienced rash or pruritus than those not experience these skin reactions (98).

The FACT-EGFRi-18, an 18-item patient questionnaire, assesses the influence of EGFRIs-related skin, nail, and hair toxicities on physical, emotional, social, and functional impact, which proved useful to clinicians and researchers in prevention protocol and clinical study. In Dutch practice, the FACT-EGFRi-18 was identified as an appropriate measurement for dAEs-related QoL (99).

In addition, a valid instrument, Eruption Scoring System (ESS), was introduced for cetuximab-related dAEs, which covered evaluation of the consequences of skin toxicity on the QoL, similar to FACT-EGFRi-18 and the severity of dermatological toxicity induced by cetuximab, compared with the standard CTCAE system (100).

7. Conclusion

It is no doubt that EGFRIs prolong the survival time of lung cancer and mCRC patients. The dAEs is potentially should be taken into consideration by oncologists and dermatologists when taking the implementation of such target strategies. Just as Tischer B *et al.* promoted, these four missing information should be addressed in further study: patient's voice, the communication between physician and patient regarding dAEs, acceptance

of skin toxicities compared with other AEs, and the balance of the risk of skin toxicities and the efficacy of the therapy (3).

Recognizing EGFRIs induced dAEs and understanding possible mechanism, then correct evaluating skin toxicity and choosing proper treatment for practitioners and patients are critical. We systematically reviewed the recent literatures of dAEs associated with the most frequently used EGFRIs in lung cancer and mCRC, including the frequency of occurrence, clinical appearance, methods of grading, underlining mechanisms, algorithm of management and the association of skin toxicity, clinical outcomes, quality of life. Our goal is to provide an adequate decision regarding treatment dose or discontinuation, impacting therapeutic efficacy and patient survival when dAEs occur, contributing better use of target drugs.

Acknowledgements

This project was supported by Capital's funds for health improvement and research (2018-2-4065). We sincerely thank patients from outpatient from 2014 to 2018 for providing their pictures.

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(Received October 12, 2018 Revised November 28, 2018; Accepted December 2, 2018)