

## Cutaneous adverse reactions specific to epidermal growth factor receptor inhibitors

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### Abstract

Classical antineoplastic therapy is encumbered by extensively studied adverse reactions, most often of systemic nature. The emergence of new generations of anticancer treatments, including epidermal growth factor receptor inhibitors, besides improving the response to treatment and the survival rate, is accompanied by the occurrence of new specific side effects, incompletely studied. These side effects are most often cutaneous (hand foot syndrome, acneiform reactions), and in some cases are extremely severe, requiring dose reduction or drug discontinuation. The prevention of the cutaneous adverse effects and their treatment require a close collaboration between the oncologist and the dermatologist. The occurrence of some of these skin adverse effects may be a favorable prognostic factor for the response to the cancer treatment and the overall survival.

**Keywords:** cutaneous adverse reactions, inhibitors of the EGF receptors, oncology

**Abbreviations:** EGFR = epidermal growth factor receptors; EGFRi = epidermal growth factor receptors inhibitors

### Introduction

New chemotherapeutic agents have the ability to specifically target cancer cells. They assure an increased survival and less systemic toxicities, compared to conventional cytotoxic chemotherapies [1,2]. Despite this, targeted chemotherapies have numerous cutaneous adverse reactions, which may cause serious discomfort and negatively affect compliance to treatment. The presence and severity of cutaneous adverse event have a positive correlation with the patient's response to treatment and overall survival, especially for epidermal growth factor receptor inhibitors [3].

### Epidermal Growth Factor Receptor Inhibitors

EGFR is a transmembrane tyrosine kinase receptor, whose overexpression causes gene amplification and mutation, leading to cell proliferation, cell survival, ability of invasion and metastasis, tumor-induced neoangiogenesis [4]. EGFR inhibitors are targeted chemotherapy agents approved for the treatment of many advance-stage epithelial cancers (non-small cell lung cancer, colorectal cancer, squamous cell carcinoma of the head and neck) [4,5]. There are two classes of EGFR inhibitors: **monoclonal antibodies** (cetuximab,

panitumumab, matuzumab) that bind to the extracellular tyrosine kinase domain of EGFR; and **small-molecule tyrosine kinase inhibitors** (gefitinib, erlotinib, lapatinib, afatinib) which target the intracellular domain [4]. EGFR inhibitors target aberrantly activated or overexpressed EGFR in tumor cells, causing cellular apoptosis by inhibiting metastasis, growth, proliferation, differentiation and angiogenesis [6]. EGFR inhibitors have a good safety profile compared with classical cytotoxic chemotherapies. They cause frequent cutaneous adverse events because EGFR is highly expressed in the skin and adnexal structures (mainly in the basal and suprabasal keratinocytes, the outer root sheath of hair follicles, sebaceous epithelium) [7]. The papulopustular rash and xerosis are the most common cutaneous adverse reactions. Less frequent, patients develop paronychia, abnormal scalp, facial hair, and/ or eyelash growth, maculopapular rash, mucositis and post inflammatory hyperpigmentation [7]. These adverse events can impair the patient's quality of life and adherence to treatment and in severe cases may require dose reduction or even temporary/ permanent interruption of therapy [8].

### Papulopustular rash

Papulopustular rash is the most common cutaneous adverse effect of EGFRi, which occurs in 80% of the patients early in the course of treatment [7,9].

Although terms like acneiform, acne-like and even acne have been used to describe this rash, it differs from acne from the clinical, histopathological and therapeutical point of view. The rash manifests itself by folliculocentric erythematous papules and pustules that predominately affect seborrheic-rich areas (scalp, face- particularly the nose, nasolabial folds, perioral region, upper trunk and "V" region of the neck and chest) [14]. The periorbital region and the palmoplantar surfaces are usually spared [16]. Unlike acne, there are no comedones, lesions can extend to the lower trunk, extremities and buttocks and can be associated with pruritus, pain, stinging, irritation [7,15]. The onset typically occurs in the first two weeks of treatment, but it can vary from as early as 2 days to as late as 6 weeks [7].

The rash evolves through four stages [22]

- First week: dysesthesia with erythema and edema
- Second and third week: eruption of papulopustular lesions
- Third and fourth week: crusts formation
- One month and longer: persistent erythema, xerosis and telangiectasia in the area affected by the rash

The evolution of the rash is characterized by waxing and waning of lesions. The vast majority of patients present partial or complete resolution of the lesions despite continuing the treatment with EGFI. Complete resolution can be seen 4 weeks after treatment discontinuation [23,24].

The rash may cause long-term cutaneous sequelae like post-inflammatory hyperpigmentation, telangiectasia and erythema [25].

EGFR are expressed in the undifferentiated basal and suprabasal keratinocytes, outer layer of the hair follicles and the sebaceous glands, with a critical role in regulating keratinocyte proliferation, differentiation, migration and survival [18]. The inhibition of this receptor results in reduced proliferation, diminished growth and apoptosis of keratinocytes, decreased cell migration and enhanced differentiation [19]. The inflammatory response mediated by keratinocyte-derived cytokines, recruits macrophages, mast cells and granulocytes [20]. This inflammatory response can be caused by the alteration of the growth and differentiation of follicular epithelium, which results in follicular occlusion, rupture of follicular infundibulum and neutrophils chemotaxis [21]. The initial lesion is a sterile neutrophilic suppurative infiltrate. Due to a compromised epidermal barrier, infection with *Staphylococcus aureus* can play a role in the late phases of the eruption, but the initial folliculitis is sterile [21].

EGFR inhibitors and radiotherapy have a synergistic anti-tumor activity, but radiotherapy increases EGFR side effects [44]. Papulopustular eruptions are dose dependent and those associated with monoclonal antibodies tend to be more frequent and severe compared with low-molecular tyrosine kinase inhibitors

[17]. Papulopustular rash could be a surrogate marker for efficacy of EGFR treatment [10-12]. Patients who developed a papulopustular rash while on erlotinib or gefitinib for non-small cell lung cancer had a lower risk of death (HR 0.30; 95% CI 0.21-0.43) and disease progression (HR 0.50; 95% CI 0.41-0.61) than patients without a rash [12]. Patients who developed more than one type of cutaneous toxicity proved to have an even better survival rate [26]. Increasing the dose for patients with grade  $\leq 1$  may improve the response rate to treatment [13].

As for all cutaneous adverse reactions, the severity of papulopustular rash due to EGFR are graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 4.0 (see **Table 1**) [27]: Grade 1: papules and/ or pustules covering <10% of the body-surface area (BSA) with or without symptoms of pruritus or tenderness, Grade 2: papules and/ or pustules covering 10-30% of the BSA with or without symptoms of pruritus or tenderness; with psychosocial impact, Grade 3: papules and/ or pustules covering >30% of the BSA with or without symptoms of pruritus or tenderness; limiting self-care activities of daily living, associated with local superinfection with oral antibiotics indicated, Grade 4: covering any percentage of the BSA with or without 4 Dermatology Research and Practice symptoms of pruritus or tenderness; associated with extensive super-infection with intravenous antibiotics indicate life threatening consequences, and Grade 5: Death Therapy can be divided into prophylactic and active treatment [35].

General measures include avoiding sun exposure, hot showers, lotions that contain alcohols, perfumed soaps and detergents and the use of broad-spectrum sunscreen with SPF >30 and moisturizing creams twice a day [35].

Prophylactic treatment with oral tetracyclines (doxycycline or minocycline each 100mg twice a day) together with low-potency topical corticosteroids twice a day on face and chest for 6 to eight weeks can be started in the same manner as the EGFR therapy [36].

The severity of the eruptions guides the approach to treatment [30-33,36]:

Patients with grade 1 eruption can receive low potency topical corticosteroids and topical antibiotics (clindamycin gel 1%; erythromycin gel/ cream 3%; metronidazole cream/ gel 0.75%-1%) twice a day for 4 weeks. Patients are reevaluated after 2 weeks, and if the eruption does not improve, they are treated as those with grade 2 eruption.

Patients with grade 2 rash require low potency topical corticosteroids twice a day on the face and neck and fluocinonide cream 0,05% twice a day on chest and back, in association with tetracycline (doxycycline 200mg per day or minocycline 200 mg per day) for 4 to 6 weeks. Doxycycline is safer especially in patients with renal impairment and minocycline is less photosensitizing.

If the patient was already on an oral tetracycline, he can receive a first generation oral cephalosporin (cephalexin 500mg twice per day, cefadroxil 500mg twice per day) or trimethoprim 160mg/ sulfamethoxazole 800mg twice per day for 4 weeks.

Patients are reevaluated after 2 weeks of treatment and if no improvement can be found, they should be treated as those with a grade  $\geq 3$  eruption.

Patients with grade  $\geq 3$  eruption, intolerable grade 2 rash, rash that interferes with self-care activities – adjusting the dose of EGFR inhibitors until the rash improves to grade  $\leq 2$ ; accompanied by oral antibiotics such as doxycycline 100mg twice per day or minocycline 100mg twice per day, first generation oral cephalosporin (cephalexin 500mg twice per day; cefadroxil 500mg twice per day) or trimethoprim 160mg/ sulfamethoxazole 800mg twice per day for 4 weeks in association with oral prednisone 0,5 mg/ kg up to a maximum of 40mg/ day for 7 days. Patients are reevaluated after 2 weeks of treatment.

Refractory grade  $\geq 3$  rash oral tetracycline are discontinued before starting low dose isotretinoin (20-30mg per day) for at least two months [30]. A significant improvement can be seen after 4 weeks [34]. Isotretinoin may cause or aggravate xerosis, photosensitivity and cheilitis. Emollients and photoprotection may improve some of these symptoms.

In case none of these measures show any improvement, dose adjustment, interruption or discontinuation of EGFR inhibitors could be taken into consideration.

Pruritus can be alleviated with oral H<sub>1</sub>antihistamines sedative or non-sedative [28], aprepitant (a neurokinin 1 receptor antagonist); GABA agonists (gabapentin, pregabalin) can be used in case oral antihistamines are ineffective [29]. Pruritus can also occur as a result of xerosis and general measures to prevent dryness should be employed.

## Xerosis and fissures

Xerosis is the second most common cutaneous adverse reaction to EGFR inhibitors that affects up to 35% of the patients [38]. It presents itself as dry, itchy, scaly patches mostly limited to regions affected by papulopustular rash, but tending to involve a larger surface area [17]. It can evolve with fissures of tips of fingers, toes, dorsal aspect of interphalangeal joints, and asteatotic eczema. Older people with personal history of eczema and prior exposure to cytotoxic therapy are more frequently affected [7]. Treatment requires topical emollients, short-term low-potency topical corticoids in case of asteatotic eczema. Disruption of the normal skin barrier can lead to superinfection with *Staphylococcus aureus* and rarely herpes simplex virus [37]. In case superinfection is suspected, cultures should be obtained and treatment with oral or topical antibiotics

instituted [37]. Fissures can be treated with hydrocolloid dressings, occlusive propylene glycol solutions or liquid cyanoacrylate glue [7].

## Hair changes

A variety of hair changes have been described in patients treated with EGFR inhibitors, such as trichomegaly (elongation and curling of eyelashes), hypertrichosis and scalp changes (brittleness, slow growth, scarring/ non-scarring alopecia) [7]. Hirsutism and trichomegaly are a rare side effect that develops after 2-5 months of treatment with EGFR inhibitors. They persist for the entire duration of the treatment. Eyelashes become wavy, curly and aberrant, and may cause corneal irritation and even ulceration [7]. They can be clipped at every 2-4 weeks, and patient who still experiences irritation can be referred to the ophthalmologist. Hirsutism can be treated with laser hair removal with/ without topical eflornithine cream [41].

Non-scarring alopecia appears after 2-3 months of treatment in the form of frontal or patchy patterns. It may progress to diffuse alopecia, and resolves after discontinuation of therapy, although the hair quality may not be the same. Minoxidil 2%, 5% can be employed in the treatment of non-scarring alopecia. Follicular pustules can cause scarring alopecia of the scalp, facial and chest hair. Prevention and treatment of papulopustular rash should be employed in order to prevent scarring alopecia. Treatment options include topical hydrocortisone 0.2%, steroid shampoos and class I steroid lotions [39], bath oils or mild shampoo followed by antibiotic spray [40].

## Nail changes

Nail changes appear after two or more months of treatment, typically in the form of paronychia (painful inflammation of the nail fold) and periungual pyogenic granuloma-like lesions [7]. Nail matrix inflammation can cause subsequent onycholysis and onychodystrophy. Paronychia is characterized by tender inflammation of the nail fold of finger and toes, due to the direct inhibition of keratinocytes in the nail matrix [7]. The first fingers and toes are most frequently affected. Paronychia is not an infectious process but has the potential to become superinfected [7]. Cultures may be necessary to determine the proper antibiotic treatment. Treatment is aimed at reducing periungual trauma and inflammation, preventing superinfections and eliminating excessive granulation formation. Topical corticosteroid, topical calcineurin inhibitors and oral tetracycline can reduce periungual inflammation [42]. Excessive granulation formation can be treated by electrocauterisation, silver nitrate and nail avulsion [43].

## Maculopapular rash

Maculopapular appears later than the papulopustular rash especially on the face and limbs. It is more pruritic, can become chronic and is accompanied by a dry pulpitis of the fingers, feet xerosis and photosensitivity. The treatment requires topical corticosteroids, antihistamines and sunscreen.

## Oral complications

EGFRI can cause mild to moderate mucositis, stomatitis, aphthous-like ulcers, xerosis of vaginal and perineal mucosa, that appear in the course of treatment and usual resolve themselves without specific intervention [22]. EGFRI can cause severe mucositis in combination with radiotherapy or cytotoxic agents [7]. Oral hygiene and a soft diet may prevent oral mucositis. Local anesthetics and antiseptics, mucosal-coating agents (magic mouthwash) and systemic analgesics can be used. Dose modification or treatment interruption can be necessary in case of severe mucositis.

## Conclusion

Cutaneous adverse reactions are common side effects of epidermal growth therapy having a significant impact on the patient's physical, emotional and psychosocial health and may affect compliance to treatment. Severe impairment requires dose reduction or temporary or definitive interruption therapy, preventing the complete administration of treatment at an effective dose and for an optimal period. Therefore, guidelines for prevention and management of these the skin toxicities of antineoplastic therapy must be established and implemented.

## Disclosure

None

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