

Erlotinib-induced Adverse Skin Reactions

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Abstract: Erlotinib is low molecular-weight quinazolin derivatives which selectively inhibit the epidermal growth factor receptor (EGF-R) tyrosine kinase activity of the intracellular domain, block autophosphorylation and the subsequent signaling cascades. EGF-R is expressed on basal keratinocytes, sebocytes, the outer root sheath of hairs, and endothelial cells in the skin, and plays important roles in the regulation of differentiation, proliferation, apoptosis, attachment and migration of keratinocytes, inflammation, and wound healing. Therefore, inhibition of EGF-R causes a number of cutaneous adverse reactions. Among them, severe skin lesions are very stressful, and impair quality of life of patients. Moreover, they even bring disadvantages such as drug withdrawal or interruption. Several review papers describe representative or common skin lesions which appear either during the first a few weeks or at later phases. Common skin manifestations include papular and pustular follicular eruptions (acneiform eruption), xerosis, paronychia, pruritus, and abnormalities of hairs; however, other than those eruptions, several unusual lesions are also induced. Early intervention of dermatologists and management of skin lesions are quite important, because discontinuance of the drug is unfavorable for patients with clinical benefits for cancers. In this brief review, various cutaneous manifestations seen in Japanese patients treated with erlotinib (Tarceva) are shown, and current management of representative severe conditions is also described.

Keywords: EGF-R inhibitor, skin, side effect, erlotinib.

INTRODUCTION

Erlotinib is a novel oral tyrosine kinase inhibitor targeting the epidermal growth factor receptor (EGF-R) and it has been proven to be highly effective in the treatment of chemotherapy-resistant non-small cell lung cancer and pancreatic cancer. In the 75% of patients treated with erlotinib developed skin reactions, most of which developed within 3 weeks of starting erlotinib [1, 2]. The most frequent skin lesion is an acneiform eruption, but xerosis, paronychia, periungual granuloma, pruritus, hair changes, telangiectasia and hyperpigmentation are also known [3-5]. Additionally, uncommon mucocutaneous eruptions such as erosion, nodules, and purpura are also seen. Some of those eruptions appear within a few weeks of treatment onset, while others appear later. In this review, various adverse cutaneous reactions, not only representative but also less frequent conditions, are described which were triggered by erlotinib (Tarceva) in Fukushima Medical University in these 5 years.

PHARMACOLOGY OF ERLOTINIB

EGF-R is a member of transmembrane receptor tyrosine kinases family, encoded by the *c-erb-B* proto-oncogene. EGF-R consists of an extracellular ligand-binding receptor domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain. Erlotinib binds to the ATP-binding site of the tyrosine kinase domain of EGF-R, thereby inhibits the downstream signaling pathways for

cellular proliferation, motility, differentiation, and angiogenesis. In the skin, EGF-R is expressed by basal keratinocytes, sebocytes, the outer root sheath and some endothelial cells and plays a role in the normal differentiation and development of skin follicles and keratinocytes [6, 7]. EGF-R plays important roles in the regulation of differentiation, proliferation, apoptosis, attachment and migration of keratinocytes, inflammation, and wound healing. EGF-R signals are carefully regulated by inducible feedback inhibitors [8]. Therefore, inhibition of EGF-R causes a number of cutaneous adverse reactions [9]. For example, inhibition of EGF-R downregulates Ki-67 expression in the epidermis, due to reduction of keratinocyte proliferation [10].

SKIN MANIFESTATIONS

Skin rash is reported to occur in 75% of patients treated with erlotinib. The most frequently noted eruptions are papulopustular follicular eruptions (acneiform eruption), paronychia, pruritus, dry skin, hair changes, mucositis, and so on. Usually, folliculitis appears after a few (1 to 2) weeks after the initiation of therapies, and exacerbates thereafter [11]. On the other hand, several skin lesions such as paronychia as well as unusual or uncommon manifestations also occur with late onset.

Folliculitis (Acneiform Eruption)

Folliculitis is the most common side effect (48% up to 75%) exhibiting acneiform eruptions on the face, chest, back, and pubic region (Fig. 1) [12, 13]. Clinical presentations vary such as tiny pustules, inflammatory red papules, erythema with small pustules on the surface, and firm nodules. According to the guidelines of the American National Cancer Institute (Common Terminology Criteria for Adverse

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Fig. (1). A number of acneiform eruptions on the trunk.

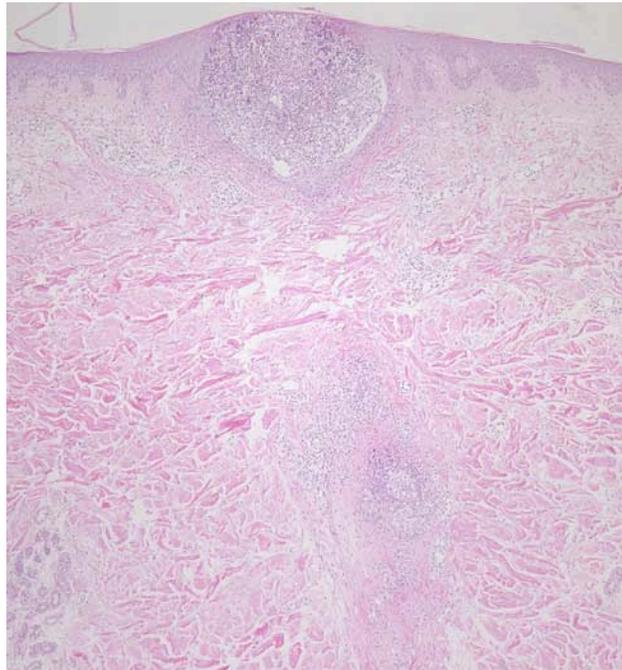


Fig. (2). A biopsy specimen from folliculitis shows intraepidermal neutrophilic abscess and perifollicular inflammation in the dermis.

Events (CTCAE)), rash is classified into Grade 1 (papules and/or pustules covering <10% of body surface areas, which may or may not be associated with symptoms of pruritus or tenderness), Grade 2 (papules and/or pustules covering 10-30% body surface areas, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL), Grade 3 (papules and/or pustules covering >30% body surface areas, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated), Grade 4 (papules and/or pustules covering any % body surface areas, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences), and Grade 5 (death). In general, rash development classified to grade 2 or higher grade is suggested to be a favorable reaction to highly respond with high clinical benefits and show prolonged survival duration [14-16]. On the other hand, Multinational Association of

Supportive Care in Cancer (MASCC) grading for papulopustular eruption adopts the objective measures (number of papulopustules, areas of erythema or edema <1cm in size), as well as health-related quality of life.

Erlotinib acts through competitive binding of the adenosine triphosphate-binding domain of the receptor, and inhibits the proliferation of various cancer cells. EGF-R is expressed in the basal layer of the epidermis, outer root sheath of the hair follicles, and sebaceous and sweat gland apparatus. Therefore, inhibition of EGF-R may result in abnormal epidermal differentiation leading to follicular obstruction and subsequent inflammation. Acneiform eruptions spare the previously irradiated skin, where hair follicles and sebaceous glands are destroyed [17, 18]. Although EGF-R usually does not exert effects on sebocytes [10], further studies are necessary. Biopsy specimens show cellular infiltrates containing neutrophils around the hair follicles, and also intraepidermal neutrophilic abscess formation (Fig. 2), which are preceded by T cell infiltration surrounding the follicular infundibulum [7].



Fig. (3). Paronychia and pyogenic granuloma on the fingernail.



Fig. (4). Scaly erythema on the forehead, around the eyes, and nasolabial areas, along with folliculitis.

Therapies are usually performed by topical clindamycin, metronidazole, nadifloxacin, and adapalene gel. In more severe cases, topical corticosteroids are not effective, and oral tetracyclines (minocycline or doxycycline) are used. Some patients present with severe follicular eruption, and are forced to stop the drug temporarily. Decrease of the drug, unless discontinuance, is the effective approach for relieving symptoms; however, folliculitis may deteriorate repetitively during the course. To date, several studies have been reported on the curative and preventive/prophylactic management of EGF-R inhibitor-induced folliculitis [19]. Although not randomized and evidence level is low, curative studies have shown that oral antibiotics are effective.

Administration of doxycycline (100 mg/day) resulted in a preventive effect for patients receiving elrotinib with grade

2-3 severity, compared with placebo (39% versus 80%) at 4 months [19]. Additionally, including various kinds of EGF-R inhibitors (erlotinib, cetuximab, panitumumab, gefitinib), several studies have examined the preventive effects of doxycycline (100mg) or minocycline (100mg) for 6-8 weeks, as well as topical hydrocortisone [20-23], some of which failed to show a statistically significant effect of tetracycline (500 mg twice a day for 4 weeks), as compared with placebo [20, 21]. In a STEPP trial including patients receiving panitumumab with grade 2-3, doxycycline (100 mg twice a day) reduced the incidence of grade 2 to 3 toxicity as compared with placebo (29% versus 62%) at the endpoint of 6 weeks [23]. Another study for patients receiving cetuximab showed that minocycline (100 mg/day) resulted in a favorable response at 4 weeks, rather than at 8 weeks. Steroid-induced prominent telangiectasia is sometimes seen on the face. In a prospective randomized trial, half-side test of proactive topical pimecrolimus treatment showed greater decrease in lesion numbers by the investigators' evaluation at weeks 2 and 5, whereas not significant by patients' assessment [24]. Overall, for patients with grade 2 or higher, topical hydrocortisone 1% cream combined with moisturizer and sunscreen, and oral minocycline (100mg/day) or doxycycline (100 mg/day) are recommended as a preventive therapy, and topical alclometasone 0.05% cream, fluocinonide 0.05% cream, or clyndamycin 1%, and oral doxycycline (100 mg/day), minocycline (100 mg/day) or isotretinoin (20-30 mg/day) are recommended for curative therapy [25].

Paronychia

Paronychia appears on the fingers and toes 1 to 3 months of erlotinib therapy, which occurs as painful erythema and occasionally develops pyogenic granuloma-like lesions (Fig. 3). Periungual redness and abscesses are observed in 40-50% of patients [26, 27]. Those changes are either triggered by nail-cut and minor trauma, or occur spontaneously. Bacterial infections develop at the nail lesions [28], which may be secondary, not primary event. Various therapies similar to ingrown nail are used, such as biotin intake, topical antibiotics, topical corticosteroids, silver nitrate, cryotherapy, electrocautery, and taping. Tetracycline is sometimes effective, which may be by inhibiting inflammation and reactive oxygen species, in addition to its antibiotic efficacy.

Seborrheic Dermatitis-like Eruption

Seborrheic dermatitis-like scaly erythema are observed on the face and trunk (Fig. 4), which may be intermingled with acneiform eruptions or xerotic eczema. Topical corticosteroids, calcineurin inhibitors, anti-fungal ointment, and metronidazole gel are used.

Xerosis

Dry skin with thin scales or pityriasis on the surface is frequently observed on the back and extremities in patients treated with erlotinib (Fig. 5), with ratios of 12 to 35 % in clinical trials [16]. Xerotic skin develops after 1 to 2 months from onset of erlotinib therapy. *In vitro* studies have shown that inhibition of EGF-R causes arrest of keratinocyte growth and initiates terminal differentiation [29], which may explain the clinical symptoms of xerosis. Patients are encouraged to moist their body by emollient creams.



Fig. (5). Xerosis with rippled-pattern scales on the back.



Fig. (6). Prurigo nodules on the buttocks.

Pruriginous Reaction

Prurigo-like lesions are sometimes seen on the lower extremities or buttocks (Fig. 6). Pruriginous eruption may be induced by scratching because of pruritus. Also, occurrence of acquired reactive perforating collagenosis (ARPC) is reported which was simultaneously developed with follicular eruption and paronychia [30]. ARPC is histologically characterized by necrobiotic basophilic collagen bundles which run transversely through the epidermis. Clinically, a number of umbilicated papules and nodules with central keratotic plugs develop on the trunk and extremities. ARPC is triggered by minor trauma, such as folliculitis, arthropod bites, and scabies infection. Koebnerization seems to play an important role. Scratching of patients suffering from pruritus may cause microtrauma and necrobiosis of the dermal structure. Insufficient blood supply as a result of vasculopathy may be associated as the underlying factor in ARPC. Follicular occlusion caused by altered differentiation of the epithelium due to inhibition of EGF-R may induce ARPC.

Eyelash Trichomegaly

Prolonged, curly eyelashes are sometimes seen after 7 weeks to 5 months, or other studies show mean duration of

173 days (Fig. 7). Trichomegaly is caused by premature maturation of the hair of the eyelashes. Prolonged eyebrow, curly hairs, and even the darkening of the hair may be simultaneously seen in a single individual [31]. EGF-R plays a role in the regulation of hair growth cycles, as a switch to begin and end the anagen phase of the hair cycle [32]. It is also suggested that hair growth speed is different depending on different location, such as hair, cheek, ear, eye, and trunk.

Alopecia

Alopecia has been reported in 5% of patients treated with EGF-R inhibitors after several months [9]. Abscess formation due to folliculitis on the scalp is occasionally seen (Fig. 8), which later results in, either non-scarring or scarring, alopecia. Histological examination of the scalp alopecia of patients treated with EGF-R inhibitors shows marked inflammatory infiltrate that consists of lymphocytes, plasma cells and some neutrophils and eosinophils [18]. Scarring alopecia showing an increased number of telogen and catagen hairs with perifollicular chronic inflammation and perifollicular fibrosis is also reported [33]. *In vitro* models have shown that the activation of the EGF-R is involved in triggering the transition from anagen to catagen [34]. EGF-R is appeared to be an important mediator in order to enter into

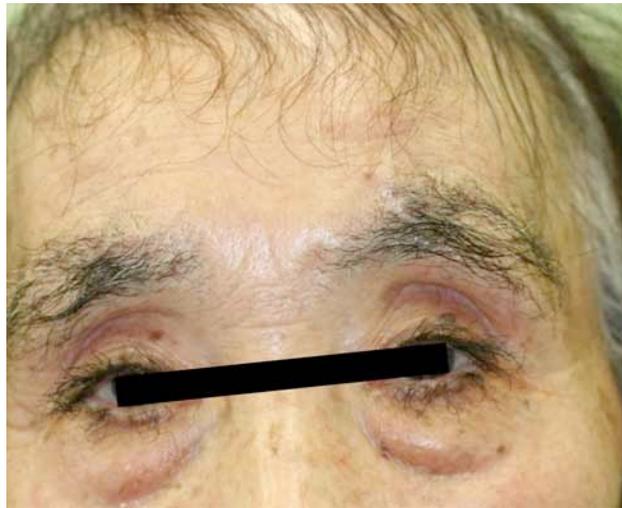


Fig. (7). Prolonged, curly eyelashes and eyebrows. Note that scalp hairs also show curling.



Fig. (8). Abscess with deep ulcers on the scalp.

the catagen stage for the regulation of hair cycle. Inhibition of EGF-R may result in the corruption of regulatory hair cycle and increased production of inflammatory mediators. EGF-R null mice exhibit alopecia [35], and skin graft from EGF-R null mice onto nude mice that express EGF-R shows follicles with an abundant inflammation and leads to alopecia by 10 weeks [36]. Frontal alopecia resembling male-pattern baldness is also seen [3, 37]. This type of hair loss can result from severe abscess on the scalp. Another possi-

bility may be that EGF-R modifies androgen hormonal signaling. Topical corticosteroids, minoxidil, and oral tetracycline for causative conditions such as severe folliculitis, are used.

Purpura

Purpuric drug eruption due to the EGF-R inhibitors is a rare skin reaction, which appear at later stages. So far, only few cases of purpuric eruption associated with erlotinib have



Fig. (9). Severe purpuric plaques on the bilateral lower legs. Xerosis is also seen.

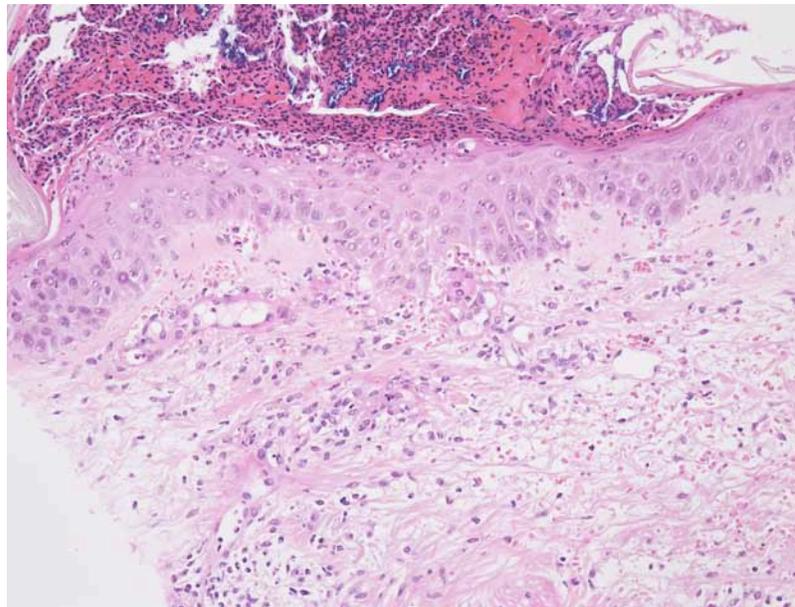


Fig. (10). Histological features of purpuric lesions showing subcorneal neutrophil infiltration, perivascular infiltration of inflammatory cells, fibrin deposition, and extravasation of red blood cells in the upper dermis.

been reported [37]. Purpura is most frequently seen on the lower extremities, and often associated with xerosis or folliculitis. Purpuras vary from pin-point tiny purpuras to severe purpuras coalescing large plaques mimicking Henoch-Schönline purpura (Fig. 9). Purpuric lesions are also seen on the trunk, intermingled with folliculitis and xerotic scales. Histologically, prominent extravasation of red blood cells, fibrin deposition in the blood vessels, and cellular infiltrates of lymphocytes and neutrophils are seen in the upper dermis (Fig. 10), but features of leukocytoclastic vasculitis are not observed. Inhibition of EGF-R on the endothelial cells of cutaneous vessels may contribute to induce minor vascular impairment and extravasation of erythrocytes, leading to purpuric eruption. On the other hand, EGF-R targeted ther-

apy affect the immune response with increased inflammatory cell chemoattractants. Perivascular infiltrations lead to vessel wall damage that results in ecstatic vessels and extravasation of erythrocytes [9]. Long after the condition of dermal congestion and platelet aggregation, extravasation may be induced and purpuric reaction occur eventually. Topical corticosteroids are usually chosen, and in cases of severe purpuric eruptions, dose-reduction or temporal withdrawal is needed.

Other Rare Skin Lesions

Painful aphthae appear on the oral mucosa, lips, and tongue (Fig. 11). If they increased in number, sometimes they disturb patients' quality of life. Superficial erosive lesions are observed on the buttock (Fig. 12). Also, painful



Fig. (11). Aphtha on the tip of the tongue.



Fig. (12). Erosions and superficial ulcers on the buttock.



Fig. (13). Erythema exclusively involving the umbilicus.

erosions may appear on the genital or anal regions. Eczematous eruptions with pruritus are often seen. Erythema on the umbilicus are rarely seen (Fig. 13), which may be included in seborrheic dermatitis. Otherwise, photosensitivity is reported in some patients, and development of xanthoma on the sun-exposed areas is also shown [38]. A recent study has

suggested a correlation between skin phototype and rash severity, and lower skin phototype may induce severe grade rash [39]. Furthermore, acute generalized exanthematous pustulosis characterized by severe generalized aseptic pustules has been reported [40].

CONCLUSION

Because the cutaneous toxicity is dose-related, the most effective way for the management of skin rash is the interruption of erlotinib. However, since the occurrence of skin rash is associated with the response rates and survival duration [1, 41], discontinuance of the drug is unbeneficial for the treatment of cancers. Thus, role of dermatologists is important to control skin rash tolerated, as long as the rash does not reach grade 3 (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL). Manuals of the management of skin lesions by expert opinion have been proposed, *i.e.* proactive treatments, or dose-escalation trial, depending on the severity grades, from different regions [42-48]. However, randomized control studies are still few, and for only limited and frequently seen conditions. We need to explore more effective treatments for cutaneous lesions, and further studies are necessary to investigate which type of skin eruption is the most relevant surrogate marker for clinical prognosis, or to compare the responders and non-responders among patients with cutaneous toxicities.

CONFLICTS OF INTEREST

The author confirms that this article content has no conflicts of interest.

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