Skin toxicities of targeted therapies

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Epidermal growth factor receptor (EGFR) inhibitors

Over the last few years, EGFR inhibitors have successfully joined the armamentarium of anti-cancer drugs with an increasing number of indications such as colorectal cancer, head and neck cancer, non-small cell lung cancer and breast cancer [1]. EGFR-targeted drugs consist of monoclonal antibodies to EGFR (e.g. cetuximab, panitumumab), small-molecule tyrosine kinase inhibitors specific for EGFR (e.g. erlotinib, gefitinib), dual kinase inhibitors inhibiting EGFR and HER2 (lapatinib), pan-erbB inhibitors inhibiting EGFR and other erbB receptors (canertinib) and other less specific inhibitors such as vandetanib inhibiting EGFR, vascular endothelial growth factor receptor (VEGFR) and RET [1].

Clinical picture

Probably owing to the abundant expression of EGFR in the epidermis and its appendages (hair follicles, sebaceous glands) [2], EGFR-inhibitors (biologics or small molecules, specific or less specific) are responsible for an entirely unique constellation of class-specific side effects on the skin occurring in most patients. Briefly, EGFR-inhibitor-induced skin toxicity consists of an acneiform eruption, skin dryness leading to eczema and fissures, nail changes, hair changes, telangiectasia, hyperpigmentation and mucosal changes [3–7].

Acneiform eruption

The most frequently reported side effect of EGFR inhibitors is a dose-dependent acneiform eruption, occurring in 50% to 100% of patients [4,8] (Figs. 1–3).

The eruption is more or less confined to the seborrheic areas (rich in sebaceous glands): the face (especially the nose, the cheeks, the forehead and the chin), the scalp, the neck and retroauricular area, the shoulders and the upper trunk (typically V-shaped reflecting the density of the sebaceous glands in that skin area). Sometimes the lower parts of the back, the abdomen, the buttocks and even the arms and legs can be involved as well whereas the palms of hands and soles of feet (containing no hair follicles) are spared [3,4,9–11].

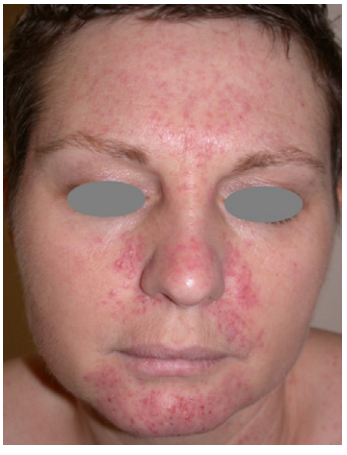

Fig. 1. Grade 2 acneiform eruption with erythematous papules and pustules on the face caused by an experimental EGFR-HER2 oral dual-kinase inhibitor.

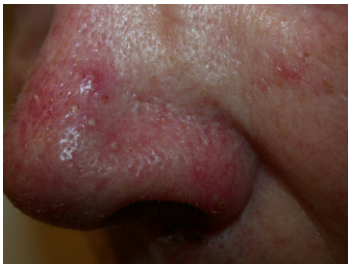

Fig. 2. Close-up of acneiform eruption (in a patient on erlotinib) with follicular pustules, erosions and telangiectasia on the wing of the nose.

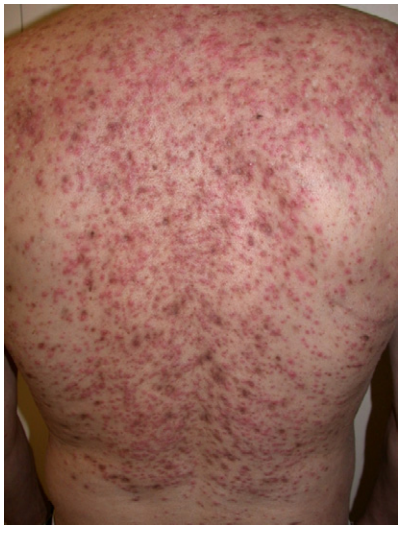

Fig. 3. Grade 3 acneiform eruption on the back with overt hyperpigmentation in a patient on cetuximab.

The eruption tends to be more severe and widespread with monoclonal antibodies than with oral tyrosine kinase inhibitors (for which gastro-intestinal toxicity is a dose-limiting factor) [11].

The skin lesions consist of sometimes itchy, erythematous follicular papules that may evolve into pustules. The pustules often have a flat shape and may confluate to lakes of pus that dry out with the formation of yellow crusts. The crusts may leave erosions when scratched off. In severe cases of acneiform eruption, the interfollicular epidermis may be inflamed as well in the form of acute exsudative dermatitis [4]. In other cases, a seborrheic dermatitis-like picture is seen on the face when the pustules leave an erythema covered with small greasy squames [12]. Rarely, the rash presents with an oedematous, warm erythema of the face mimicking an erysipelas [4].

The papulopustular eruption can appear just a few days (2–3 days for biologics, 7–10 days for small molecules) after treatment with the EGFR inhibitor, often reaching a maximum 2 to 3 weeks following initiation of therapy [13]. More rarely (11%), the rash occurs in a delayed fashion after the first 3 weeks of treatment. A slow spontaneous improvement of the rash is the rule when the EGFR inhibitor is continued even in the absence of dermatologic supportive treatment [14]. However, a flare up of the rash can occur following each infusion (in the case of intravenously administered monoclonal antibodies). The eruption generally disappears in a few weeks time when EGFR inhibitor treatment is discontinued, often leaving residual hyperpigmentation and xerosis [4].

Acneiform eruption by EGFR inhibitors is essentially sterile but the skin is markedly more prone to superinfection with *Staphylococcus aureus*, usually emerging from colonisation of the nose. Bacterial superinfection results in impetiginisation, in which gold- to yellow-coloured crusts dominate the clinical picture, or in bacterial folliculitis; the latter should be suspected in case of follicular pustules in non-seborrheic areas such as the (lower) arms or legs [4]. Very rarely, superinfection of the skin leads to severe systemic infections with *Staphylococcus aureus* [15].

Sun exposure is often reported to contribute to the development or flare-up of the acneiform rash [16]. Likewise, fair skin phototypes (pale eyes, red or blond hair) are much more prone to papulopustular eruption by EGFR inhibitors than individuals with dark skin.

Skin areas that previously underwent radiotherapy are characteristically spared from the acneiform eruption [17]. Concomitant cetuximab and radiotherapy on the other hand appear to increase the incidence of severe radiodermitis [18].

No relationship has yet been observed between the appearance or severity of the rash and a history of oily skin, acne or rosacea [4].

Nomenclature

EGFR-inhibitor-induced rash is acneiform, i.e. it looks like acne because of its follicular distribution in the seborrheic areas and its papulopustular morphology [4]. However, it should clearly be distinguished from acne vulgaris: indeed, comedones (blackheads and whiteheads) – the hallmark of true acne [19] – are lacking and so are nodules. Moreover, itchiness is not infrequent in EGFR inhibitor-induced acneiform but is absent in acne vulgaris. Finally, scalp involvement is rare in acne but frequent in patients receiving EGFR inhibitors.

The pruritus, speed of onset and scalp involvement also distinguish the EGFRI-induced acneiform eruption from acneiform eruptions caused by other drugs like systemic steroids [19].

Sometimes the facial lesions are accompanied by telangiectasia (see below), diffuse erythema and profound cutaneous tenderness, characteristics that are reminiscent of rosacea [19]. Some authors therefore consider the EGFR inhibitor-induced rash as a drug-induced rosacea. But the localisation outside of the face (which is extremely rare in true rosacea) as well as the possible itchiness differentiates it from rosacea.

Some authors use the term ‘folliculitis’ to indicate the acneiform papulopustular eruption in patients on EGFR inhibitors [20]. *Strictu sensu*, individual lesions can be considered as folliculitis, i.e. inflammation of the follicle. However, this term does not take

into account the specific distribution of the EGFR inhibitor-induced eruption in the skin areas with sebaceous glands (inflammation of the pilosebaceous unit in acne or rosacea is not called 'folliculitis' either). Moreover, 'folliculitis' is most commonly used to indicate infectious folliculitis (which is not the case for the papulopustular rash in patients on EGFR inhibitors). Therefore, we prefer not to use the term as it may lead to confusion.

Histopathology

Histology of papulopustular skin lesions shows an early infiltration with T-lymphocytes, which is quickly followed by a hyperkeratotic, ectatic appearance of the follicular infundibula and a florid, neutrophilic suppurative infiltrate [3,10,11]. Consequently, the most common picture is that of neutrophilic folliculitis and perifolliculitis. Intraepidermal acantholysis is sometimes present but the significance of this finding is unknown [3]. The pustules are notably sterile with negative cultures or staining for bacteria, fungi, yeasts (including *Malassezia furfur*) or Demodex mites [10]. The (pre-existing?) presence of *Propionibacterium acnes* or *Malassezia furfur* could only be demonstrated in a few exceptional cases [3].

Pathophysiology

The pathophysiologic mechanisms behind EGFR inhibitor-related skin toxicity have been extensively reviewed elsewhere [4,5] but remain largely elusive. Anyhow, dermatologic toxicities of EGFR inhibitors appear mechanism-based (i.e. linked to inhibition of EGFR in the skin) as they are 1/ observed with all EGFR-targeted drugs (antibodies, specific and non-specific tyrosine kinase inhibitors) but not with HER-2 inhibitors (trastuzumab), 2/ dose dependent, and 3/ similar to the changes seen in transgenic mice targeting cutaneous EGFR [4].

Classification

In clinical studies, the acneiform eruption caused by EGFR inhibitors is usually classified according to the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI-CTC v2.0) [21] or the more recent National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCv3.0) [22]. Only a small portion (most often less than 5%, but can be up to 18%) of the patients experience a grade 3 reaction. However, these criteria exhibit some shortcomings that do not always allow accurate classification of the skin rash. In this respect, version 2 attaches great value to body surface involvement which is, however, very difficult to score in a follicular eruption; version 3 introduces a special category on acneiform eruption that is at the same time very pragmatic and highly susceptible to interpretation [4]. A version 4 of NCI-CTC is currently being prepared, in which the item on acneiform eruption will allow more discriminative quantitative assessment. In addition, an alternative tool to quantify the severity of acneiform eruption by EGFR inhibitors has recently been proposed [23].

Xerosis, eczema and fissures

Patients receiving EGFR inhibitors often gradually develop a dry skin over weeks, resembling the xerosis in atopic eczema [4,12]. Old patient age, previous therapy with cytotoxics and a history of atopic eczema will accentuate the cutaneous dryness, which manifests with dry, scaly, itchy skin, especially of the limbs and skin areas that have been affected by acneiform eruption. The xerosis may develop into chronic asteatotic eczema. When secondary infection of the xerotic skin with *Staphylococcus aureus* occurs, a flare-up of acute oozing dermatitis and sometimes yellow crusting may be seen [4]. Rarely, the compromised epidermal barrier in these patients is the portal of entry for secondary infection with herpes simplex virus, manifesting with a monomorphous picture with numerous tiny vesicles. The fingertips and toes may develop a dry pulpitis with dry scaly eczema. Painful fissures may arise on the fingers (Fig. 4) and toes, mainly on the tips, the nail folds and

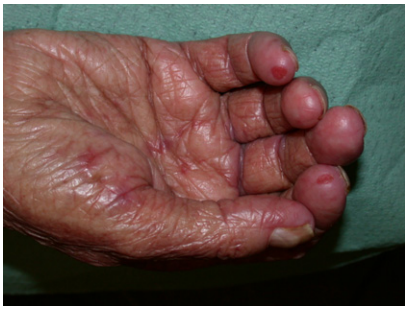

Fig. 4. Fissures on the fingertips and palm of the hand in a patient on panitumumab.

the knuckles [4]. Along with the xerosis, increased skin fragility and easy bruising are observed in patients receiving EGFR inhibitors [3]. Stoma patients receiving EGFR inhibitors tend to be more prone to peristomal dermatitis and bacterial superinfection.

Nail changes

Nail changes are seen in 10–15% of patients and usually do not start earlier than 4–8 weeks after

the initiation of the EGFR inhibitor [3,4,12,13,24,25]. Paronychia manifesting with inflammation of the nail fold (mainly of the big toe; other toes and fingers may be involved as well) is usually the first sign [3] (Fig. 5). This paronychia can be very painful and

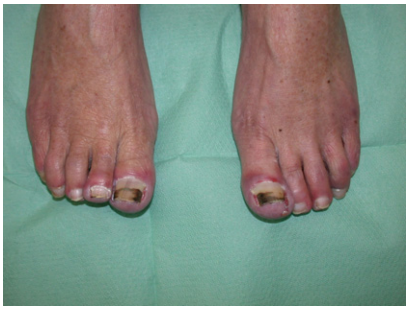

Fig. 5. Paronychia of the toenails in a cetuximab-treated patient.

mimics an ingrown toenail in the severe cases where pyogenic granuloma of the nail fold develops [4]. The paronychia is probably caused by horny material (caused by epidermal cell growth arrest and differentiation induced by the EGFR inhibitor) that gets stuck between the nail plate and nail fold and pricks, like a needle, into the nail fold [26]. Although the nail fold inflammation is initially sterile, superinfection with *Staphylococcus aureus* is not uncommon. In addition, painful fissures sometimes arise in the nail folds. The nails tend to grow more slowly; also, they are more brittle and sometimes crack [4].

Hair changes

During prolonged treatment with EGFR inhibitors, changes in body hair can be noticed. Very characteristic are the long, curly, rigid eyelashes, termed trichomegaly [27] (Fig. 6). The eyebrows become

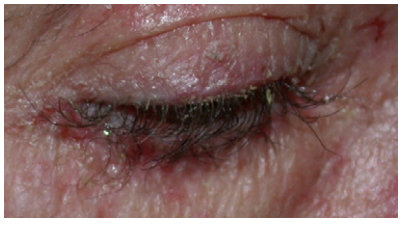

Fig. 6. Trichomegaly of the eyelashes and blepharitis caused by cetuximab.

thicker and more rigid as well, with lateral thinning sometimes. Rarely, the eyebrows extend to the lateral periorbital area or fuse on the midline. Scalp hairs grow more slowly and adopt a finer, more brittle and curly aspect [4]. Mild to moderate non-scarring alopecia of the scalp may also occur, sometimes in an androgenetic pattern. In addition, less shavings of the beard are required. Mild hair loss can be seen on the arms or legs whereas hypertrichosis with small vellus hairs may develop on the face and the female lip [4].

Telangiectasia

Early during the development of acneiform eruption, or sometimes with subsequent flare-ups of the rash, scattered telangiectasia may appear on the face, on and behind the ears, on the chest, back and limbs, and usually in the vicinity of a follicular pustule [4] (Fig. 2). This telangiectasia together with facial erythema, tenderness and follicular papulopustules in the absence of comedones creates a rosacea-like picture of the face. Unlike other telangiectasia, the lesions tend to fade over months usually leaving some hyperpigmentation [4].

Hyperpigmentation

Post-inflammatory hyperpigmentation is typically seen following acneiform eruption or other causes of skin inflammation such as eczema or an inflamed sebaceous cyst [4,24] (Fig. 3). Sun exposure aggravates hyperpigmentation.

Mucosal changes

Conjunctivitis can be seen, either due to dryness (xerophtalmia) or to mechanical irritation by trichomegalic eyelashes [28]. Dry mouth, apthous stomatitis [3] or a geographic tongue may be encountered in the oral mucosa. The genitalia are occasionally involved with dry vulvovaginitis (especially in postmenopauzal women) or balanitis.

Treatment and clinical management

General measures and treatment principles

As evidence-based controlled trials are still very sparse [29,30], treatment of EGFR-inhibitor skin toxicity mainly relies on reported personal experience [4–6,20,31–33], anecdotal or small series case reports [3] and recommendations from expert consensus conferences [34–36]. As a result, there are important geographical variations and even inconsistencies in the clinical management of EGFR inhibitor skin toxicity: e.g. with respect to acneiform eruption, topical corticosteroids are avoided in Europe [37] but are frequently used in the US [35].

Adequate sun protective measures (hat, clothes, sun blocking creams) are advised as sun exposure induces or aggravates acneiform eruption [16] and induces hyperpigmentation [4]. The patient is also instructed to avoid skin care products that dry out the skin (like

bath foam, shower gel, soap, very hot water) and to switch to bath/shower oil and lukewarm water. An emollient/hand cream can be used on the limbs and hands to prevent xerosis and fissures, especially after a bath/shower, swimming or sauna. The use of greasy ointments on the face and trunk is avoided as this may aggravate acneiform eruption [38].

The right vehicle choice is essential to successful topical treatment of EGFR inhibitor skin reactions. For an acute pustular or oedematous reaction, drying vehicles like compresses, gels or oil in water creams can be used but emollient ointments are inappropriate as they occlude the skin pores and thus worsen follicular inflammation. In the chronic stage of eruption with dry, flaky skin, drying vehicles need to be switched to a rich water in oil cream or an ointment to prevent xerosis. Therefore, topical treatment is tailored to the situation of the individual patient and may change during time, meaning that there is no topical treatment scheme that is universally applicable for all patients at all times [38].

When an EGFR inhibitor (e.g. cetuximab) is combined with radiotherapy (e.g. for head and neck cancer), the management remains unaltered as the abovementioned therapies are not interfering with radiotherapy [39].

Recently, increasing attention has been paid to prophylactic treatment of acneiform eruption, as it occurs in 80% of patients on EGFR inhibitors. Recent studies demonstrated that preventive use of minocycline 100 mg qd [29], oral tetracycline 500 mg bid [30] and a regimen consisting of doxycycline 100 mg bid, topical hydrocortisone 1%, emollients and a sunscreen decreased severity of acneiform eruption. However, as only around 10% of patients develop severe reactions (benefitting most from prophylactic treatment) and most of the patients respond reasonably well to reactive treatment, there is no reason to adopt such a strategy. Moreover, prophylactic treatment might result in loss of skin toxicity as an efficacy marker [38].

Treatment of acneiform eruption

For the authors, topical metronidazole and oral minocycline are the standard of treatment. As a topical therapy, metronidazole is preferred (as a 2% preparation in cetomacrogol cream or as 0.75% Rozex® cream) because of its mildness, as it is normally used for the very sensitive skin of rosacea patients [38]. Topical anti-acne agents such as erythromycin, clindamycin and benzoylperoxide are effective [31,34] but much more aggressive as they are meant for young resilient acne skin. Moreover, EGFR inhibitor-induced acneiform eruption of the face probably shares more characteristics with inflammatory rosacea than with acne. Topical metronidazole can be used twice a day or in between as needed on the first appearance of papulopustular lesions. Topical retinoids (adapalene, tazarotene) are used by some but lack rationale (no comedones). Moreover, tazarotene was recently shown to be ineffective and too irritating for the facial skin in a left-right comparison study [29]. Topical corticosteroids should be avoided on the face and on the trunk as the possible risks in those areas (induction of steroid rosacea or acne, atrophy, telangiectasia, chronic abuse with tachyphylaxis and steroid dependence) outweigh the advantages [38]. For papulopustular lesions on the scalp, an exception can be made as this skin site – in contrast to the face, chest and upper back - is quite resistant to local steroid side effects. Calcineurin antagonists (tacrolimus or pimecrolimus), being used as first-line therapy in some American centres [40], are effective but their use is hampered by skin irritation and a high price (off-label and not reimbursed). Topical menadione (vitamin K3, an EGFR phosphatase inhibitor with promising preclinical properties) [41] is not yet available for clinical use and it is uncertain whether it will meet expectations. We also instruct patients to stick to the prescribed topical treatment and discourage the use of all kinds of over the counter products that are marketed for skin irritation (e.g. tea tree oil), which very often cause contact allergy [38]. Camouflage techniques have been used with success to hide the skin changes provoked by EGFR inhibitors [20]. However, they are not advised in the acute phase of the rash (occlusive effect).

Acneiform eruption-associated itchiness can easily be controlled with an oral antihistamine of choice (e.g. cetirizine, loratadine, hydroxyzine). The initiation of oral tetracyclines is mostly based on clinical judgement (insufficient response to topical metronidazole, extensive disease). The preferred type of tetracycline may vary. Minocycline 100 mg qd is our cycline of choice but it is avoided by some because of the rare occurrence of drug-induced lupus, hepatitis or hyperpigmentation. Doxycycline 100 mg qd (may cause photosensitivity) or lymecycline 300 mg qd are alternatives. Like metronidazole, tetracyclines are not administered for their antibiotic properties but rather for their anti-inflammatory properties; usually they are given for months. In case of severe grade 3 reactions, the tetracycline dose is doubled until a grade 2 is reached again [38]. For grade 3 reactions with numerous or confluent pustules, extensive exsudation or marked oedema, saline compresses (15 minutes for two to three times a day) are very helpful for rapid

clearance of the inflammation. Compresses dry out the skin very effectively. Therefore, they should only be applied for a limited duration of time (a few days) and each application should be followed by repeated application of metronidazole cream [38].

Acneiform eruption by EGFR inhibitors is essentially sterile but the skin is highly prone to superinfection with *Staphylococcus aureus* [4]. As tetracyclines are rarely active against *S. aureus*, a penicillinase-resistant penicillin (e.g. flucloxacillin 500 mg tid) or cephalosporin (e.g. cefuroxim axetil 500 mg bid) can be added for 5 days; usually a swab is taken so that the antibiotic can be switched accordingly in case of resistance. Superinfection with herpes simplex virus is rare but requires oral (e.g. aciclovir, valaciclovir) or intravenous (aciclovir) antiviral drugs [38].

In case of a grade 3 reaction, dermatologic treatment is given while continuing the EGFR inhibitor at an unchanged dose; a re-evaluation then takes place after 1 week. Very often, a grade 3 acneiform eruption improves so rapidly on dermatologic therapy that there is no need for dose adjustment or interruption of the EGFR-inhibitor. Only in rare cases (<5% of cases) where a grade 3 reaction is more persistent, despite appropriate dermatologic support, should consideration be given to lowering (or interrupting) the dose of EGFR inhibitor in order to achieve a decrease in skin toxicity grading (personal experience) [38].

Despite its efficacy for EGFR inhibitor-dependent rash, we plead against the use of oral isotretinoin as it may possibly interfere with EGFR-inhibitor anti-tumour activity by downregulating EGFR expression. Moreover, isotretinoin shares a large number of side effects with EGFR inhibitors (xerosis, sensitivity for *S. aureus* superinfection, paronychia, pyogenic granuloma), which may lower tolerability. Systemic steroids are also to be avoided in the treatment of acneiform eruption as they may induce a similar eruption themselves; in addition, they may hamper the antibody-dependent cell-mediated cytotoxicity that is ascribed to EGFR-antibodies [38].

Treatment of xerosis, eczema and fissures

Skin xerosis obviously benefits from the general hydrating measures described above. In addition, an appropriate vehicle choice is indispensable. In this respect, alcoholic lotions or gels for treating acneiform eruption should be discouraged in favour of oil in water creams (e.g. metronidazole cream) and saline compresses for severe rash should be limited in time. On the limbs, greasy (water in oil) creams or even ointments can be used for moderate to severe xerosis. The right balance should, however, always be kept since occlusive ointments may facilitate the development of folliculitis lesions [38].

When eczema is present, a topical weak to medium strength corticosteroid cream is recommended for a short term (1 to 2 weeks). Salicylic acid can be added to the steroid when fingertip eczema is present. When the eczema becomes wet, superinfection should be suspected and a swab for bacterial (or viral) culture can be taken. Treatment with topical (e.g. fusidic acid) or, in severe cases, systemic anti-*S. aureus* antibiotics can be added for 5–10 days (e.g. flucloxacillin 500 mg tid or cefuroxim axetil 500 mg bid). In the rare case of herpes simplex virus superinfection, treatment with systemic antiviral drugs is necessary [38].

Fissures can be treated with propyleneglycol 50% aqueous solution under plastic occlusion (daily for 30 min), salicylic acid 10% ointment, a hydrocolloid dressing or liquid cyanoacrylate glue [38].

Treatment of paronychia

Paronychia is often very distressing and painful for patients as it can impede walking and normal use of the fingers. Unfortunately, paronychia is also very challenging to manage as no treatment yields complete relief. Wearing shoes that are not too tight is an important preventive measure to minimise friction and pressure on the nail fold. Paronychia caused by EGFR inhibitors is not infective in nature but renders the nail folds very sensitive to infection [4]. Therefore, antiseptic (e.g. chloramine, polyvidon iodine) soaks or creams are advised on a daily basis. When superinfection is suspected, swabs can be taken and oral anti-*S. aureus* antibiotics (e.g. flucloxacillin) given. Using an ultrapotent topical steroid cream on the nail folds (possibly under occlusion) at the earliest signs of paronychia may prevent it from worsening. On settled paronychia, a drying paste containing an antiseptic (e.g. chlorhexidine), an anti-yeast (e.g. nystatin) and a potent topical corticosteroid can be helpful in alleviating symptoms [38]. Oral tetracyclines can be helpful as well in treating paronychia [42]. Oral non-steroidal anti-inflammatory drugs can be administered to control the pain. Silver nitrate application on a weekly basis improves pyogenic granuloma. Despite the clinical appearance mimicking an ingrown nail, partial nail bed excision has no effect on EGFR inhibitor-caused paronychia. Total nail extraction with destruction of nail matrix cures the paronychia but the permanent loss of the nail limits the usefulness of this technique. In severe, recalcitrant cases, interruption of the EGFR inhibitor may be considered; but just as it takes many weeks for the paronychia to appear after

Table 1
Overall survival (months) correlated with severity of rash [43]

	N	Grade 0	Grade 1	Grade 2	Grade 3	Log-rank p*
9923/CRC	120	4.3	6.2	10.6	13.1	0.0008
0141/CRC	57	2.4	6.4	6.4	10	0.04
9816/SCCHN	78	2.0	5.5.	6.7	4.1	0.0002
9814/Pancreas	41	2.3	5.7	8.0	13.9	0.0007

*Grade 0 versus Grades 1–3

the start of therapy, paronychia may take weeks to improve after cessation of the EGFR inhibitor [38].

Treatment of hair changes, hyperpigmentation and telangiectasia

Eyelashes that cause conjunctival irritation due to their excessive length can be trimmed. Hypertrichosis is treated with eflornithine cream or by laser epilation.

Sun protection and adequate treatment of acneiform eruption and eczema are most important to avoid subsequent hyperpigmentation [38]. Bleaching creams are not very helpful but camouflage by a beautician can help to correct the skin colour [20]. Left untreated, the hyperpigmentation may fade spontaneously over months.

Telangiectasia caused by EGFR inhibitors will also gradually disappear over months. Therefore, electrocoagulation or pulsed dye laser therapy are only rarely applied to accelerate disappearance. Excellent results can also be achieved with camouflage [20].

Treatment of mucosal changes

Xerophtalmia, conjunctivitis and blepharitis can be managed with artificial tears, trimming of the eyelashes, topical antibiotics and topical corticosteroids (eye drops or ointment). When superinfection with *S. aureus* occurs, a swab is taken and an oral antistaphylococcal antibiotic can be added. Refractory cases should be sent to an ophthalmologist as complications such as corneal ulcers may occur [28].

Tetracycline or antiseptic mouthwash alleviates stomatitis symptoms. For aphtous ulcers of the mouth, topical steroids or anaesthetics can be used.

Dryness of the nose or the vagina responds fairly well to lubricants or ointments containing an antibiotic or antiseptic [37].

Nursing perspective

Although most of these side effects, such as skin toxicity, are not life-threatening and rarely necessitate the cessation of EGFR inhibitor therapy, there is a clear medical need for supportive treatment and timey dermatological referral, if severe. Also, psychosocial support is important, as the rash usually affects the skin of the face and this sometimes has a dramatic impact on patients' self-esteem and quality-of-life.

Appropriate education of patients is needed and nurses again play a pivotal role: explaining skin problems, the general measures that can be taken, and the do's and do not's that help manage the skin problem. A nurse is also the first person the patient should contact in case of concern. The oncologist also has an important role: while mild to moderate cases of skin toxicity can be well managed by standard treatment, patients with severe skin toxicity must be referred to a dermatologist. So the approach is multidisciplinary and all players on the field need proper education and training to help patients understand and cope with these toxicities.

As the number of patients treated with EGFR inhibitors is increasing rapidly in European oncology centres it is essential that existing knowledge and experience about managing these side effects is rapidly disseminated.

Associations with outcome of therapy, predictive role

Intriguingly, there is some evidence to suggest positive correlations between the severity of skin toxicity and outcome measures [4,34,38]. Most of the published data have shown that patients in whom skin toxicity develops show a higher response rate than those without rash and significant correlations between occurrence of rash and increased survival have been found, with a trend towards improved overall survival and longer progression-free survival with increasing severity of rash. Several attempts have been made to systematise data and present potential correlations between cutaneous manifestations and clinical efficacy of targeted agents. Back in 2003–2004, Perez-Soler and Saltz [43,44] reviewed ongoing clinical trials and extracted relevant information as reported by authors (Table 1). Since then, several randomised and pivotal studies, although not designed to prove this

Table 2
Response, time-to-progression and overall survival correlated with the severity of rash after cetuximab and irinotecan in irinotecan refractory metastatic CRC (BOND study) [8]

Maximum grade of skin reaction	No. of patients (percentage)	Response (%)	mTTP (months)	mOS (months)
Grade 0	32 (14.7%)	6.3	1.4	3.0
Grade 1	58 (26.6%)	8.6	1.5	6.5
Grade 2	99 (45.4%)	27.3	4.2	10.3
Grade 3	29 (13.3%)	55.2	8.2	13.7

mTTP: median time-to-progression; mOS: median overall survival.

Table 3
Overall survival correlated with skin rash after cetuximab in chemorefractory CRC [47]

	Worst ever grade of rash (LTA1) OS (months)	Worst grade of rash by day 28 (LTA2) OS (months)
Grade 0	2.6 months	4.3 months
Grade 1	4.8 months	4.6 months
Grade 2+	8.4 months	9.1 months
HR: Gr. 2+ vs Gr. 0	0.33 (95% CI 0.22–0.50; $P < 0.001$)	0.52 (95% CI 0.37–0.74; $P = 0.0002$)
HR: Gr. 2+ vs Gr. 1	0.54 (95% CI 0.41–0.72; $P < 0.0001$)	0.53 (95% CI 0.39–0.72; $P < 0.0001$)

OS: overall survival; HR: hazard ratio; gr: grade; vs: versus; CI: confidence interval.

correlation, reported trends of association between the severity of skin toxicity and clinical outcome (i.e. response rates, progression-free and overall survival) based on retrospective analyses.

Similar observations were shown by the BOND study [8] where correlation with response rates was noted in colorectal cancer (Table 2).

The CO-17 trial [45,46] demonstrated that cetuximab monotherapy (versus best supportive care) improved overall and progression-free survival and maintained quality-of-life in patients previously treated for advanced colorectal cancer that expressed the EGFR. All analyses demonstrated a strong correlation between rash development and clinical benefit in colorectal cancer patients treated with cetuximab (response and survival).

The time factor in evaluating the occurrence of skin manifestations was taken into consideration in two exploratory landmark-type analyses (LTA 1 and 2). In patients who received cetuximab and experienced rash, the median time to onset of rash was 10 days and 90% experienced a rash within 29 days. The hazard ratio (HR) of overall survival between the "rash" and "no rash" groups was 0.58 (95% confidence interval (CI) 0.38–0.87; $P = 0.009$). The median overall survival and corresponding HR from the two landmark-type analyses are presented in Table 3.

More recently, the CRYSTAL study [48] reiterated the association between the severity of rash and progression-free and overall survival but not with response in K-Ras wild type patients with metastatic colorectal carcinoma in a first-line setting. Early rash (at 21 days of treatment) was considered in this analysis (Table 4).

These observations suggest that skin toxicity could be an important clinical surrogate marker of efficacy of cetuximab. However, prospective studies designed to test these correlations and multivariate models to account for confounding factors are still to be developed.

Furthermore, as a logical next step, whether the severity of initial cutaneous manifestations is indeed predictive of outcome, some strategies for dosing EGFR inhibitors in individual patients to a level that causes detectable skin rash are being studied and developed. Some research groups state that the rash is a surrogate indicator of an adequate degree of receptor saturation by cetuximab [50]. However, dose escalating studies in an attempt to achieve a desired level of skin toxicity are showing contradictory results.

The Everest study [51] evaluated the effect of cetuximab dose escalations on activity and skin rash. One hundred and sixty six patients with EGFR-

Table 4
Analysis of progression-free and overall survival according to the highest grade of acne-rash during the first 21 days of treatment in the cetuximab + FOLFIRI group of the Crystal study [48,49]

	Worst grade of acne-like rash during the first 21 days of treatment (K-Ras wild type only)	
	No rash (Grade 0)	Any rash (Grade 1–3)
N	59	108
Median PFS (95%CI)	7.5 (6.7–12.6)	10.5 (8.8–14.2)
N	63	109
Median OS (95%CI)	20.5 (12.9–26.5)	25.7 (22.4–31.7)
N	61	109
Best response (95%CI)	59% (45.7–71.5)	60.6% (50.7–69.8)

PFS: progression-free survival; OS: overall survival; 95%CI: 95% confidence interval.

expressing, irinotecan-refractory metastatic colorectal cancer participated in this randomised, multicentre trial. All patients received 3 weeks of standard treatment with cetuximab and irinotecan. Patients showing no rash or rash grade 1 were randomised to continue with the standard regimen or to follow a dose escalation schedule of cetuximab (up to 500 mg/m^2 every 2 weeks) until severe rash occurred. Results showed that cetuximab can be safely scaled up to 500 mg/m^2. A modest increase in worst grade skin toxicity was observed as well as a trend towards increased response in the dose increase group (30% versus 13%).

Another smaller study of 26 patients with solid tumours, run in 2008 [52], attempted to boost up the response rate by dose escalating cetuximab to 400 mg/m^2. Grade of rash was not dose dependent using the CTCAE v3.0 and did not correlate with response in this limited cohort.

Panitumumab is another monoclonal antibody targeting the EGFR indicated in chemorefractory colorectal cancer. Studies of panitumumab have also shown associations between skin toxicity severity (clinical toxicity grading) and response rate, progression-free and overall survival [53,54].

A pooled analysis from five clinical trials (four phase II studies and one phase III study) by Berlin and colleagues [55] examined the association between severity of skin toxicity and panitumumab efficacy in metastatic colorectal cancer progressing on or after 5-fluorouracil (5FU)-, oxaliplatin- and/or irinotecan-based regimens. Patients received panitumumab 6 mg/kg every 2 weeks (Q2W) or 2.5 mg/kg weekly (QW) until disease progression or intolerability. Tumours were assessed using modified World Health Organisation (WHO) or RECIST criteria (blinded central review in 4/5 studies). Endpoints included objective response rate (ORR), progression-free survival, and overall survival. Progression-free and overall survival were measured from enrolment. Only patients with at least two infusions (exposure over 2 weeks for QW dosing or over 4 weeks for Q2W dosing) were analysed to help correct for lead-time bias. 612 of 640 patients were included in the analysis set. The median duration of progression-free survival was 8.4 weeks (95%CI 8.0–11.3), the median survival was 6.9 months (95%CI 6.2–7.9), and the ORR was 9.0% (95%CI 6.8–11.5). The most common skin toxicities (any grade, grade 3/4) were erythema (54%, 4%) pruritus (53%, 2%), acneiform dermatitis (52%, 5%), and rash (39%, 2%). ORR, progression-free and overall survival appeared to favour patients with grade 2–4 skin toxicity versus patients with grade 0–1 skin toxicity (Table 5). In this large combined analysis, severity of skin rash was correlated with increased efficacy of panitumumab in terms of ORR, progression-free and overall survival.

Subsequently, in 2008, Weiner and colleagues [56] reported that the incidence of skin rash was dose dependent in a dose escalating study of panitumumab given in monotherapy in 96 patients with metastatic colorectal cancer.

However, most of the actual clinical study reports fail to clearly define the degree of this association, consider the time factor of skin rash occurrence or other confounding factors.

The EGFR inhibitor erlotinib is currently indicated for metastatic pancreatic cancer and non-small cell lung cancer. Similar to other targeted agents, skin rash has been proposed as a potential marker of erlotinib efficacy in multiple tumour types [57].

The recent phase III study of gemcitabine/erlotinib ± bevacizumab [58] provided a further opportunity to consider skin toxicity associated with outcome of er-

Table 5
Pooled data from five clinical trials of panitumumab - response, progression-free and overall survival correlated with skin rash [55]

Efficacy by worst grade of skin toxicity	Grade 0–1 Skin toxicity $N = 240$	Grade 2–4 Skin toxicity $N = 372$	Hazard or Odds Ratio (Grade 2–4 : 0–1)	P Value
Objective Response				
Responders, n (%)	8 (3.3%)	47 (12.6%)	4.2 (95%CI 1.9–9.0)*	$P = 0.0003$
Progression-free survival (weeks)				
Median (95% CI)	8.0 (7.6–8.0)	13.1 (10.0–15.4)		
Mean (95% CI)	12.1 (10.9–13.5)	17.6 (16.1–19.1)		
Overall survival (months)				
Median (95% CI)	4.5 (3.8–5.5)	8.5 (7.8–9.5)	0.47 (0.38–0.58)**	$P < 0.0001$

*Odds ratio; **Hazard ratio; 95%CI: 95% confidence interval.

Table 6
Overall survival correlated with the severity of rash after gemcitabine/erlotinib ± bevacizumab in pancreatic cancer [58,59]

	Rash grade					
	0		1		⩾2	
	GE-P $n = 123$	GE-B $n = 91$	GE-P $n = 101$	GE-B $n = 110$	GE-P $n = 77$	GE-B $n = 105$
Median OS (months)	4.3	5.0	7.1	7.4	8.3	8.4

GE-P: gemcitabine-erlotibin–placebo; GE-B: gemcitabine-erlotibin–bevacizumab; OS: overall survival.

lotinib. Six hundred and seven chemotherapy-naive patients with metastatic pancreatic adenocarcinoma were randomised to gemcitabine-erlotinib-placebo (GE-P) or gemcitabine-erlotinib-bevacizumab (GE-B); patients received bevacizumab/placebo 5 mg/kg every 2 weeks plus erlotinib (100 mg/d) and gemcitabine (1000 mg/m^2) given weekly for 7 weeks during the first 8-weekly cycle, followed by weekly for 3 weeks during subsequent 4-weekly cycles. The addition of erlotinib to gemcitabine produced a significant benefit in progression-free survival (HR 0.73, $P = 0.0002$), and a trend, but no significant benefit, towards longer overall survival (median 7.1 months versus 6.0 months for GE-P; HR 0.89; $P = 0.21$). Overall survival was the endpoint of this trial.. There was a clear trend towards longer overall survival with increased grade of rash (Table 6) [59]. The observed relationship between higher grades of rash and longer overall survival confirmed the findings of the phase III PA.3 study of gemcitabine ± erlotinib, in patients with advanced pancreatic cancer. Studies are under way to prospectively investigate the relationship between rash and efficacy with erlotinib-based regimens in pancreatic cancer.

For all targeted agents, the reported data remain unclear and not validated. Prospective trials, carefully designed to prove the association between occurrence and severity of cutaneous manifestations and measures of clinical efficacy, are needed. Multivariate models to account for confounding factors such as genetic signatures or clinical parameters must be developed in order to better integrate the actual knowledge into clinical decision-making and patient selection [60].

Careful reporting of results is also mandatory, in order to create a better pool of data to be systematised. Several factors are to be considered:

Definition of skin toxicity definition: acne-like rash versus complete set of terms of cutaneous symptoms. Grading tools currently used such as NCI CTCAE v.3 are not sufficient to characterise the specificity of skin toxicity induced by EGFR inhibitors. Version 4 will eventually include a better classification. A more specific scoring system (with specific description and grading) and time factor considerations (i.e. early versus late onset of skin manifestations) are necessary for defining the relationship between skin effects and tumour response.

Treatment parameters: report on doses employed, eventual dose escalations, dose intensity in each subgroup to assess the relationship between dose

and severity of skin reaction. Until further knowledge is developed, for maximal clinical benefit, agents should be used at the maximum tolerated dose.

Efficacy analysis: report on response rate, intensity of response, duration of response, time to progression or progression-free survival, overall survival with clear definitions and specify the exact intervals measured.

Per grade subset analyses: Data are sometimes contradictory depending on separations per grade. Each subgroup (per grade: 0 to 4) must be reported or, otherwise, use the "no rash" versus "any rash" separation. All efficacy parameters should be reported with confidence intervals in these subgroup analyses. Eventual differences noticed should be tested and *P* values or hazard ratios reported.

Account for time factor/treatment duration: Retrospective comparisons of survival are inherently biased as patients who show response are more likely to receive treatment for a longer period which would influence survival and, meanwhile, having more exposure to the drug, they have more opportunity to develop skin toxicities. Alternatively, patients who do not respond may not survive long enough to develop a skin reaction. Although some authors suggest that the skin rash shows no relationship to treatment duration [60], early skin toxicity i.e. occurring before or at week 3 or week 6, must be differentiated from the toxicity occurring "during the whole study duration" in any correlation analysis. Although, in most cases, skin manifestations occur before week 3, the time factor might sometimes be confusing while reporting and comparing subsets of patients. There is a need to determine whether the time-point considered is relevant, whether reporting early rash is actually a valuable parameter that would influence patient selection and, ultimately, outcome.

Other confounding factors: Gene signatures, KRas, BRaf and other molecular markers – correlations are to be verified in multivariate analyses.

The association between specific dermatological side effects and the clinical outcome of targeted agents is still to be proven by validating retrospective data in prospective trials. However, the most important issue remains the evaluation of the relevance of these findings for the greatest benefit of patients and, especially, for patient selection in clinical daily practice.

Multikinase inhibitors (sorafenib, sunitinib, imatinib)

Sorafenib is a small molecule inhibitor of VEGFR, platelet-derived growth factor receptor (PDGFR), Flt-3 and Raf indicated for hepatocellular and renal cell carcinoma. Sunitinib, inhibiting VEGFR, PDGFR, RET, Flt-3 and c-kit, is used for gastro-intestinal stromal tumours and renal cell carcinoma. Imatinib, blocking c-kit, PDGFR and Bcr-Abl, is indicated for some haematologic disorders (e.g. chronic myeloid leukaemia, hyper-eosinophilic syndrome), gastro-intestinal stromal tumours and dermatofibrosarcoma protuberans [61].

Clinical picture

Sorafenib (34%) and sunitinib (19%) may cause hand-foot skin reactions (HFSR) that should be distinguished from hand-foot syndrome, seen with classic chemotherapy such as 5-FU, anthracyclines and taxanes [62,63]. HFSR is dose-dependent and very characteristically localised to skin areas of friction or pressure (heels, metatarsal heads, areas of friction caused by shoes or manual labour). It emerges in the first 2–3 weeks of treatment as sharply demarcated, erythematous, painful, oedematous and blistering lesions that evolve into extremely tender, inflamed calluses [62,63] (Fig. 7). Pathologic examination reveals

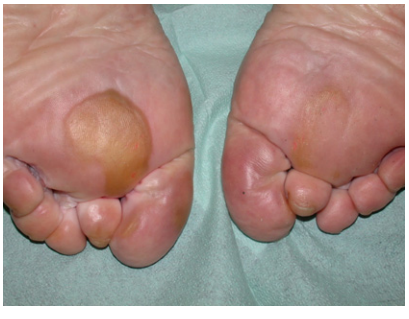

Fig. 7. Hand-foot skin reaction induced by sorafenib. Note the sharply demarcated, painful, inflammatory blisters and calluses on pressure points of the sole and toes.

epidermal keratinocyte apoptosis, vacuolar degeneration and dyskeratosis with the formation of intraepidermal blisters followed by massive acanthosis, papillomatosis and parakeratotic hyperkeratosis [64].

Asymptomatic subungual splinter haemorrhages are seen in not less than 40–70% of patients on sorafenib or sunitinib. Sensitivity of subungual capillaries to microtrauma due to inhibition of VEGFR (with impaired angiogenesis) may be involved in its pathogenesis [63].

Dryness of the skin and/or mucous membranes (occasionally with stomatitis) are present in approximately 25% of patients receiving sorafenib/sunitinib [65].

In the first weeks of treatment, sorafenib (and more rarely sunitinib) may cause a sometimes flaky erythema of the scalp and the face sparing the periorbital area, resembling seborrhoeic dermatitis. Itchy genital lesions can be observed as well. These lesions disappear spontaneously after some weeks. Sometimes, facial papulopustular lesions can be seen, reminiscent of a mild form of the acneiform eruption seen with EGFR inhibitors [65].

A temporary, diffuse mild to moderate alopecia of the scalp can also be encountered with sorafenib and to a lesser extent sunitinib [65].

Sorafenib can be responsible for a transient dysaesthesia of the scalp skin with a burning and painful sensation, even in the absence of skin lesions [65].

Other cutaneous side-effects of sorafenib include a transient maculopapular rash in one in three patients, changes in hair texture (drier, curlier hair) and inflammatory actinic keratoses, milia or cysts [65].

Sunitinib often provokes a yellow skin discolouring, caused by accumulation of this yellow molecule in the integument. Owing to its inhibition of c-kit, a reversible hair depigmentation can be seen 4–6 weeks after initiation of the drug. Finally, some patients on sunitinib may develop facial (especially periorbital) oedema [20].

Various skin reactions have been described with imatinib [61,66]:

- A dose-dependent, periorbital, facial or even generalised oedema, similar to that seen with sunitinib, appearing 2 weeks after starting the drug with very gradual regression later on.
- Maculopapular eruptions (and, rarely, even more severe drug reactions such as vasculitis, acute generalised exanthematous pustulosis or toxic epidermal necrolysis necessitating permanent drug withdrawal).
- Skin depigmentation but seldom also a paradoxical hyperpigmentation (especially of the nails) or repigmentation of grey hair.
- Xerosis cutis and pruritus.

Treatment and clinical management

General preventive measures are advised to patients receiving sorafenib/sunitinib in order to minimise the impact of hand-foot skin reaction: avoid drying of the skin by using lukewarm water, bath/shower oil (instead of soap or bath foam), wear protective gloves, application of hand- and foot-creams; avoid friction and wear comfortable fitting clothes and shoes with silicone padded soles to absorb possible pressure on the skin; treat pre-existing calluses or hyperkeratoses or mild hand-foot skin reaction with urea- or salicylic acid ointment [65]. Moderate HFSR is treated with ultrapotent topical steroids and topical lidocaine to control the pain. Oral analgetics can be added accordingly. For severe reactions, a (temporary) dose adjustment or interruption of the multikinase inhibitor is proposed when supportive dermalogic treatment offers insufficient relief. Xerosis cutis is tackled with the aforementioned general measures, emollients and sometimes oral antihistamines. The seborrheic dermatitis-like facial lesions respond well to topical ketoconazole or weak steroids. For the maculopapular eruption with sorafenib or imatinib, topical or systemic steroids and sometimes interruption of the drug are advised [65].

Conclusions

With the widespread use of EGFR inhibitors and other targeted therapies in the metastatic and adjuvant setting of various cancers, it will be paramount to provide supportive and adequate treatment for the majority of patients experiencing skin toxicity. Understanding the clinical picture of skin toxicity is crucial for optimal management of patients with targeted agents.

Conflict of interest statement

None declared.

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