Review paper

The incidence and management of cutaneous adverse events of the epidermal growth factor receptor inhibitors

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Abstract

Overexpression of the epidermal growth factor receptor (EGFR) is found in many cancers, including those of the head and neck area, non-small-cell lung cancer, and colorectal, cervical, prostate, breast, ovary, stomach, and pancreatic cancer. The EGFR inhibitors are used at present in the treatment of such cancers. Skin lesions that develop during and after cancer treatment may be due to specific cytostatics, molecular-targeted drugs, radiation therapy, complementary therapy, or the cancer itself, and hence knowledge is essential to distinguish between them. The mechanism through which skin toxicity arises during treatment with EGFR inhibitors is not well known, but seems to be due to the modification of the RAS/RAF/MEK/ERK signal path associated with its activation, which results in the similarity between the adverse effects of EGFR inhibitors and the treatment of melanoma with BRAF and MEK inhibitors. The most common side effects are pruritus, xerosis, papulopustular rash, hand-foot skin reaction, alopecia and dystrophy of the hair, and paronychia. This work presents options for prevention and suggestions for managing these adverse events, which are of importance in the care of patients undergoing oncological treatment.

Key words: EGFR inhibitor, dermatological adverse effects, BRAF inhibitor, MEK inhibitor.

Introduction

Although chemotherapy has long been associated with high incidence of side effects, skin complications have often been neglected or ignored by oncologists as minor issues. The advancement of molecular biology and the introduction of targeted therapy into day-to-day clinical practice, through which we can precisely act on the molecules involved in the pathomechanism of tumor development, has been accompanied by an increased interest in skin complications. Knowledge of the mechanisms of action of both conventional and targeted therapies is essential to understand the etiopathogenesis of such skin toxicity. Proper therapeutic treatment is however associated with maintaining good quality of life for patients, despite any side effects. Knowledge of possible complications concerning skin and its appendages and of their treatment and prevention so as to maintain or merely modify antineoplastic therapy is thus an important element of cooperation between oncologists and dermatologists.

The development of skin lesions during or after cancer treatment may be indicative of the side effects of a particular cytostatic drug, molecular drug, radiotherapy, adjuvant therapy, or the cancer itself. It should also be noted that some cutaneous side effects that arise during treatment with molecular-targeted drugs, such as dry skin, papulopustular rash, paronychia, and changes in the hair structure, may appear similar, despite the use of different drugs.

Epidermal growth factor receptor (EGFR) belongs to the Erb family of tyrosine kinase receptors, responsible for signaling from the outside to the inside of the cell. EGFR plays an important role in many physiological processes, and its main stimulators are EGF and TGF-α. The epidermal growth factor receptor family consists of 4 membrane receptors with tyrosine kinase activity: EGFR

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(ErbB1, Her1), ErbB2 (Her2), ErbB3 (Her3), and ErbB4 (Her4) [1–3]. Overexpression of these receptors is found in many cancers, including malignant head and neck neoplasms, non-small-cell lung cancer, colorectal, cervical, prostate, breast, ovarian, stomach, and pancreatic cancer [4]. An excessive expression, and also defective mechanisms of EGFR inhibition lead to the progression of cancer through the activation of the signaling pathways responsible for cell proliferation and differentiation, the suppression of apoptosis, increased survival and metastasis, and angiogenesis. It is also associated with more advanced disease at the time of diagnosis and is an unfavorable prognostic factor [1, 5]. In clinical practice, drugs that affect the activity of EGFR are increasingly used. Among them the following should be particularly noted:

a) EGFR-blocking monoclonal antibodies: cetuximab and panitumumab;
b) EGFR tyrosine kinase inhibitors:
   – first generation: gefitinib and erlotinib,
   – second generation: trastuzumab, dacomitinib, necitumumab,
   – third generation: osimertinib, rociletinib, pertuzumab, olmutinib, poziotinib, varlitinib, sapitinib, vandetanib;
c) multitarget tyrosine kinases inhibitors: lapatinib, neratinib, afatinib, canertinib [6–10].

EGF receptors are located in the membranes of epithelial cells and of mesenchymal cells, such as fibroblasts and chondrocytes. In the skin, EGFR activation regulates epidermal growth by stimulating proliferation and differentiation, and by inhibiting keratinocyte apoptosis [11, 12]. Stimulation of the receptor is associated with the transmission of a signal corresponding to the transfer of keratinocyte from the G1 phase to the S phase of the cell cycle [13]. EGF also affects the development of sweat and sebaceous glands and inhibits the growth of hair; it is also involved in angiogenesis by enhancing the expression of fibroblast growth factor binding protein (FGF-BP), a protein that binds and activates FGF-1 and FGF-2 [14].

Inhibition of EGFR activity significantly impairs epidermal homeostasis. The blocking of the domain function through receptor tyrosine kinase activity leads to inhibition of DNA synthesis and the blocking of the transition from the G1 to the S cell cycle phase [1]. As a result, increase of terminal keratinization markers in the basal layer of the epidermis is observed; this is responsible for the premature differentiation and retention of keratinocyte growth (including p27KIP1, KRT1, STAT3) [1, 11]. Under physiological conditions, these markers are found only in the upper layers of the epidermis. There is also inhibition of the maturation process through the influence on intercellular connections and the promotion of adhesion, which prevents the normal migration of keratinocytes from the basal layer to the stratum corneum of the epidermis. This results in a pronounced thinning of the epidermis, including the stratum corneum, which leads to impairment of the protective function due to an increase in its permeability [15]. The release of cytokines and the activation of the cells involved in the inflammatory response are responsible for excessive skin sensitivity and paronychia, associated with injuries [11]. As a result of these processes, characteristic skin lesions are formed, such as papules and pustules; the damaged barrier additionally increases the risk of developing secondary bacterial infections and other complications.

The inhibition of EGFR also strengthens UV-induced keratinocyte apoptosis. Under physiological conditions, UV radiation damages the DNA of keratinocytes by affecting the formation of free radicals. An increased expression of EGFR and intensification of proliferative signals occur in response. Disorders of this process can cause induced lesions or exacerbation of skin lesions upon exposure to UV radiation. Within the hair follicles, this process results is an increase in the expression of genes that stimulate inflammatory processes, apoptosis, and the blocking of ducts, leading to bursting [15, 16].

The mechanism leading to skin toxicity during treatment with EGFR inhibitors is not well known, but it is undoubtedly the result of modifications of the signals associated with its activation, particularly the RAS/RAF/MEK/ERK pathway, which affects cell cycle regulation, including proliferation and the differentiation of epidermis cells [17]. The disturbance of signal transmission in this pathway is responsible for the common features of skin lesions.

Adverse drug reactions of a similar nature include EGFR-directed monoclonal antibodies, EGFR tyrosine kinase inhibitors, and inhibitors of BRAF and MEK used to treat melanoma [18]. Despite the unmistakable similarities, the observed lesions may, however, vary slightly in character and severity (Table 1). This is due to the fact that the molecules used in molecular therapies modify the signal associated with EGFR activation to different degrees [19]. These observations indicate the need to adapt prophylactic and therapeutic treatments not to the type of the drug, but rather to the group of drugs that modify the pathways associated with EGFR activation (Table 2). Similar treatment to prevent the development of undesirable effects and to control their progression if they occur can be successfully used for the whole group of signal modifying drugs EGFR→RAS/RAF/MEK/ERK. The differences arising from the different summary of product characteristics will relate to the cases in which it is necessary to adjust the dose or interrupt the treatment, depending on the severity of the side effects (CTCAE, the Common Terminology Criteria for Adverse Events) [19, 20].

Xerosis

Xerosis is a problem in up to 33% of patients treated with EGFR inhibitors and is significantly dependent on

Table 1. Frequency of individual adverse reactions of EGFR inhibitors. Percentages are taken from the references (REF) cited and information in the summary of product characteristics

Drug name	Class	References	Papulopustular rash (PPR)	Pruritus Xerosis Skin fissuring	Nails Periungual involvement	Hair changes	Mucous membranes	Serious adverse events (level 3 or 4)
Cetuximab	MoAb	1 37 38	General 90% Grade 3–4 7–17	Pruritus: General 10% Grade 3–4 1%	General 16% Grade 3–4 < 1%	Alopecia General 5% Trichomegalia 12%	General 11% Grade 3–4 < 1%	TEN/SJS 3 cases (5)
dAE 80%			PPR Grade 3–4 3–10%					sdAE 15%
Panitumumab	MoAb	19	General 57% Grade 3–4 7%	Dryness: General 10% Grade 3–4 0%	General 25% Grade 3–4 2%	Trichomegalia 6%	General 6% Grade 3–4 < 1%	
dAE 90%				Pruritus: General 57% Grade 3–4 2%				sdAE 34%
Necitumumab	II gen TKI (MoAb)	1 3 39 40	Grade 3–4 7–15% PPR General – 65.5–67.8% Grade > 3 3.2–3.4%	Dryness: General 24.1–29.0% Grade > 3 6.5–6.9% Pruritus: General 20.7–41.9% Fissuring of skin: General 20.7% Grade > 3 3.2%				sdAE 6.3%
dAE 77.9%								
Erlotinib	I gen TKI	1 2 19 3,41	Grade 3–4 6–22.3% Grade > 3 8.8% General 75% Grade 3–4 9%	Dryness: General 12% Grade 3–4 0% Pruritus: General 13% Grade 3–4 < 1%	General 14% Grade 3–4 < 1%	Alopecia General 6% Trichomegalia 11%	General 19% Grade 3–4 < 1%	
dAE 75%		11,12	PPR General 35.1%					sdAE 9%
Afatinib	Multi-directional TKI	2 5 6, 42 12	Grade > 3 15% General 79–89% Grade 3 6–9% Grade 3–4 15–16% Grade > 3 16.2% PPR	Dryness: General 29–33% Grade 3 0–0.4% Pruritus: General 18–56% Grade 3 0–0.4%	Paronychia General 40–56% Grade 3 2–11% Grade > 3 11.4% (7)		Stomatitis/ mucositis Grade 3–45%	TEN/SJS 1 case (5)
dAE 70%		11	General 78%					sdAE 14%
Gefitinib	Multi-directional TKI	2 19 41, 43	Grade > 3 3.5% General 47% Grade 3–4 2%	Dryness: General 11% Grade 3–4 0% Pruritus: General 8% Grade 3–4 < 1%	General 11% Grade 3–4 < 1%		General 1%	TEN/SJS 1 case (5)
dAE 20%								sdAE 8%

Table 1. Cont.

Drug name	Class	References	Papulopustular rash (PPR)	Pruritus Xerosis Skin fissuring	Nails Periungual involvement	Hair changes	Mucous membranes	Serious adverse events (level 3 or 4)
Dacomitinib	II gen TKI	44	PPR General 53.8–68% (6) Grade > 3 64.5% (7)				Stomatitis 46%	
Lapatinib dAE 25–45%	Multi-directional TKI	19 45	General 47% Grade 3–4 < 1%	Dryness: General 13% Grade 3–4 < 1% Pruritus: General 12% Grade 3–4 < 1%	General 11% Grade 3–4 < 1%	Alopecia General 13%	General 44%	
Trastuzumab	II gen TKI	19 46	General 20%			Alopecia General 7%		
Rociletinib		12, 13 47, 8	General 4% < 1%					
Osimertinib (mereletinib, tagrisso) dAE 24%	III gen TKI	13 48 8	General 24–41% Grade 3–4 0.5–1.2% PPR General 40%	Dryness: General 31% Pruritus: General 14%	Paronychia General 17–25%			sdAE 1.2%
Pertuzumab	III gen TKI (MoAb)	49 50	General 51.7% More frequently Grade 1–2 Frequency increased with the number of cycles PPR General 20–40%	Dryness 10.6%	Paronychia General 7.1%	Alopecia General 60.9%	Stomatitis General 18.9%	

dAE – dermatological adverse effects, sdAE – severe dermatological adverse effects, MoAb – monoclonal antibody, TKI – tyrosine kinase inhibitor, PPR – papulopustular rash.

the dose of the drug. Usually, it is most severe within the extremities and intensifies during therapy. In case of using EGFR tyrosine kinase inhibitors, skin dryness was found in 11% of those treated with gefitinib and 12% of those with erlotinib. Relatively dry skin was reported by 3% of patients treated with lapatinib [19]. It appears relatively late, about 30–60 days after the start of treatment; it is directly due to the inhibition of proliferation and differentiation of keratinocytes. Dry skin is also a cause of increased susceptibility to injuries and fissures, whose secondary causes include bacterial and viral infections. Deep painful fissures are most often seen in the area of fingertips, heels, periungual skin and dorsal surface of the interphalangeal joints [20]. The risk of skin dryness during treatment increases with age, pre-eczema, and prior cytotoxic use. Proper skin care significantly reduces xerosis.

Pruritus

Pruritus, an unpleasant sensation leading to scratching, occurs among 57% of patients treated with panitumumab, 10% of those with cetuximab, and 13% of those treated with erlotinib [19]. During treatment, generalized or localized itching was observed, ranging in strength from mild to severe pruritus. It often coexists with xerosis and papulopustular rash [11]. It is therefore worth stressing that proper skin care and the management of papulopustular rash can significantly alleviate symptoms. The mechanism that leads to pruritus during therapy with drugs that inhibit EGFR activity has not been explained. It is also unknown what effect its development has on its classical mediators, such as histamine and neurotransmitters, including serotonin, opioids, and γ-aminobutyric acid [21, 22].

Table 2. Dermatological adverse reactions of EGFR inhibitors and suggestions for interventions [19]

CTCAEv4.0	Clinical presentation	Management
Xerosis		
Grade 1	< 10% of the body surface area, without erythema or pruritus	Continuation of the therapy without changing the dose. Emollients/moisturizing creams containing humectants should be applied at least 1–2 times a day. UV protection should be used. *Monitoring: assess severity after 2 weeks. If there is no improvement or intensification, use the recommendations for grade 2.*
Grade 2	10–30% of the body surface area, with erythema or pruritus, impaired basic activity of the patient	Continuation of the therapy without changing the dose. Treatment as for grade 1 and additionally, apply greasy ointments containing, e.g. vaseline or cholesterol, at the location of the most intense lesions. The efficacy of H1 blockers has not been demonstrated. *Monitoring: assess severity after 2 weeks. If there is no improvement or intensification, use the recommendations for grade 3.*
Grade 3	> 30% of the body surface area, with pruritus, significant limitation of self care activities of daily living	Continuation of the therapy without changing the dose. *Not recommended: changing the dose or interrupting the therapy, according to product characteristics; to be considered in cases of significant psychosocial effects.* Proceed as in grade 2 In the case of coexisting eczema, lichenification, fissures and/or secondary infections, use moderate to severe or strong glucocorticosteroids or combination preparations containing glucocorticosteroids and antibiotics up to 1–2 times daily. The efficacy of H1 blockers has not been demonstrated (in case of pruritus, antihistamine drugs of the first generation can prove useful, for example, hydroxyzine of 30–75 mg/day or medium and low doses of systemic glucocorticoids). *Monitoring: assess severity systemic after 2 weeks. If there is no improvement or worsening of lesions, consider changing the dose or interrupting the therapy, according to the product characteristics.*
Pruritus		
Grade 1	Moderately intensive, limited to a particular part of the body, requires topical treatment	Continuation of the therapy without the dose modification. Proper skin care. Protection against UV radiation. Emollients or moisturizing creams containing humectants and/or topical antipruritic agents containing Polidocanol, menthol, camphor, Pramocaine etc. should be applied at least 1–2 times a day. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation, use the recommendations for grade 2.*
Grade 2	Increased local or periodically generalized, present lesions resulting from scratching, impairment of basic patient activity, requires systemic treatment	Continuation of the therapy without the dose modification. *Not recommended: changing the dose or interrupting the therapy, consistent with the product characteristics; possible in case of significant psychosocial effects.* As in grade 1 and also periodically use topical medium–strong or strong glucocorticosteroids 1–2 times a day. H1 l generation antihistamines, e.g. hydroxyzine 30–75 mg/day. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation, use the recommendations for grade 3.*
Grade 3	Increased local or permanently generalized, significant limitation of self care activity or impairment of sleep, requires oral corticosteroids or immunosuppressive therapy	As in grade 2, and also: In the case of coexistence of eczema, lichenification, fissures, or secondary infection, use moderate to strong or strong glucocorticosteroids or combination preparations containing glucocorticosteroids and antibiotics, 1–2 times daily until improvement. H1 antihistamines: periodic and low doses of systemic glucocorticosteroids (e.g., prednisolone up to 0.5 mg/kg/day). Single reports of symptomatic relief following use of gabapentin and pregabalin, doxepin, aprepitant. *Monitoring: assess severity after 2 weeks. If there is no improvement or worsening of lesions: consider changing the dose or interrupting the therapy, according to the product characteristics.*
Papulopustular rash		
Grade 1	Papular and/or pustular lesions covering < 10% of the body surface area, not associated with itching or pain	Continuation of the therapy without the dose modification. Proper skin care. Protection against UV radiation. Apply externally, 1–2 times a day until improvement, complex preparations containing glucocorticosteroids and antibiotics, for example betamethasone dipropionate and gentamicin, followed by creams or emulsions with metronidazole, or less frequently with antibiotics (erythromycin, clindamycin). *Monitoring: assess severity after 2 weeks. If there is no improvement or worsening of lesions, apply the recommendations for grade 2.*

Table 2. Cont.

CTCAEv4.0	Clinical presentation	Management
Grade 2	Papular and/or pustular lesions covering 10–30% of the body surface area; may cause pruritus, pain, and adverse psychosocial effects	As in grade 1 and: In case of severe papulopustular rash, apply tetracycline antibiotics, such as limecycline, initially one tablet twice daily (tablets of 408 mg limecycline corresponding to 300 mg tetracycline), followed by the dose reduction to one tablet once daily, doxycycline at doses of 100–200 mg/day and tetracycline at doses of 0.5–1.5 g/day. *Monitoring: assess severity after 2 weeks. If there is no improvement or worsening of lesions, apply the recommendations for grade 2.*
Grade 3	Papular and/or pustular lesions covering > 30% of the body surface area; may cause pruritus, pain, and adverse psychosocial effects, secondary infection requiring oral antibiotic therapy, limiting self-care	As in grade 2 and: Apply tetracycline antibiotics, such as limecycline, initially one tablet twice daily (408 mg tablets of limecycline, corresponding to 300 mg tetracycline) followed by the dose reduction to one tablet once a day, doxycycline of 100–200 mg/day, and tetracycline in doses of 0.5–1.5 g/day. *Monitoring: assess severity after 2 weeks. If there is no improvement or worsening of lesions, consider changing the dose and/or interrupting the therapy, depending on the product characteristics.*
Grade 4	Papular and/or pustular lesions covering > 30% of the body surface area; may cause pruritus, pain, and adverse psychosocial effects, with extensive secondary infection requiring oral antibiotic therapy; potentially life-threatening	Break in therapy, according to the product characteristics. Empirical or targeted antibiotic therapy. *Monitoring: 2–3 times a week – dermatological control.*
Hand-foot skin reaction		
Grade 1	Minor changes (erythema, edema, hyperkeratosis), painless	Continuation of the therapy without the dose modification. Proper skin care. Emollients and/or moisturizing creams containing humectants should be applied at least 1–2 times a day. In addition, creams containing urea or ointments containing salicylic acid, or preparations containing both salicylic acid and urea for hyperkeratotic lesions. Topical glucocorticosteroids (strong and very strong, depending on potency, e.g. clobetasol propionate) 1–2 times a day for erythematous changes. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation of lesions, apply recommendations for grade 2.*
Grade 2	Symptoms of moderate severity: epidermal exfoliation, blisters, bleeding, edema, hyperkeratosis pain, limiting daily activity	Continuation of the therapy without the dose modification or change the dose in line with the product characteristics. Proper skin care. In the case of local pain, creams with lidocaine and prilocaine, and gels containing lidocaine or benzocaine, may be used. In addition, nonsteroidal anti-inflammatory drugs and non-anti-inflammatory analgesics can be used. Data available in the literature demonstrate the beneficial effects of gabapentin, complex preparations containing codeine, and protective ointments containing active antioxidants. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation of lesions, apply recommendations for grade 3.*
Grade 3	Symptoms of severe severity: epidermal exfoliation, blisters, bleeding, edema, hyperkeratosis pain, limiting self care activities of daily living	Interrupt the therapy in line with the product characteristics. Proper skin care. It is important to remove the hyperkeratosis before restarting the therapy after a temporary discontinuation of treatment. *Monitoring: assess severity after 2 weeks. In case of improvement, consider changing the dose or interrupting the therapy in line with the product characteristics. If there is no improvement or aggravation of lesions, end the therapy.*
Alopecia		
Grade 1	Loss of < 50% of the initial volume of hair, not requiring wearing a wig	Continuation of the therapy without the dose modification. Exclude the deficiencies of iron, endocrinopathy, gastrointestinal disease leading to malabsorption and body weight loss over 10 kg. Check TSH. Vitamin D_3, nutritional/protein deficiency. Off-label minoxidil 5% twice daily. *Monitoring: assess severity after 4 weeks.*

Table 2. Cont.

CTCAEv4.0	Clinical presentation	Management
Grade 2	Loss > 50% of the initial volume of hair, requiring wearing a wig; may have psychosocial effects	Continuation of the therapy without the dose modification. As in grade 2 and off-label clobetasol in foam, shampoo or solution once daily for 3–4 weeks. *Monitoring: assess severity after 4 weeks.*
Paronychia		
Grade 1	Edema and/or erythema of the nail fold with or without epidermal injury	Continuation of the therapy without the dose modification. Proper care including proper nail clipping, avoiding leaving sharp or frayed edges, avoiding cutting too deep of the lateral edges of the nail. Protection against mechanical injuries through the avoidance of uncomfortable footwear and of certain sports that involve heavy loads and repetitive injuries. Treatment with 10% iodopividone solution or octenidine with ethanol. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation of lesions, apply recommendations for grade 2.*
Grade 2	Edema and/or erythema of the nail fold with accompanying pain associated with the damage and/or separation of the nail plate causing impairment of the instrumental activities of the patient; requires topical and systemic treatment	Continuation of the therapy without the dose modification. As in grade 1 and: Treatment with 10% iodopividone solution or octenidine with ethanol. Antifungal drugs topical or systemic (e.g. ketoconazole, fluconazole). Oral antibiotics used for not less than 14 days, mostly clindamycin. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation of lesions, apply recommendations for grade 3.*
Grade 3	Nail changes significantly limit self care activities of daily living and require surgery or *i.v.* antibiotic therapy	Continuation of the therapy without dose modification. *Not recommended: changing the dose and /or interrupting the therapy in the case of significant psychosocial effects.* As in grade 2 and: Surgical procedure: cut the nail fold; and in the case of undernail abscess, drain the pus. In the case of an ingrown nail: partly (wedge) or completely remove the nail plate. *Monitoring: assess severity after 2 weeks. If there is no improvement or aggravation of lesions, consider changing the dose and/or interrupting the therapy in line with the product characteristics.*
Severe skin reactions: Erythema multiforme		
Grade 1	Erythema multiforme (target) lesions covering < 10% of the body surface area, not causing skin tenderness	Interrupt the therapy in line with the product characteristics. Determine the inducing factor: viral infection (HSV, EBV, etc.), drug-induced. Discontinue all medicines that can induce hypersensitivity reactions. Oral antiviral treatment if infectious etiology is confirmed. Topical/systemic glucocorticosteroids. *Monitoring: daily dermatological control.*
Grade 2	Erythema multiforme (target) lesions covering 10–30% of the body surface area, causing skin tenderness	Interrupt the therapy in line with the product characteristics. As in grade 1 and: Treatment by a dermatologist (topical/systemic glucocorticosteroids/cyclosporine A 3–5 mg/kg/day). *Monitoring: daily dermatological control.*
Grade 3	Erythema multiforme (target) lesions covering > 30% of the body surface area, minor erosions of mucous membranes of the mouth and genitals	Interrupt the therapy in line with the characteristics of the product. As in grade 2 and: Treatment as in Stevens-Johnson syndrome: treatment by a dermatology specialist. Multidisciplinary care: ophthalmological, laryngological, urological/gynecological. Analgesic treatment, monitoring of secondary infections. Discontinue all medicines that can induce hypersensitivity reactions. *Monitoring: daily dermatological control.*
Grade 4	Erythema multiforme (target) lesions covering > 30% of the body surface area, minor erosions of mucous membranes of the mouth and genitals associated with fluid-electrolyte abnormalities, requiring hospitalization in a burn treatment unit	Complete cessation of the therapy. As in grade 2 and: Treat as toxic epidermal necrolysis: treatment by a dermatology specialist. Multidisciplinary care: ophthalmological, laryngological, urological/gynecological. Analgesic treatment, monitoring of secondary infections. Hospitalization in the burn/intensive care unit. *Monitoring: daily dermatological control.*

Table 2. Cont.

CTCAEv4.0	Clinical presentation	Management
Stevens-Johnson syndrome		
Grade 3	Lesions of the erythema, purpura, and erosions cover < 10% of the body surface area, are associated with erosive lesions of the mucous membranes of the mouth, genitals, and conjunctiva	Complete cessation of the therapy. Hospitalization in the burn/intensive care unit: treatment by a dermatology specialist. Sanitary regime, treatment of extensive erosions and wounds. Multidisciplinary care: ophthalmological, laryngological, urological/gynecological. Determine the inducing factor: viral, mycoplasmic, drug-induced. Discontinue all medicines that can induce hypersensitivity reactions. Analgesic treatment (e.g. opioids), monitoring of secondary infections. *Monitoring: daily dermatological control.*
Grade 4	Lesions of the erythema, purpura, and erosions cover 10–30% of the body surface area, are associated with erosive lesions of the mucous membranes of the mouth, genitals, and conjunctiva	Complete cessation of the therapy. As in grade 3 and: Hospitalization in the burn/intensive care unit: treatment by a dermatology specialist. *Monitoring: daily dermatological control.*
Lyell's sydrome (toxic epidermal necrolysis)		
Grade 4	Lesions of the erythema, purpura, and erosions covering ≥ 30% of the body surface area, separation of the epidermis, erosion/ulceration of the mucous membranes and conjunctiva, serious general condition of the patient, fluid-electrolyte abnormalities	Complete cessation of the therapy. Hospitalization in the burn/intensive care unit: treatment by a dermatology specialist. Sanitary regime, treatment of extensive erosions and wounds. Multidisciplinary care: ophthalmological, laryngological, anesthetist, urological/gynecological. Determination of disease severity using the SCORTEN scale. Treatment of fluid-electrolyte disorders, protein deficiency, monitoring of multi-organ capacity. Analgesic treatment (e.g. opioids), monitoring of secondary infections. *Monitoring: daily dermatological control.*

Papulopustular rash

Papulopustular rash is one of the most common skin complications of EGFR activity modifying therapy [23]. It is reported in 45–100% of patients, depending on the literature data. It is most common during therapy with cetuximab and panitumumab, for monoclonal antibodies which the percentage of patients with lesions is 88–90% and 100%, respectively. Most cases are mild to moderate, with less than 5–18% of patients experiencing severe changes that significantly affect quality of life. When using EGFR tyrosine kinase inhibitors, rash is reported in 43–54% of gefitinib and 75% of erlotinib users. During treatment with lapatinib, papulopustular rash was reported in 13–47% of patients [19]. The discrepancies in the data for the individual drugs in the literature are mainly due to the classification of the different types of skin rashes into one group.

Skin lesions of pustular and papular types may be monoform or multiform, and mainly affect the face, scalp, and upper chest and back (the seborrheic areas). In severe cases, the lower parts of the body, buttocks, and limbs may also be affected. In the literature, they are usually described as acne-like (or acneiform), but unlike acne vulgaris, comedos or purulent cysts are not found [24]. The lesions develop in several stages, often after exposure to UV radiation. Although UV radiation may exacerbate changes, studies have not shown photoprotection to prevent their development, because the presence of the rash depends primarily on the type and dose of the drug used. Excessive sebum secretion is not associated with an increased risk of lesions, but attention should be drawn to the fact that prior predisposition to folliculitis and acne can be associated with skin adverse events during therapy with EGFR inhibitors. In more than 75% of patients, the first lesions appear in the first 1–2 weeks of treatment. Erythema and edema usually appear first, accompanied by sensory disturbances, and then between the second and fourth week, folliculitis and/or pustular lesions and pruritus occur. At about 4 weeks, the lesions stabilize and, if properly treated, disappear, leaving transient erythema and telangiectasia [11, 12, 24]. The duration and severity of symptoms depend on the dose of the drug, and the symptoms may also self-relieve, despite continued therapy. Complete disappearance of lesions is observed about one month after the end of treatment. Persistent hyperpigmentation was observed in patients with dark skin complexion. The lesions may be accompanied by paronychia.

Paronychia

Paronychia and nail lesions occur in 25% of patients treated with panitumumab and 16% of those treated with

cetuximab [19]. For gefitinib and erlotinib therapy, they are reported in 3–10% and 14% of patients, respectively. Relatively infrequently (1%), paronychia is seen among patients treated with lapatinib.

Paronychia is an inflammation characterized by edema, redness, and soreness in the area around the nail plate. It can affect one or more fingers and toes. In most cases, it has a mild course but, in some cases, bleeding granulation and pockets develop, from which squeezing elicits pus. In such cases, there are usually secondary bacterial and fungal infections. Paronychia frequently accompanies papulopustular rash. It develops later on, usually 4–8 weeks after starting treatment [1, 19].

Hair changes (alopecia and changes in hair structure)

Alopecia is reported in 6% of patients treated with erlotinib and 5% of those treated with cetuximab [19]. Nonscarring hair loss is reversible, slow, and usually does not lead to complete baldness. These changes can be accompanied by alterations in the hair structure (curly hair, thin), along with a change in color [11, 19]. This applies mainly to the scalp, but may also affect other areas of the body. The lesions develop 2–5 months after the onset of treatment. Blocking the signal mediated by EGFR leads to the blockade on the hair growth cycle, that is, the hair transitions from the anagen to the telogen phase. Disturbance of the normal hair cycle is the cause of delayed hair growth and changes in structure [19, 25]; inflammation processes are additionally activated within the hair follicle. Alopecia and structural changes are not the only described changes to hair during treatment with EGFR inhibitors. Patients may also have excessive eyelash growth (trichomegalia) and excessive hypertrichosis, including of the face. In these cases, it is recommended to trim eyelashes and use depilatory treatments, including laser depilation and eflornithine creams [11, 21].

Severe skin reactions

Serious drug-induced skin reactions have been occasionally reported, including cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell's syndrome) [11, 19, 25]. Therapy (such as systemic glucocorticosteroids, cyclosporine A) should be applied depending on the severity of the skin lesions and the accompanying symptoms (mucous membrane and/or conjunctiva erosions or systemic involvement). In case of anaphylaxis (acute urticaria, Quincke's edema), standard antishock treatment should be implemented. In case of a serious skin drug reaction, it is very important to exclude its induction by drugs taken for other reasons.

Recall reaction

Recall reactions are rare, unforeseeable skin reactions occurring in previously irradiated sites [26]. The occurrence of a memory reaction depends on personal characteristics as well as on the type of the cytotoxic drug used. The drugs that most commonly contribute to the occurrence of these skin disorders include gemcitabine, capecitabine, methotrexate, docetaxel, etoposide, and doxorubicin. Such reactions have also been observed following the application of new oncological treatment therapies, such as pemetrexed [27, 28] and gefitinib [29], and also in the combinations of trastuzumab with vinorelbine [30], and of bevacizumab with gemcitabine [31]. It is not certain whether the dose of the drug affects the onset of the recall reaction, as similar complications have been observed with different doses. Recall reactions are as common in monotherapy as in complex therapy. No relationship between radiation doses and the risk of these lesions has been demonstrated [32].

The exact pathomechanism has not yet been understood. Several hypotheses have been advanced, but none of them has been confirmed by reliable research [26, 33–36]. It is believed that the pathomechanism involves damage to DNA that has been exposed to ionizing energy after the subsequent use of chemotherapy.

The skin lesions observed in this reaction vary in severity. The most common lesions seen with recall reactions are mild to moderate urticaria and erythema with accompanying dryness and desquamation of the skin or pruritus. However, with the increase in the severity of skin toxicity in the course of this reaction, painful swelling, blisters, or papulopustular rash appear. In very severe cases, ulcerations may develop and even necrotic lesions may occur [26, 33, 34]. The characteristic histopathological changes observed in these complications are mixed non-specific inflammatory infiltrates [32, 35]. These lesions mostly occur in the mild and moderate form. In contrast, severe lesions occur only in 10% of cases.

Summary

The correct treatment of cutaneous side effects may significantly improve the effectiveness of antineoplastic therapy. Skin lesions negatively affect the quality of life of patients, and controlling their symptoms may reduce the need to modify the dose and to interrupt treatment. It should be noted that, despite the sometimes great intensity of lesions, most of them do not in themselves represent a threat to the life or health of patients. The direct relationship they have with the cancer treatment indicates that their occurrence should be expected in each patient. In addition, it may be the case that prophylactic and therapeutic treatment will not alter the outcome, but only improve it, due to the presence of a provoking agent, namely, taking the medicine. Informing the patient of the causes of this situation may, in difficult cases, incline the patient to continue treatment. This is particularly justified in that some studies have documented the association of cutaneous toxicity with better therapeu-

tic outcomes. Treatment algorithms should help guide proper treatment which, as one gains experience, can be modified and smoothly adapted to particular patients. In some cases, however, cutaneous toxicity will become the crux of a clinical problem that requires the cooperation of professionals in many fields.

Conflict of interest

The authors declare no conflict of interest.

References

1. Bianchini D, Jayanth A, Chua YJ, et al. Epidermal growth factor receptor inhibitor-related skin toxicity: mechanisms, treatment, and its potential role as a predictive marker. Clin Colorectal Cancer 2008; 7: 33-43.
2. Wheeler DL, Dunn EF, Harari PM. Understanding resistance to EGFR inhibitors – impact on future treatment strategies. Nat Rev Clin Oncol 2010; 7: 493-507.
3. Marcinkowska M, Stańczyk M, Klajnert-Maculewicz B. Przeciwciało monoklonalne trastuzumab i dendrymery w terapii celowanej raka piersi. Postepy Hig Med Dosw (online) 2015; 69: 1313-24.
4. Sobańska K, Szałek E, Kamińska A, et al. Tyrosine kinase inhibitors in anticancer therapy. Farm Współ 2011; 4: 185-90.
5. Wojtukiewicz MZ, Rybałtowski M, Sierko E. Podstawy biologiczne terapii ukierunkowanej na receptor czynnika wzrostu naskórka (EGFR). Nowotwory J Oncol 2008; 58: 260-71.
6. Macdonald JB, Macdonald B, Golitz LE, et al. Cutaneous adverse effects of targeted therapies. Part I: Inhibitors of the cellular membrane. J Am Acad Dermatol 2015; 72: 203-18.
7. Wang S, Cang S, Liu D. Third-generation inhibitors targeting EGFR T790M mutation in advanced non-small cell lung cancer. J Hematol Oncol 2016; 9: 34.
8. Pirker R. Third-generation epidermal growth factor receptor tyrosine kinase inhibitors in advanced nonsmall cell lung cancer. Curr Opin Oncol 2016; 28: 115-21.
9. Ou SH. Second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs): a better mousetrap? A review of the clinical evidence. Crit Rev Oncol Hemtol 2012; 83: 407-21.
10. Liao BC, Lin CC, Yang JCH. Second and third-generation EGFR-TKIs in advanced nonsmall cell lung cancer. Curr Opin Oncol 2015; 27: 94-10.
11. Sobańska K, Szałek E, Grześkowiak E. Cutaneous toxicity of small-molecular EGFR inhibitors. Farm Współ 2013; 6: 33-40.
12. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer 2006; 6: 803-12.
13. Peus D, Hamacher L, Pittelkow MR. EGF-receptor tyrosine kinase inhibition induces keratinocyte growth arrest and terminal differentiation. J Invest Dermatol 1997; 109: 751-6.
14. Pastore S, Lulli D, Girolomoni G. Epidermal growth factor receptor signalling in keratinocyte biology: implications for skin toxicity of tyrosine kinase inhibitors. Arch Toxicol 2014; 88: 1189-203.
15. Abdullah SE, Haigentz M Jr, Piperd B. Dermatologic toxicities from monoclonal-antibodies and tyrosine kinase inhibitors against EGFR: pathophysiology and management. Chemother Res Pract 2012; 2012: 351210.
16. Chanprapaph K, Vachiramon V, Rattanakaemakorn P. Epidermal growth factor receptor inhibitors: a review of cutaneous adverse events and management. Dermatol Res Pract 2014; 2014: 734249.
17. Manousaridis I, Mavridou S, Goerdt S, et al. Cutaneous side effects of inhibitors of the RAS/RAF/MEK/ERK signaling pathway and their management. J Eur Acad Dermatol Venereol 2013; 27: 11-8.
18. Mandalà M, Massi D, De Giorgi V. Cutaneous toxicities of BRAF inhibitors: clinical and pathological challenges and call to action. Crit Rev Oncol Hematol 2013; 88: 318-37.
19. Lacouture M. Dermatologic principles and practice in oncology: conditions of the skin, hair, and nails in cancer patients. Wiley-Blackwell, New York 2014.
20. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) U.S. Department of Health And Human Services, National Institutes of Health National Cancer Institute.
21. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011; 19: 1079-95.
22. Reguiai Z, Bachet JB, Bachmeyer C, et al. Management of cutaneous adverse events induced by anti-EGFR (epidermal growth factor receptor): a French interdisciplinary therapeutic algorithm. Support Care Cancer 2012; 20: 1395-404.
23. Macdonald JB, Macdonald B, Golitz LE, et al. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. J Am Acad Dermatol 2015; 72: 221-36.
24. Segaert S, Chiritescu G, Lemmens L, et al. Skin toxicities of targeted therapies. Eur J Cancer 2009; 45 Suppl 1: 295-308.
25. Galimont-Collen AF, Vos LE, Lavrijsen AP, et al. Classification and management of skin, hair, nail and mucosal side-effects of epidermal growth factor receptor (EGFR) inhibitors. Eur J Cancer 2007; 43: 845-51.
26. Azria D, Magne N, Zouhair A, et al. Radiation recall: a well recognized but neglected phenomenon. Cancer Treat Rev 2005; 31: 555-70.
27. Barlési F, Tummino C, Tasei AM, et al. Unsuccessful rechallenge with pemetrexed after a previous radiation recall dermatitis. Lung Cancer 2006; 54: 423-5.
28. Hureaux J, Le Guen Y, Tuchais C, et al. Radiation recall dermatitis with pemetrexed. Lung Cancer 2005; 50: 255-8.
29. Miya T, Ono Y, Tanaka H, et al. Radiation recall pneumonitis induced by Gefitinib (Iressa): a case report. Nihon Kokyuki Gakkai Zasshi 2003; 41: 565-8.
30. Kodym E, Kalinska R, Ehringfeld C, et al. Frequency of radiation recall dermatitis in adult cancer patients. Onkologie 2005; 28: 18-21.
31. Saif MW, Ramos J, Knisely J. Radiation recall phenomenon secondary to bevacizumab in a patient with pancreatic cancer. JOP 2008; 9: 744-7.
32. Mizumoto M, Harada H, Asakura H, et al. Frequency and characteristics of docetaxel-induced radiation recall phenomenon. Int J Radiat Oncol Biol Phys 2006; 66: 1187-91.
33. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 2001; 59: 237-45.
34. Yeo W, Johnson PJ. Radiation-recall skin disorders associated with the use of antineoplastic drugs. Pathogenesis, prevalence, and management. Am J Clin Dermatol 2000; 1: 113-6.
35. Kitani H, Kosaka T, Fujihara T, et al. The "recall effect" in radiotherapy: is subeffective, reparable damage involved? Int J Radiat Oncol Biol Phys 1990; 18: 689-95.
36. Smith KJ, Germain M, Skelton H. Histopathologic features seen with radiation recall or enhancement eruptions. J Cutan Med Surg 2002; 6: 535-40.

37. Uemura M, Kim HM, Hata T, et al. First-line cetuximab-based chemotherapies for patients with advanced or metastatic KRAS wild-type colorectal cancer. Mol Clin Oncol 2016; 5: 375-9.
38. Conen KL, Fischer N, Hofbauer GF, et al. Cetuximab in metastatic squamous cell cancer of the skin: a Swiss case series. Dermatolog 2014; 229: 97-101.
39. Kuenen B, Witteveen PO, Ruijter R, et al. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. Clin Cancer Res 2010; 16: 1915-23.
40. Tamura Y, Nokihara H, Honda K, et al. Phase I study of the second-generation, recombinant, human EGFR antibody necitumumab in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2016; 78: 995-1002.
41. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugsand targeted therapies for cancer Part II. Targeted therapies. J Am Acad Dermatol 2014; 71: 217.e1-217.
42. Lacouture ME, Schadendorf D, Chu CY, et al. Dermatologic adverse events associated with afatinib: an oral ErbB family blocker. Expert Rev Anticancer Ther 2013; 13: 721-8.
43. Burotto M, Manasanch EE, Wilkerson J, et al. Gefitinib and erlotinib in metastatic non-small cell lung cancer: a meta-analysis of toxicity and efficacy of randomized clinical trials. Oncologist 2015; 20: 400-10.
44. Ou SH, Soo RA. Dacomitinib in lung cancer: a "lost generation" EGFR tyrosine-kinase inhibitor from a bygone era? Drug Des Devel Ther 2015; 9: 5641-53.
45. Abdel-Rahman O, Fouad M. Risk of mucocutaneous toxicities in patients with solid tumors treated with lapatinib: a systematic review and meta-analysis. Curr Med Res Opin 2015; 31: 975-86.
46. Yuan-Yuan C, Lin-Wei W, Fang-Fang C, et al. Efficacy, safety and administration timing of trastuzumab in human epidermal growth factor receptor 2 positive breast cancer patients: a meta-analysis. Exp Ther Med 2016; 11: 1721-33.
47. Tran PN, Klempner SJ. Profile of rociletinib and its potential in the treatment of non-small-cell lung cancer. Lung Cancer (Auckl) 2016; 7: 91-7.
48. https://ec.europa.eu/health/documents/communityregister/2017/20170322137470/anx_137470_pl.pdf
49. http://reference.medscape.com/drug/perjeta-pertuzumab-999749#4
50. Boix-Perales H, Borregaard J, Bech Jensen K, et al. The European Medicines Agency Review of Pertuzumab for the treatment of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer: summary of the scientific assessment of the committee for medicinal products for human use. Oncologist 2014; 19: 766-73.