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Review Article

Skin problems and EGFR-tyrosine kinase inhibitor

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Abstract

Epidermal growth factor receptor inhibition is a good target for the treatment of lung, colon, pancreatic and head and neck cancers. Epidermal growth factor receptor-tyrosine kinase inhibitor was first approved for the treatment of advanced lung cancer in 2002. Epidermal growth factor receptor-tyrosine kinase inhibitor plays an essential role in the treatment of cancer, especially for patients harbouring epidermal growth factor receptor activating mutation. Hence, skin toxicity is the most concerning issue for the epidermal growth factor receptor-tyrosine kinase inhibitor treatment. Skin toxicity is bothersome and sometimes affects the quality of life and treatment compliance. Thus, it is important for physicians to understand the background and how to manage epidermal growth factor receptor-tyrosine kinase inhibitor-associated skin toxicity. Here, the author reviewed the mechanism and upfront preventive and reactive treatments for epidermal growth factor receptor inhibitor-associated skin toxicities.

Key words: EGFR-TKI, skin rash, rash acneiform, minocycline

Introduction

Many kinds of molecular targeting agents are developed and introduced for the treatment of cancer in this decade (1–5). The toxicity of molecular targeting agents is quite unique and completely different from the cytotoxic chemotherapeutic agents. The epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) showed good response for non-small cell lung cancer (NSCLC), and gefitinib was first approved in 2002 for NSCLC patients (6). EGFR-TKIs are now approved for NSCLC and pancreatic cancer in Japan and play an important role in the treatment of NSCLC, especially for patients harbouring EGFR activating mutation, which occurred in 10–15% of Caucasian and 30–40% of Asian NSCLC patients (7–12).

EGFR is highly expressed in skin and gastrointestinal epithelial cells (13,14). The blockade of epidermal growth factor signalling by EGFR-TKI induced cutaneous and gastrointestinal toxicities. Skin toxicity involved rash acneiform, skin fissure and xerosis, and these are related to pruritus. The other problems are skin fissures/cracks and paronychia, which are sometimes painful. Thus, severe dermatological toxicity induced psychological problems as well as physiological issues. These decrease the quality of life (QoL) and may also affect treatment compliance. The severity of skin rash may also correlate with efficacy for the treatment (15). The skilful evaluation and management of EGFR-TKI-associated skin rash are important for patients and medical staffs during EGFR-TKI treatment. Here, the author reviewed the skin-problem-associated EGFR-TKIs and the upfront management of EGFR-TKI-associated skin rash.

Mechanisms and physiological functions of EGFR in skin

EGFR is widely expressed in the normal skin tissue such as epidermis, sebaceous, glands, eccrine glands and dendritic cells. EGFR plays an important role in the development and physiology of normal epidermis. The epidermis is mainly developed from keratinocytes, and this

differentiation and migration to the skin surface are regulated by EGFR signalling (16).

EGFR activation is occurred by its ligands as EGF, transforming growth factor-α, amphiregulin and heparin binding EGF (HBEGF). This ligand-binding activation regulates keratinocyte proliferation by introducing the down-signal activation, phosphoinositide 3-kinase-AKT and mitogen-activated protein kinase pathways (17). The inhibition of EGFR increases the expression of cyclin-dependent kinase inhibitor $p27^{KIP1}$ (18–20), which leads the keratinocytes to the cell cycle arrest in G1 phase. It induces keratins 1 and 10, which are known as terminated differentiated markers and premature differentiation (21). Transducers and activators of transcription-3 (STAT-3), which is activated by EGFR signalling, is also the key molecule for skin homeostasis. The disruption of STAT-3 in transgenic mice impaired wound healing and hair cycle (22).

The blockade of EGFR signalling affects the secretion of cytokines. The blockade induces chemokine (C-C Motif) ligand 2 (CCL2), CCL3, CCL5, CCL18, C-X-C motif chemokine 9 (CXCL9), CXCL10, XCL1, fractalkine (CX3CL1) or C-X-C chemokine receptor type 4 (CXCR4) and reduces CXCL8 (23). These stimulate inflammation and the initiation of immune response (24). The EGFR inhibition also increases interferon-α and -β expressions or signalling via regulating IFN regulatory factor 5 and IFN consensus sequence-binding protein 1 (25). The changes in cytokine secretion recruit the neutrophils, lymphocytes and monocytes and induce inflammation.

Pathologically, the inhibition of EGFR with cetuximab, an anti-EGFR monoclonal antibody, leads the infiltration of superficial dermal inflammatory cells to the surrounding hyperkeratotic and ectatic follicular infundibula, abacterial suppurative superficial folliculitis (26). Intraepidermal acantholysis is also observed after cetuximab treatment.

EGFR signalling also plays a role in anti-apoptosis for keratinocyte and dendritic cells from ultraviolet B (UVB) (27,28).

In summary, EGFR inhibition leads the negative impacts for skin as premature differentiation, inducing inflammation and apoptosis, skin atrophy, telangiectasia and photosensitivity (29).

Genetic alteration and EGFR-inhibitor-associated rash severity

The activating EGFR mutation is somatic. The EGFR in the skin is considered to have the wild-type EGFR in patients harbouring EGFR activating mutation. Thus, there was no correlation between skin toxicity and EGFR activating mutation (30). The number of CA single sequence repeats (CA-SSR) in intron 1 in the EGFR gene affected the efficacy and skin toxicity for patients treated with gefitinib (31). The lower number of CA-SSRs related to the higher expression of EGFR. The incidence of skin toxicity occurred in 48% with 35 or less alleles and in 33% with more than 35 alleles ($P = 0.04$). The T allele of −216G/T in the promoter EGFR polymorphism was also associated with significantly higher risk of treatment-related rash ($P = 0.004$) (32).

Klinghammer et al. showed a substitution G→A in EGFR exon 13 resulting in an amino acid substitution in position 521 (EGFR R521K) increased the grade > 1 skin toxicity in patients with cetuximab–docetaxel treatment (14 vs. 7%, $P = 0.024$) (33). Patients carrying the C/C genotype in the EGFR position 994 without amino acid substitution treated with anti-EGFR monoclonal antibody showed significantly less skin toxicity than those with other genotypes (34).

The other polymorphism was the ABCG2 16 702 G/A polymorphism. This also related to the frequency of skin toxicity. G/G genotype developed higher frequency of grade ≥2 skin rash ($P = 0.027$) (35).

Human leukocyte antigen (HLA) polymorphisms may also affect the incidence of skin rash (36). The frequency of skin rash was significantly lower in patients with HLA-A*02:01 or HLA-A*03:01 alleles [hazard ratio (HR) 0.227, $P = 0.002$ and HR 0.292, $P = 0.011$, respectively].

Thus, some gene polymorphism and gene mutation coding EGFR may affect the incidence of EGFR-TKI-associated toxicity.

Types and incidence of EGFR-TKI-associated dermatological toxicity

Types of EGFR-TKI-associated dermatological toxicity

The types of EGFR-TKI-associated skin toxicity are summarized in Table 1. Generally, the acne-like skin rash and pruritus are experienced in 1–2 weeks after starting EGFR-TKI treatment. Dry skin is also developed in 2–3 weeks. In contrast, skin fissure/cracks or nail change occurred 1–2 months later.

Incidence of EGFR-TKI-associated dermatological toxicity

The incidence of EGFR-TKI-associated skin toxicity is summarized in Table 2. The incidence of skin rash was 66–71% in gefitinib (37–40), 73–99% in erlotinib (39,41–45) and 81–100% in afatinib (46–48), respectively. The frequency of grade 3 or higher skin rash toxicity was 2–5% in gefitinib, 2–19% in erlotinib and 15–20% in afatinib, respectively. The WJOG5108L trial, which was the randomized phase 3 trial to compare the progression-free survival directly between gefitinib and erlotinib, revealed that the frequency of grade 3 or higher skin rash was significantly higher in erlotinib (18%) than in gefitinib (2%) ($P < 0.001$) (39). The frequency of grade 3 or higher skin rash was significantly higher in afatinib (15%) than in erlotinib (9%) from the pooled analysis. ($P = 0.003$) (49).

Correlation of treatment efficacy and EGFR-related skin rash

Several studies showed that the skin rash might be associated with efficacy for patients with EGFR-TKI treatment. Two large randomized

Table 1. EGFR inhibitor-associated dermatological toxicity

Organ site	Clinical manifestation
Skin	Acneiform rash (papulopustular rash)
	Xerosis
	Erythema
	Photosensitivity
	Fissures and crack
	Hyperpigmentation
	Telangiectasia
	Pruritus
Nail	Paronychia
	Onyxis
Hair	Trichomegaly in eyelash
	Hypertrichosis in eyelash, eyebrow and mustache
	Alopecia in scalp hair
Eye	Conjunctivitis
	Blepharitis
	Xerotic
	Keratitis
	Lacrimation

EGFR, epidermal growth factor receptor.

Table 2. Incidence of EGFR-TKI-associated skin toxicity

EGFR-TKIs	Study	Area	Rash		Dry skin		Pruritus		Stomatitis		Paronychia		References
			All (%)	≥G3 (%)	All (%)	≥G3 (%)	All (%)	≥G3 (%)	All (%)	≥G3 (%)	All (%)	≥G3 (%)	
Gefitinib	NEJ002	Japan	71	5	–	–	–	–	–	–	–	–	Maemondo et al. (37)
	WJTOG3405	Japan	74	2	47	0	–	–	19	0	28	1	Mitsudomi et al. (38)
	WJOG5108L	Japan	75	2	–	–	–	–	–	–	–	1	Katakami et al. (39)
	IPASS	Asia	66	3	24	0	19	0.7	17	0.2	14	0.3	Mok et al. (40)
Erlotinib	DELTA	Japan	93	13	–	–	–	–	–	–	–	–	Kawaguchi et al. (41)
	JO22903	Japan	83	14	77	1	64	3	63	1	67	1	Goto et al. (42)
	JO25567	Japan	99	19	58	0	42	0	60	3	65	4	Seto et al. (43)
	WJOG5108L	Japan	92	18	–	–	–	–	–	–	–	4	Katakami et al. (39)
	OPTIMAL	China	73	2	–	–	–	–	13	1	4	0	Zhou et al. (44)
	EURTAC	Europe	80	13	–	–	–	–	–	–	–	–	Rosell et al. (45)
Afatinib	Lux-Lung 3	Japan	100	20	46	0	20	0	91	35	93[a]	26[a]	Kato et al. (46)
	Lux-Lung 3	Global	89	16	29	0.4	19	0.4	72	9	57	11	Sequist et al. (47)
	Lux-Lung 6	Asia	81	15	–	–	11	0.4	52	5	33	0	Wu et al. (48)

[a]These events are described as 'Nail events' in the literature.

phase III (BR21 and PA3) combined analysis data showed that the development of skin rash during the erlotinib treatment correlated with the survival advantage. The HRs for overall survival (OS) with development of ≥grades 1 and 2 skin rash were 0.41 ($P < 0.001$) and 0.29 ($P < 0.001$), respectively (15). The HRs for progression-free survival (PFS) with development of ≥grades 1 and 2 skin rash were 0.45 ($P < 0.001$) and 0.35 ($P < 0.001$), respectively.

Recently, a meta-analysis for the correlation of treatment efficacy and the development of EGFR-related skin rash was reported, which included 33 trials involving 6798 patients (50). This analysis revealed that the response rate (ORR) and disease control rate (DCR) were higher in patients with skin rash than those without it. The HRs of ORR and DCR were 3.28 ($P = 0.228$) and 1.96 ($P = 0.003$), respectively. The PFS and OS were also significantly higher in patients with skin rash than those without it. The HRs of PFS and OS were 0.45 ($P = 0.001$) and 0.40 ($P = 0.000$), respectively. However, there are several limitations to interpret this analysis. EGFR-TKIs are mainly prescribed for patients with activating EGFR mutation, and efficacy of EGFR-TKI is quite different between patients with activating EGFR mutation and wild-type mutation; hence, this analysis was neither limited to the EGFR mutation nor available for this information. The ethnicity and types of EGFR status or the other clinical background might also be heterogeneous. Thus, the relationship between efficacy and skin rash is not still confirmed, especially for patients with activating EGFR mutation.

Management and prevention of EGFR-TKI-associated skin rash

Skin rash is common among patients treated with EGFR inhibitors. Some guidelines to manage the EGFR inhibitor-associated skin rash are available (51–58). However, most of the statements are made from the expert opinion or consensus, case report, single-arm prospective trial or retrospective analysis, and only a few randomized trial data are incorporated in these guidelines.

Here, the author focused mainly on the preventive or reactive treatment of skin rash.

Sun protectant

EGFR signalling also plays an important role in the protection from UVB damage in skin. Previously, the prevention study (N05C4) with sunscreen was conducted (59). Fifty-four patients who were treated with EGFR-TKIs or anti-EGFR monoclonal antibody were randomly assigned to taking the sunscreen as a sun protection factor of 60 twice daily or placebo for 4 weeks. The incidence of the skin rash in 8 weeks was 78 and 80% in sunscreen and placebo, respectively ($P = 1.00$). The severity and patient-reported outcome were also similar. The preventive use of single agent of sunscreen did not have enough evidence to support for the prevention of EGFR inhibitor-associated skin rash. However, some trials included sunscreen as the usual skin care. Thus, sunscreen may be effective if combined with other methods.

Topical or systemic corticosteroid

Generally, topical steroid cream or ointment is prescribed for the treatment of EGFR inhibitor-associated skin rash, especially for acneiform rash. If patients experienced more severe skin rash, systemic dexamethasone or prednisolone is also prescribed. Unexpectedly, there is no randomized trial to evaluate the efficacy for treatment or prophylactic usage of the topical or systemic corticosteroid for the EGFR inhibitor-associated skin rash. These treatments are mainly acknowledged from the clinical experience, theoretical background (inhibition of releasing the cytokine or chemokine-mediated EGFR) or expert opinion. This treatment is already effective and prevalent. It would be difficult to conduct randomized trials in future.

Antibiotics

The efficacy of systemic or topical use of antibiotics was reported so far. There were several reports that the efficacy of systemic tetracycline, doxycycline or minocycline was evaluated for the treatment or prophylaxis for the EGFR inhibitor-associated skin rash (60–64). Topical nadifloxacin cream was also evaluated for the treatment of cetuximab-induced skin rash in the uncontrolled prospective study (65).

The first trial to evaluate the efficacy of oral minocycline was published in 2007 (61). This trial was conducted to evaluate whether proactive oral minocycline prevents the cetuximab-induced skin rash. In total, 48 patients were enrolled and assigned to the group, with 100 mg of minocycline once daily or placebo for 8 weeks. The numbers of lesions in face were significantly lower in patients receiving minocycline at weeks 1, 2 and 4. The lesion counts in the minocycline arm vs. placebo were 17.1 vs. 47.9 at week 1 ($P = 0.05$), 34.3 vs. 132.5 at week 2 ($P = 0.025$) and 61 vs. 110.2 at week 4 ($P = 0.008$),

respectively. The frequency of moderate-to-severe pruritus at week 4 was also significantly decreased in the minocycline arm than in the placebo arm (20 vs. 50%, $P = 0.05$).

Lacouture et al. (62) also conducted the open-label randomized phase 2 trial for patients with metastatic colon cancer receiving panitumumab (STEPP). Ninety-five patients were randomly assigned to receiving the proactive treatment consisting of skin moisturizers, sunscreen, topical steroid and doxycycline or reactive treatment, according to the severity of skin toxicity. The incidence of grade 2 or more skin rash during 6 weeks was 29% in the proactive group and 62% in the reactive group (odds ratio 0.3, 95% confidence limit 0.1–0.6). QoL was also less impaired in the proactive group.

Jatoi et al. (60) conducted a double-blind placebo-controlled randomized trial for patients treated with EGFR inhibitor including EGFR-TKI (N03CB). In total, 61 patients, including 8 gefitinib treatments, were assigned to the preventive tetracycline arm or placebo. The incidence of physician-reported skin rash was 70% in tetracycline and 75% in placebo ($P = 0.61$), although the incidence of grade 2 or more, or >50% surface area, at week 4 was significantly lower in the tetracycline arm (17%) than in the placebo arm (55%) ($P = 0.009$). Thus, tetracycline was suitable for prevention of EGFR inhibitor-related skin rash.

Recently, the results of two randomized trials were presented for the prophylaxis of only specified EGFR-TKI-associated skin rash (Table 3). One is the prospective trial for proactive usage of tetracycline for patients with afatinib, irreversible EGFR-TKI (63). Ninety patients who was taking 40 mg of afatinib daily were randomly assigned to taking 250 mg of tetracycline twice daily for 4 weeks (tetracycline group) or control group. The incidence of any grade of skin rash was significantly lower in the tetracycline group than in control group (44.5 vs. 75.6%, $P = 0.046$). The grade 2 or more skin rash was also significantly lower (15.6 vs. 35.6%, $P = 0.030$). The tetracycline arm neither impaired efficacy nor increased toxicity.

Melosky et al. (64) conducted the 'Pan-Canada rash trial'. This trial was a three-arm randomized trial for 150 NSCLC patients receiving 150 mg of erlotinib daily in two- or three-line setting to compare the efficacy of proactive usage of minocycline. Arm 1 received the prophylactic minocycline 100 mg twice a day with erlotinib. Arm 2 received the reactive skin rash treatment according to the toxicity grade. Arm 3 received the skin rash until toxicity was considered as severe (grade 3). The overall incidence of skin rash was comparable in all the arms (84, 84 and 82% in arms 1, 2 and 3, respectively). However, the incidence of grade 3 or more skin rash was 12% in arm 1, 8% in arm 2 and 28% in arm 3 ($P = 0.0455$, arm 1 vs. 3; $P = 0.0092$, arm 2 vs. 3), respectively. The mean time to onset of any grade maximum rash was 17.4 days in arm 1, 13.3 days in arm 2 and 12.0 days in arm 3 ($P = 0.0147$, arm 1 vs. 2 and 3), respectively.

Thus, preventive tetracycline and minocycline decrease the severe skin toxicity for patients with EGFR-TKI without impairing the survival and increasing any other toxicity. There is no comparison in these tetracycline classes of agent. However, doxycycline was suitable for patients with renal dysfunction and minocycline is less photosensitive in general.

The mechanism of these agents is not fully understood. This mechanism is expected not to come from the direct antibiotic effect because papulopustular rash is abacterial. These are considered from the anti-inflammatory effects as inhibition of mitogen-induced lymphocyte proliferation (66,67), suppression of neutrophil and lymphocyte chemotaxis (68,69), upregulation of anti-inflammatory cytokine interleukin (IL)-10 (70) and downregulation of IL-6 (71).

The efficacy of reactive topical therapy with nadifloxacin and prednicarbate cream was also evaluated for 29 patients treated with

Table 3. Randomized trial for EGFR-TKI-associated skin rash

Author	EGFR-TKIs	Intervention	Study drug	Observation	Patients (*n*)	Primary endpoints	Secondary endpoints	Results	References
Arrieta et al.	Afatinib	Preventive	Tetracycline 250 mg twice a day	4 weeks	90	Incidence of toxicity	Dose reduction rate Anti-tumour efficacy	Skin rash (all grades) 75.5% (control) 55.5% (preemptive) ($P = 0.046$) Skin rash (grade ≥2) 35.6% (control) 15.6% (preemptive) ($P = 0.030$)	(63)
Melosky et al.	Erlotinib	Preventive	Minocycline 100 mg twice a day	Until PD	150	Time to occurrence and incidence of rash	Survival	Rash (grade 3) 12%* (prophylactic) 8%** (reactive) 28% (control) Mean (days) to any rash onset 17.4 days*** (prophylactic) 13.3 days (reactive) 12.0 days (control)	(64)

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PD, progressive disease.
* $P = 0.0455$ (prophylactic vs. control).
** $P = 0.0092$ (reactive vs. control).
*** $P = 0.0147$ (prophylactic vs. combined reactive and control).

cetuximab-induced skin rash (65). The author concluded that this topical combination is effective for the majority of patients with a reduction of papules, pustules and erythema at weeks 1, 2 and 6.

Retinoid

Topical retinoids are prescribed for acne vulgaris. Retinoid binds the nuclear gene transcription factors, retinoic acid receptor (RAR) family. RAR-beta and mainly gamma are the prevalent receptors in keratinocytes. Retinoid induces the transcription of genes and activates the retinoid signalling pathway (72,73). Retinoic acid also induces the HBEGF and amphiregulin, which are ligands for EGFR. This theoretical background reduces EGFR inhibitor-induced skin toxicity (74). Three retinoid creams, isotretinoin, tazarotene and adapalene, are evaluated with other agents, so far.

Isotretinoin is 13-cis retinoic acid, and both pill and topical cream are used for severe acne vulgaris.

Bidoli et al. (75) preliminarily investigated the efficacy for the reactive use of isotretinoin and clindamycin for 56 NSCLC patients treated with erlotinib. Totally, seven patients with erlotinib developed grade 2/3 skin rash and received both oral clindamycin and oral isotretinoin. Six of seven grade 2/3 patients were effective, and the skin toxicity improved to grade 0/1 without severe adverse events. There are two case reports which showed benefits of the reactive treatment with oral isotretinoin for cetuximab-induced skin rash (76,77).

The efficacy of the preventive use of topical tazarotene was evaluated in the first minocycline trial in 2007 simultaneously (61). All enrolled patients used tazarotene on one half of face in each group. However, 33% of the patients discontinued tazarotene because of local irritation. In the evaluable patients, the total counts of rash on face by the photograph at week 4 was no difference between tazarotene arm and observation arm. Thus, tazarotene is not recommended.

Adapalene is also available for topical retinoid. Adapalene has the inhibition of proliferation of keratinocytes and comedolytic and anti-inflammatory properties from reducing the leukocyte migration and anti-cycloxygenase activity (73,78). So far, there is no prospective study result. Some case reports showed the efficacy of adapalene for EGFR inhibitor-medicated acneiform and periungual inflammation (79,80). The efficacy of reactive use of oral or topical retinoid is not fully investigated. Isotretinoin and adapalene, not tazarotene, may be effective for the acneiform rash. Further studies are needed.

Table 4. Strategy for the management of EGFR-TKI-associated skin rash

	Systemic	Topical
Prevention	Minocycline 100 mg twice a day Tetracycline 250 mg twice a day Doxycycline 100 mg twice a day	Skin care Moisturizer Sunscreen (do not use as single agent) Hydrocortisone 1% cream Use non-irritant products Education for skin care and evaluation Avoid alcohol-based lotion or cream and perfumed products Avoid long-time sun exposure
Treatment	Minocycline 100 mg twice a day Tetracycline 500 mg twice a day Doxycycline 100 mg twice a day Prednisolone 10 mg/day (need to re-evaluate after 2 weeks)	Steroid cream/ointment Face: strong class or higher class Body and extremities: very strong or strongest class Tacrolimus ointments Topical antibiotics Nadifloxacin cream and clindamycin gel Self-care with skin cleanness, protection and moisturizer

Table 5. Strategy for the management of EGFR-TKI-associated paronychia

	Systemic	Topical
Prevention	No recommendation	Self-care (hand protection, cleanliness, nail trimming, cushioning) Keeping dry and avoid soaking water long time (if necessary, putting on washing-up gloves) Emollient Avoid irritant Avoid trauma/ injury Avoid restrictive shoes
Treatment	If infection is concomitant, apply systemic antibiotics (cephems or minocycline)	Mild Washing and cleanness Helical taping Topical steroid: very strong or strongest class Topical antibiotics Adapalene gel Moderate to severe Cryotherapy with liquid nitrogen or surgical resection for over-granulation Surgical intervention (partial nail avulsion)

Vitamin K

Vitamin K3 (menadione) has a potential role in activating EGFR signalling for human skin keratinocyte cells and A431 human squamous carcinoma cells *in vitro* in a dose-dependent manner (81). There is an uncontrolled clinical trial to investigate the treatment usage of the topical vitamin K cream for EGFR monoclonal antibody-associated skin toxicity (82).

In total, 30 patients treated with cetuximab who developed any kind of grade skin toxicity were enrolled, and skin care with 0.1% vitamin K1 cream twice daily was performed. The improvement of skin rash was observed in all patients, and the median time for the improvement of skin toxicity was 8 days and median time to downgrading was 18 days.

Randomized control trials are ongoing to investigate the efficacy of prophylaxis usage of vitamin K cream for patients with cetuximab treatment (EVITA, NCT01345526). The prospective trial to clarify the efficacy of treatment or prophylaxis with vitamin K3 lotion for cetuximab-induced folliculitis is completed in January 2015. These results are warranted. Hence, there is no report for the efficacy of vitamin K against EGFR-TKI-associated skin rash.

Aspirin

Kanazawa et al. (83) investigated the efficacy of low dose of aspirin for gefitinib-induced skin rash. This group revealed that the serum concentrations of soluble P-selection and thromboxane B2 (TxB2) were significantly increased after patients received gefitinib. Hence, the blood concentration of TxB2 was significantly decreased when low-dose aspirin was taken together with gefitinib. They also investigated the effects of combining low-dose aspirin to gefitinib treatment. In total, 40 patients were recruited and 12 patients were taking low-dose aspirin with gefitinib. Skin rash occurred in 33.3% of the patients in the aspirin group and 74.1% in the non-aspirin group, respectively, without impairing the gefitinib efficacy. The authors assumed that platelet activation was related to efficacy and complication. The treatment of gefitinib induced platelet activation, and this activated platelet introduced TxB2 and P-selectin. P-selectin might be produced by COX-2 dependence. Low-dose aspirin impaired platelet coagulation by the inhibition of COX-1. Thus, low-dose aspirin decreases the incidence of gefitinib-related toxicity. However, the relationship between EGFR-mediated skin rash and the role of TXB2 and P-selection and platelet aggregation is not fully understood; further studies are required.

Management of paronychia

Paronychia is sometimes painful and may affect daily life. However, there was no prospective randomized trial for proving the efficacy of some kinds of medication for the prevention or treatment of paronychia.

Recently, proactive use of tetracycline was prospectively evaluated for patients treated with afatinib (63). The incidence of any grade of paronychia was 28.8 and 44.4% in the tetracycline and control arms, respectively ($P = 0.126$).

There is a case report indicating the efficacy of topical adapalene for periungual inflammation (84).

Thus, the guideline for the management of paronychia mainly described from the expert opinions.

Conclusion

The author summarized the upfront strategy for the management of EGFR-TKI-associated skin rash (Table 4) and paronychia (Table 5) from available evidence and Japanese expert opinion from consensus conference in 2014 (51).

Patient education from medical staffs as well as medication is also important, such as the assessment of EGFR-associated skin toxicities and self-skin care including moisturization, cleanliness and protectant from external stimuli before and during EGFR-TKI treatment. Thus, organizing multidisciplinary team including oncologists, dermatologists, nurses, pharmacists and other medical staffs is also helpful to overcome the EGFR-associated skin adverse events, and it is important to communicate closely between patients and medical staffs.

The management of EGFR-TKI-associated skin rash becomes easier than before because of the recent advance and more sufficient clinical experience. The strategy for the management of EGFR-TKI-associated skin rash is gradually established. However, there are not enough clinical data to support. Further studies are warranted to prove the efficacy of each treatment.

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