

The Most Common Cutaneous Side Effects of Epidermal Growth Factor Receptor Inhibitors and Their Management

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ABSTRACT The use of epidermal growth factor receptor inhibitors (EGFRI) for the treatment of solid tumors is increasing due to elevated expression of epidermal growth factor receptors (EGFR) in the stimulation of tumor development. EGFR inhibitors have shown to be effective in the treatment of neoplasms of the head, neck, colon, and lung. Inhibition of EGFR may cause cutaneous reactions in more than 50% of patients. The most common skin manifestations are papulopustular lesions in the seborrheic areas (upper torso, face, neck, and scalp). Other cutaneous side effects include xerosis and hair and nail changes. The onset of eruption is usually within one to three weeks after starting therapy, although in some cases it may occur much later. All dermatologic side effects are reversible and generally resolve after adequate therapy. However, for a minority of patients side effects are severe and intolerable, demanding dose reduction or even interruption of therapy. A positive correlation has been demonstrated between the degree of cutaneous toxicity and the antitumor response. For dermatologists the goal is to provide treatment of symptoms, so that the patient may continue to benefit from the EGFRI therapy. However, frequent cutaneous manifestations, even though related to a better antitumor response, may limit use of the therapy considering the interference with patient quality of life. Early management of cutaneous side effects of EGFRI may prevent severe, extensive symptoms, the need for dose reduction, or antitumor therapy interruption. This indicates a dermatologist should play a role in early stages of treatment.

KEY WORDS: epidermal growth factor receptor inhibitors, papulopustular rash, xerosis, hair and nail changes

INTRODUCTION

Introduction of the new therapy modalities to oncology has led to new and specific cutaneous side effects. Among them, epidermal growth factor receptor inhibitors (EGFRI) in particular often present

with cutaneous toxicities. Over the past decade they have been used in the treatment of advanced malignancies, including cancers of the head and neck, brain, breast, lung, kidney, pancreas, colon, bladder,

and prostate (1). Epidermal growth factor receptors (EGFR) are 170-kD transmembrane glycoproteins of the tyrosine kinase growth factor receptor family ErbB (Erythroblastic Leukemia Viral Oncogene Homolog receptor) family, i.e. EGFR or Her-1, Her-2, Her-3, and Her-4. It is expressed in many normal human tissues, and takes part in the control of cell growth and differentiation. In some cancers the gene for EGFR (chromosome 7p12) is mutated/deregulated so EGFR become overexpressed on the cell surface (2). This overexpression can result in uncontrolled cell growth, proliferation, angiogenesis, and metastases, and is associated with a less favorable prognosis for those patients. EGFRs exert their therapeutic potential by targeting the EGFR-mediated signaling pathways in several types of cancer with overexpressed/hyperfunctioning EGFR for which they have become routine treatment (1,2).

Unlike standard chemotherapy, which affects most replicating cells, EGFRs are agents targeting pathways crucial for cancer cell growth and survival. Owing to this fact, this therapy has fewer systemic side effects in comparison with standard chemotherapeutic drugs but with a larger number of specific side effects. The majority of specific side effects derive from tissues dependent on the EGFR signaling pathway, such as the skin (3-5).

EGFRs are primarily expressed in undifferentiated, proliferating keratinocytes in the basal and suprabasal layers of the epidermis and in the outer layers of the hair follicle (6). Therapy with EGFRs leads to growth arrest, early differentiation (terminal differentiation markers STAT 3 and KRT 1 present in basal keratinocytes) and premature differentiation, which contributes to the formation of an impaired stratum corneum and results in an ineffective barrier (7). Furthermore, it can induce apoptosis either directly, or by triggering pro-apoptotic stimuli from inflammatory cells tending to accumulate in the affected area. All these events decrease the overall thickness of the epidermis – causing atrophy to take place (8).

Drugs targeting EGFR are monoclonal antibodies and low molecular weight tyrosine kinase inhibitors. Monoclonal antibodies, for example cetuximab or panitumumab, compete with the endogenous ligands (i.e. EGF – epidermal growth factor, TGF- α – transforming growth factor-alpha, etc.) and block ligand induced activation of the receptor tyrosine kinase. They also induce antibody-mediated receptor dimerization, resulting in down-regulation of the receptor. (4). In contrast, tyrosine kinase inhibitors, for example erlotinib or gefitinib, compete with adenosine triphosphate by binding to the tyrosine kinase part of the receptor and inhibit the receptor's

catalytic activity (1). The degree and incidence of skin toxicity correlate with dose and treatment duration of EGFRs (9-11).

Commonly occurring skin-specific side effects are papulopustular exanthema, dry skin, itching, hair changes, and nail alterations. With most of the patients these side effects are mild to moderate. They result in lower quality of life and are manageable. Severe toxicities (disabling, requiring hospitalization) lead to dose reduction and in some cases even therapy discontinuation (3).

SKIN-SPECIFIC SIDE EFFECTS OF EGFR

Papulopustular exanthema

Papulopustular rash is the most significant skin toxicity side effect. Pruritic, tender, erythematous papules and pustules develop on the skin with a high density of sebaceous glands – the scalp, face and upper trunk (Figure 1, Figure 2). Due to localization, this exanthema has a significant impact on the patient's quality of life and potentially on privacy during therapy (12). Pain, burning, and irritation are common symptoms affecting the majority of patients (3). The exanthema usually develops within the first 2-4 weeks of therapy. The pustular appearance of the typical exanthema is often mistaken for acne, acne-like, or acneiform eruption. Those terms imply a specific etiology and should therefore be avoided (11). Severe rash is more frequent with monoclonal antibodies than with low-weight molecule tyrosine kinase inhibitors. Within the first 6 weeks of treatment, topical corticosteroids combined with moisturizer, sunscreen, and tetracyclines are recommended. Doxycycline (100 mg bid for six weeks) is safe for use in patients with renal dysfunction, whereas minocycline (100 mg for eight weeks) is less photosensitizing and thus preferable in geographic locations with a high (seasonal) ultraviolet (UV) index (13). The beneficial effects of tetracyclines can be attributed to their anti-inflammatory and tissue-protective properties. These broad spectrum antibiotics reduce neutrophil chemotaxis and inhibit the production of proinflammatory cytokines and matrix metalloproteinase 9 (14,15). While the exanthema peak is between 4-6 weeks of EGFR therapy, postinflammatory skin alterations, erythema, and hyperpigmentations can last for months or years (16). In some studies, the subset of patients who did not develop rash was identified as that with the worst outcome. These findings suggest that a lack of rash after a significant period of therapy may be an early indication of treatment failure, requiring alternative therapy if available. Therefore some take rash for a surrogate marker of efficacy (17,18).



Figure 1. Papulopustular exanthema.

Xerosis

Abnormal keratinocyte differentiation takes place due to EGFRi therapy, resulting in atrophic stratum corneum with a decrease in protein which holds together the epidermal lorincrin. Therefore, the epidermis cannot preserve moisture, so xerosis occurs. Dry skin can turn into xerotic dermatitis (asteatotic eczema). This change usually occurs 30-60 days or more after starting therapy. Preventive modalities include oil baths in tepid water, regular application of fragrance-free moisturizing creams, avoidance of extreme temperatures and direct sunlight (19). Apart from the above-mentioned advice, treatment of mild or moderate xerosis includes: occlusive moisturizers, emollient creams, and creams with urea and vitamin K1; and for scaly areas: creams with low content of lactic acid, salicylic acid, or ammonium lactate. Special precaution is needed when treating the face, upper trunk, and hairy sites due to possible folliculitis, secondary to occlusion (5,20). In the most severe cases, where inflammation occurs due to xerosis, topical steroids are needed. Fissures and painful rhagades on the fingertips, palms, and soles represent a risk for infection. The main therapeutic approach includes wearing protective footwear or gloves, avoidance of friction, and appliance of moisturizers and emollients from the first day of EGFRi therapy. When eczema develops, topical steroids and antibiotics and in some cases hydrocolloid dressings are needed. Oral antibiotics are necessary only in rare cases when topical treatment has failed (21).



Figure 2. Papulopustular exanthema.

Radiation dermatitis enhancement

In patients undergoing both radiation and EGFRi therapy, high grade radiation dermatitis may occur. Direct injury to epidermal basal cells and connective tissue changes due to radiotherapy usually develop within the first few weeks of radiation treatment. Patients taking EGFRi therapy are at risk of more severe skin reactions. To avoid unnecessary skin toxicity, adequate radiation dosage and distribution should be given and verified. When treating radiation dermatitis, it is crucial to keep the treated area clean and dry, even when ulcerated (5,22). Eventually, high-potency topical corticosteroids should be used for the treatment. When skin infection is suspected, a thorough analysis should be performed and, if microbiologic etiology is proven, systemic therapy is indicated (1).



Figure 3. Diffuse alopecia.



Figure 4. Spontaneous regrowth after discontinuation of epidermal growth factor receptor inhibitors (EGFRi) therapy.

Pruritus

Pruritus is one of the most frequent side effects of this treatment; half of all patients taking EGFRi therapy have this unpleasant sensation. As pruritus usually develops with papulopustular exanthema, treatment modalities for rash usually worsen this condition (1). There are no specific clinical studies to evaluate therapy for EGFRi-induced pruritus. For mild to moderate itch, recommendations include antihistamines (non-sedating second generation), gentle skin care, and medium potency topical steroids (12).

Mucositis

Oral mucositis is a rare complication in patients treated with EGFRi, and can present as erythema or aphthous stomatitis. Other oral side effects include taste and salivary changes. As there are no trials for mucositis management, recommendations include thorough oral care, pain management (topical and systemic analgesics), and adequate nutritional support (23,24). Identification of concomitant oral infections such as candidiasis, herpes virus reactivations, or bacterial superinfections requires specific treatment (25).

Hair changes

Regulatory abnormalities in hair growth due to EGFRi depend on the type and localization of the hair. On the scalp and extremities, decreased growth and nonscarring alopecia occurs after months and years of therapy and may present with frontal and patchy patterns. With prolonged EGFRi therapy there is a tendency towards progression of the disease to diffuse alopecia (Figure 3). Generally, alopecia spon-



Figure 5. Thichomegaly.

taneously resolves after discontinuation of therapy (Figure 4). On the other hand, this therapy may lead to increased growth (hypertrichosis), distortion, and thickness of hair on the face and especially the eyelashes (trichomegaly) (Figure 5) (3,26). It seems that these changes are due to inhibition of EGFR, whose activation is required for progression from the anagen to the catagen phase, thus abnormally long and distorted follicles lead to the formation of long curly hair and eyelashes (3). As minoxidil has been found effective for treating nonscarring alopecia in the general patient population, it was administered to patients with alopecia provoked by EGFRi therapy. In women, significantly higher hair counts were found in groups treated with 2% and 5% minoxidil versus the placebo group. Higher incidence of pruritus and hypertrichosis was reported in the minoxidil 5% group (27-29).

Facial hirsutism and trichomegaly manifest during the first two months of therapy and tend to persist during the whole therapy with EGFRi. Therapy modalities include temporary or permanent hair removal. Abnormal eyelash growth can lead to cor-



Figure 6. Periungual inflammation – paronychia.



Figure 7. Onycholysis.

neal abrasions and ocular complications, and should therefore be treated by lash clipping every 2-4 weeks; if indicated, the patient should visit an ophthalmologist (30,31).

Alteration in periungual tissue

Periungual inflammation, also called paronychia, presenting with crusted lesions along nail folds, usually occurs after 4-8 weeks of EGFRi therapy (Figure 6). It is not an infectious phenomenon, although an occasional bacterial superinfection may occur; it is rather a foreign body reaction due to the penetration of nail plate fragments (3). Paronychia and periungual pyogenic granuloma-like lesions are one of the most frequent side effects of EGFRi therapy. Both fingernails and toenails may be affected, and trauma is an aggravating factor, rather than a causative one. Eames *et al.* have shown that a wide variety of Gram positive and Gram negative bacteria as well as *Candida albicans* (32) may be cultured from the nail lesion. Nail changes result in high morbidity for those patients due to severe pain, motion limitation, and impairment of daily activities (Figure 7, Figure 8). Preventive measures include wearing comfortable footwear and gloves, as well as avoidance of friction and trauma on the fingertips and toes. Topical treatment includes emollients, corticosteroids, and antimicrobial soaks, and if needed an anti-inflammatory dose of tetracycline to decrease periungual inflammation. In case of secondary infections, antimicrobial therapy and even surgery should be considered (3,32).

Hyperpigmentation

Rarely, patients develop progressive skin hyperpigmentation of postinflammatory origin after several months of receiving EGFRi therapy. Sun exposure worsens the hyperpigmentation, and histopathologi-



Figure 8. Onycholysis.

cal findings reveal an increase of pigment in the basal layer of the epidermis and phagocytized melanin in macrophages within the superficial dermis. To prevent the development of hyperpigmentation, patients should avoid sun exposure and use sun screen. Bleaching creams are not effective (1,14). Papulopustular eruptions and eczema caused by to EGFRi therapy should be treated promptly to avoid massive inflammation (5,33).

CONCLUSION

As EGFRi therapy is associated with many specific side effects, patients should be informed beforehand. Almost all side effects are temporary and will disappear several weeks to months after discontinuation of EGFRi therapy. Adequate preventive measures may decrease side effects to some extent, which will make patients cope better and minimize therapy reduction or discontinuation. With new approval for EGFRi therapy in oncology, dermatologists will confront more and more of these specific side effects. Cutaneous toxicities additionally aggravate the quality of life of these patients and may reduce compliance with this therapy. Thus, it is very important that we as dermatovenerologists effectively treat these side effects, encouraging patients to comply with EGFRi therapy.

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