THE MANAGEMENT OF EGFR-INHIBITOR INDUCED SKIN REACTIONS

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Summary

Today, the cornerstone of modern oncology is the discovery of targeted therapies. Although with fewer toxicities compared to conventional chemotherapy, the cutaneous adverse effects can determine the limitation of doses or even the interruption of treatment.

EGFR inhibitors produce numerous adverse skin reactions. Currently, EGFR inhibitors play an essential role in the oncological therapeutic arsenal, being used in the treatment of the following cancers: head and neck, lung, colon, prostate, breast, ovary, pancreas. Thus, recognizing the clinical signs, understanding the mechanism by which these adverse skin reactions occur, and most important knowing how to manage them is of great importance for all dermatologists.

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Introduction

The history of targeted therapies begins with both Rituximab, the first monoclonal antibody approved for the treatment of non-Hodgkin's lymphoma in 1997 and with the famous Imatinib, the first tyrosine kinase inhibitor used in 2001 for the treatment of chronic myeloid leukemia which was rightfully named at that time „the magic bullet". Starting that moment, Philadelphia chromosome-positive CML had become a manageable condition like diabetes or hypertension. Currently, in 2023, more than 150 distinct molecules are approved for the treatment of different types of cancer, with dozens of other molecules being tested and expected to enter clinical trials each year. We can say without a doubt that the targeted therapy represents the future of modern oncology.

What is targeted therapy

Targeted therapy is a type of treatment that uses specially developed molecules to destroy cancer cells, without affecting normal cells, thus, is also called precision therapy or personalized medicine.

Although, from a technical point of view, targeted therapy is considered a form of chemotherapy, these molecules work through a completely different mechanism. Due to the targeted action, unlike traditional chemotherapy, these drugs have fewer side effects. Basically, targeted therapy works by preventing cancer cells from multiplying, conventional chem-

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otherapy, on the other hand, destroys the neoplastic cells already formed along with normal cells of the body [1].

Targeted therapy can be classified into two main categories: small molecules and macromolecules (e.g., monoclonal antibodies, polypeptides, antibody–drug conjugates, and nucleic acids).

Small molecules are organic compounds with low molecular weight (less than 800 Dalton). They can penetrate the cell membrane and are designed to interfere with signaling pathways and act on targets located inside the cell. Their names give an indication of the type of molecule and its target. For example, molecules with the suffix „-ib" show that the molecule has inhibitory properties [2]. To date, there are 89 small molecules approved in the United States and China for the treatment of cancers. Their targets cover a wide range including kinases, epigenetic regulatory proteins, DNA damage repair enzymes, and proteasomes. However, the biggest challenges that these molecules have to overcome are the low response rate and the development of resistance [3].

Among macromolecules, the best represented in targeted therapy are monoclonal antibodies. Antibodies are high molecular weight glycoproteins that belong to the immunoglobulin family (Ig) and their purpose in the immune system is to recognize and neutralize foreign antigens and to amplify the immune response. Monoclonal antibodies are humanized antibodies that bind to specific neoplastic antigens. Most of them are too large to cross the cell membrane and are designed to attack a target either outside the cell or on the cell surface [4].

Monoclonal antibodies act on the surface of tumor cells through 3 main mechanisms: BLOCK - blocks certain molecules that neoplastic cells need to develop, FLAG - signals neoplastic cells so they can be identified and destroyed by the immune system, DELIVER - transports medicinal substances, toxic, radioactive particles in neoplastic cells.

In terms of side effects, comparing targeted therapy with traditional chemotherapy, the former has reduced toxicity, better tolerance and lowers the duration of hospitalization [5]. Although the lethality of adverse drug reactions (ADR) is lower than in the case of chemotherapy, targeted therapy requires extended periods of use or even indefinite administration, which determines the increased incidence of ADR (80%) throughout this process.

By far, the most frequent adverse drug reactions are limited to the skin and mucous membranes (86.4%) [6]. Other ADR include gastrointestinal damage, hypertension, coagulation abnormalities and cardiotoxicity [7].

The negative impact these skin reactions have on the patients' quality of life is significant. For example, in the case of the acneiform eruption caused by the administration of EGFR inhibitors, the oncologists reported the interruption of the treatment in 76% of the cases and the complete cessation in 32% of the cases [8].

EGFR (epidermal growth factor receptor), also known as ErbB-1 and Her1 is a transmembrane protein. It consists of 3 subunits: 1 extracellular domain, 1 transmembrane domain, 1 cytoplasmic domain [9].

EGFR overexpression is associated with various types of neoplasia, thus the development of small molecule inhibitors that specifically target these receptors is a promising strategy in the treatment of cancers [10].

Classification of EGFR Inhibitors

Although EGFR inhibitors can be classified according to numerous criteria (chemical structure, reversibility, class, pharmacological effect, etc.), at the moment, EGFR inhibitors used for the treatment of cancers are divided into two main categories: small molecule and monoclonal antibodies:

The small molecules inhibit EGFR tyrosine kinase activity by binding to the ATP binding site in the intracellular domain of the receptor. Examples: Erlotinib, Gefitinib, Afatinib, Lapatinib, Dacomitinib, Osimertinib, Neratinib, Mobocertinib.

Humanized monoclonal antibodies bind specifically to the EGFR extracellular domain and competitively inhibit the ligand binding. Examples: Cetuximab; Panitumumab; Necitumumab; Pertuzumab.

EGFR skin function

Skin expresses both EGFR, ErbB2, and ErbB4, whereas EGFR signaling is most important for growth, homeostasis, and repair. EGFR is physiologically expressed throughout the epidermis, especially in the basal layer.

The EGFR signaling pathway oversees skin homeostasis through multiple mechanisms and mediates anti-apoptotic and pro-survival effects.

The physiological role of the EGF receptor is to oversee epithelial tissue development and homeostasis. In pathological situations, however, especially in lung, breast or glioblastoma cancers, EGFR plays a central role in carcinogenesis.

EGFR inhibition - skin effects

EGF receptors are found throughout the epidermis. They contribute to keratinocyte proliferation and differentiation, hair growth and play an essential role in the innate immune response. Thus, the compromise of the skin barrier through the inhibition of the EGFR signaling pathway is explained.

Chronic pharmacological inhibition of EGFR leads to focal necrosis of keratinocytes, which further activates and maintains the recruitment and activation of immune cells, ultimately causing folliculitis [11].

Risk factors

Potential risk factors for the occurrence of severe skin reactions due the administration of EGFR inhibitors are as follow: age, sex, skin phototype, UV radiation exposure, associated therapies (conventional chemotherapy, radiotherapy). The predilection of the rash in sun-exposed areas suggests that ultraviolet radiation acts as a cofactor in the development and severity of the rash. In vitro, inhibition of EGFR in keratinocytes prior to UV exposure demonstrated decreased cell survival and increased apoptosis/necrosis after UV irradiation. In contrast, in a randomized study, daily use of SPF 60 sunscreens did not prevent or reduce the severity of skin reactions [12].

EGFR-inhibitor induced skin reactions

1. Acneiform eruption

The most common cutaneous reaction seen with EGFR inhibitors is a diffuse, papulopustular acneiform eruption, which is noted in more than two-thirds of patients receiving any of these agents. The primary lesion of EFGR inhibitor-induced acneiform eruption is the folliculocentric erythematous pustule or papule (figure 1, figure 2). Areas rich in sebaceous glands (scalp, face – particularly the nose, cheeks, nasolabial folds and perioral region) as well as the upper chest region (figure 3) are most frequently affected. Rarely, the rash can also spread to the lower chest, buttocks and extremities. The palmo-plantar region is characteristically spared [13]. Often, the rash is accompanied by itching, irritation, burning sensation and pain [14].

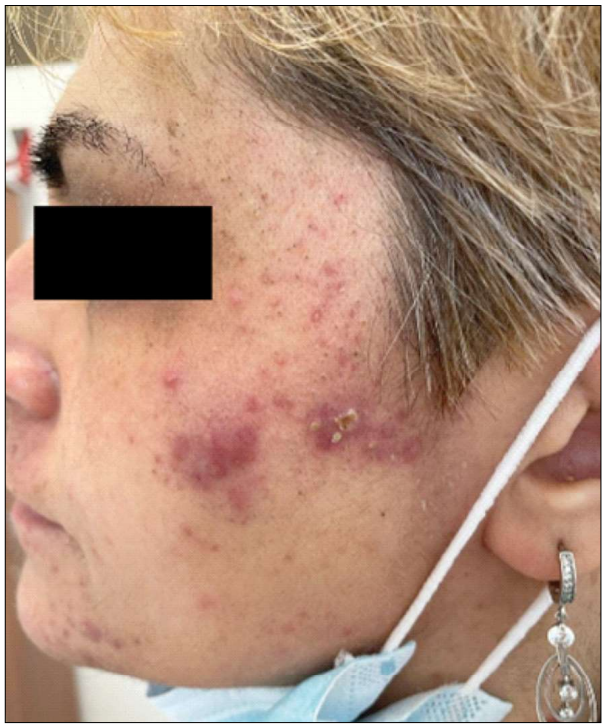
Characteristically, the rash begins in the first two weeks after the initiation of therapy, but it can also appear two months after the start of treatment [15].

In general, the rash develops in 4 distinct stages [16]:

- Week 1- dysesthesia (disturbance in the perception of sensations) accompanied by erythema and edema.
- Week 1-3 – development of erythematous papules and pustules
- Week 3-4 – formation of crusts from purulent material and necrotic keratinocytes/tissue debris.
- Week 4 and beyond – persistent erythema with telangiectasias and skin xerosis. Late-stage presentations may have purpura and ulcers favoring the buttocks and lower limbs [17].

The clinical course of the rash is characterized by periods of exacerbations and remissions. Partial or even complete resolutions may be seen despite continued EGFR inhibitor therapy [18].

Several studies have noted an association between acneiform eruption and increased overall response rate or survival [17]. This suggests that the skin eruption may be a surrogate marker for efficacy of EGFR inhibitor therapy and that acneiform eruption is not a contraindication to continued EGFR inhibitor therapy.



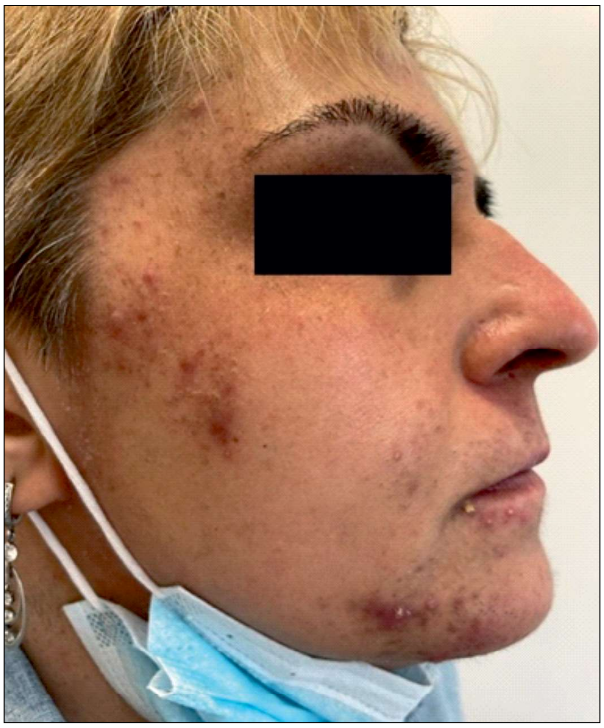


Figure 1. Acneiform eruption on the face due to EGFR inhibitors

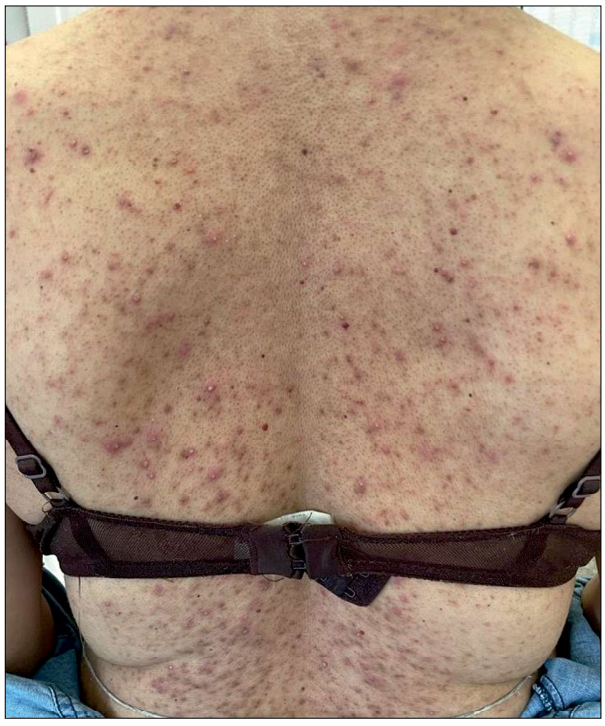


Figure 2. Acneiform eruption on the trunk due to EGFR inhibitors

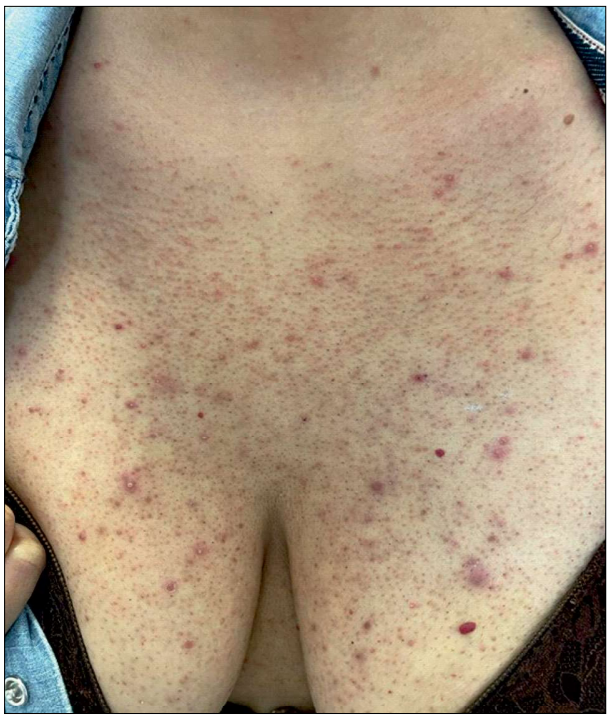


Figure 3. Acneiform eruption on the chest due to EGFR inhibitors

Grading of severity [19]

The most frequently used scale to assess the severity of cutaneous adverse reactions is the one proposed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Grade 1 - Papules and/or pustules covering <10% of the body surface area, which may or may not be associated with symptoms of pruritus or tenderness.

Grade 2 - Papules and/or pustules covering 10 to 30% of the body surface area, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (ADL); papules and/or pustules covering >30% of the body surface area, with or without mild symptoms.

Grade 3 - Papules and/or pustules covering >30% of the body surface area with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated.

Grade 4 - Life-threatening consequences; papules and/or pustules covering any percent of the body surface area, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with intravenous antibiotics indicated.

Management and prevention

General measures [20]:

- Avoid frequent washing with hot water, using hard soaps and detergents, solvents, or disinfectants.
- Limit sun exposure or use a broad-spectrum sunscreen that must be applied to exposed areas of the body every two hours when outside. It's best to use a mineral sunscreen, which are not absorbed into the skin
- Using emollients twice daily

Prevention

For the prevention, it is a common practice to use 100 mg twice a day, 100 mg daily, or oxytetracycline 500 mg twice daily for six weeks. Usually, the antibiotic is started on the same day as EGFR inhibitor therapy [17]. Topically, is prescribed a low-potent topical corticosteroid which is applied twice daily to the face and chest.

Management

The acneiform eruption is managed individually and primarily takes into account the degree of severity. Considering the importance of EGFR inhibitor therapy, the decision to stop treatment or even the dose reduction must be made together with the patient [21].

Grade 1 rash – topical low-potency corticosteroids and topical antibiotics.

Grade 2 rash – oral antibiotic 100 mg or 100 mg twice per day for four to six weeks and topical low-potency corticosteroids. If the patient is already on prophylactic antibiotic with tetracycline, alternative choices are: first-generation oral cephalosporin (eg, 500 mg twice per day, 500 mg twice per day) or (160 mg/sulfa-methoxazole 800 mg twice per day), and can be given for four weeks. We must always consider a bacterial superinfection and obtain a culture whenever is possible to determine appropriate antimicrobial therapy.

Grade $\geq$ 3 rash – in this point, we must take into consideration the dose modification or even the interruption of the treatment. This decision must involve the oncologist and the patient. We must be sensible to the patient's values and preferences.

2. Paronychia

Another frequent adverse reaction to the administration of EGFR inhibitors is paronychia which can be accompanied by pyogenic granuloma-like lesions and changes in matrix pigmentation and texture (figure 4). These modifications appear most often after 2 months of treatment, and have a incidence of 17.2%. Monitoring for bacterial superinfection is crucial (most frequently *Staphy-lococcus aureus).* Secondary to nail bed inflam-mation onycholysis or onychodystrophy may occur.

Treatment options include topical or oral antimicrobials, chemical cauterization, and partial nail avulsion [22].

3. Hair abnormalities

EGFR inhibitors determine various hair changes, the most distinctive phenomenon being trichomegaly - defined as the increase in length (12 mm or more), curling, pigmentation or

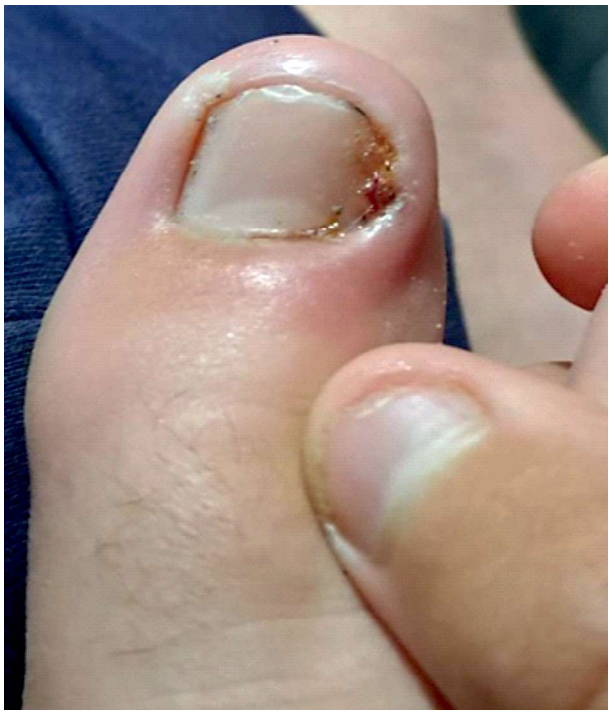


Figure 4. Paronychia

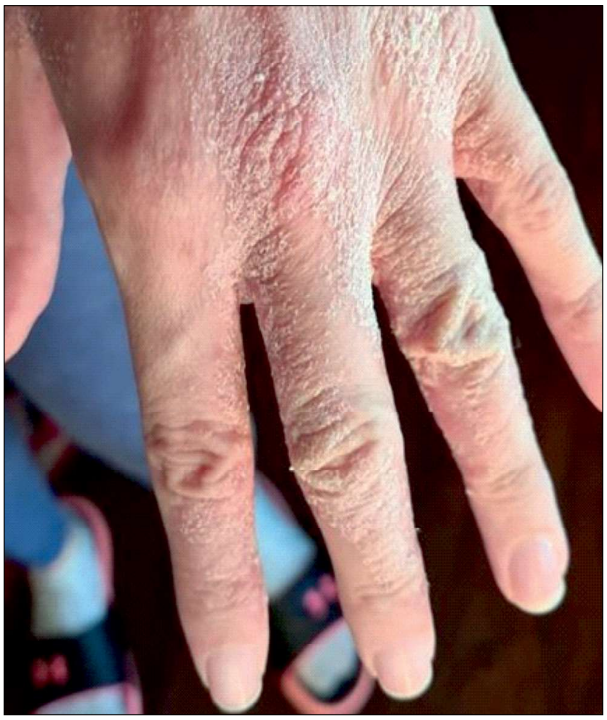


Figure 5. Xerosis

thickness of eyelashes. Inward lash curling puts patients at risk for keratitis, and eyelash trimming is recommended. Other hair abnormalities include changes in quality, texture, and growth pattern. Most of these changes begin around the second month of treatment [15].

Other common reactions include xerosis, pruritus, mucositis and photosensitivity. In the literature, all these adverse reactions in addition to the acneiform eruption and paronychia, received the acronym PRIDE (**P**apulopustules and/or **P**aronychia, **R**egulatory abnormalities of hair growth, **I**tching, and **D**ryness due to **E**pidermal growth factor receptor inhibitors) [23].

Xerosis

Xerosis (figure 5) is another common cutaneous adverse reaction and occurs in almost half of the patients treated with EGFR inhibitors [24]. It is noted that the severity is dose-dependent. It affects the extremities and in severe forms can determine asteatotic eczema and acral fissuring.

Respecting the gene-ral measures which include avoiding frequent washing with hot water, using hard soaps and detergents as well as using emollients twice daily can prevent xerosis, but sometimes topical corticosteroids may be required [25].

Pruritus

Often, pruritus is con-comitant with the acnei-form eruption, although it can also occur on normal-appearing skin. Chronic pruritus affects the vast majority of patients and has a high negative impact on the quality of life, being a source of constant psychological distress [26].

Management of pruritus mostly consists of using sedating or nonsedating oral H1 antihistamines [27]. Other agents that can be used are Gamma-aminobutyric acid (GABA) agonists such as gabapentin or pregabalin [28]. New clinical trials supports the use of (a neurokinin 1 [NK1] receptor antagonist) being effective in reducing pruritus intensity by >80 percent [29].

Conclusions

Considering the frequency of the skin reactions during targeted therapies, dermatologists play an extremely important role in the

management of these dermatologic events. Our duty is to recognize these reactions and to manage them so that the oncology patients have not only the best chance of survival, but also maintain a good quality of life.

This article aims to address adverse skin reactions following the administration of EGFR inhibitors, but emphasizing the management strategies from the latest practice guidelines, hoping that it will provide solutions to the challenges that dermatologists face when it comes to these patients.

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Conflict of interest
NONE DECLARED

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