# MANAGEMENT OF PAPULO-PUSTULAR RASH INDUCED BY EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

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## Abstract

Epidermal growth factor receptor inhibitors (EGFRI) are used for the treatment of advanced colorectal, head and neck, pancreatic, and non-small cell lung cancers. Although EGFRI have a much better tolerability profile compared with conventional cytotoxic drugs, they are associated with significant skin toxicity. The most frequent dermatologic side effect is the papulo-pustular rash (PPR). It often leads to dose reductions or discontinuation of therapy. However, therapeutic response and survival are directly proportional to PPR severity. Patients with severe PPR should not discontinue treatment as they are expected to have the best clinical outcome. Therefore, prophylactic treatment or prompt intervention are essential for rash management and maintenance of patient tolerance and compliance. Further studies are urgently needed in order to establish evidence-based approach algorithms to the management of EGFRI induced skin toxicity and to optimize the benefits of this antineoplastic therapy. Our aim is to discuss the clinical presentation, pathophysiology, and treatment options in EGFRI-induced PPR.

## Rezumat

Inhibitorii receptorului factorului de creştere epidermic (EGFRI) sunt utili în tratamentul cancerelor avansate colorectale, a celor din sfera ORL, pancreatice şi pulmonare. EGFRI au un profil de tolerabilitate mult superior medicaţiei citotoxice convenţionale, însă sunt asociaţi cu toxicitate cutanată importantă. Cel mai frecvent efect advers dermatologic este reprezentat de erupţia papulo-pustuloasă (PPR). Aceasta conduce adesea la reducerea dozei EGFRI sau întreruperea tratamentului. Totuşi, răspunsul la tratament şi prognosticul pacienţilor sunt direct proporţionale cu severitatea PPR, prin urmare administrarea EGFRI nu trebuie sistată la pacienţii cu PPR severă, aceştia având prognosticul cel mai bun. Profilaxia şi tratarea promptă a acestei reacţii adverse sunt esenţiale pentru menţinerea toleranţei şi complianţei pacienţilor. Sunt necesare studii suplimentare pentru stabilirea unui algoritm de abordare a pacienţilor ce dezvoltă reacţii adverse cutanate induse de EGFRI, bazat pe dovezi, şi pentru optimizarea tratamentului cu aceşti agenţi antineoplazici. Ne propunem să discutăm tabloul clinic, mecanismele patogenice şi opţiunile terapeutice ale PPR indusă de EGFRI.

**Keywords**: EGFR inhibitors, papulo-pustular reaction, doxycycline

## Introduction

Epidermal growth factor receptor inhibitors (EGFRI) are novel antineoplastic agents with a superior tolerability profile compared with conventional cytotoxic drugs. Nevertheless, they are associated with significant skin toxicity that often leads to dose reduction or discontinuation of therapy. The most frequent dermatologic side effect is the papulo-pustular rash (PPR). Although a series of consensus statements on the treatment of EGFRI induced PPR exist, an evidence-based approach to the management of EGFRI cutaneous side effects is lacking.

The aim of the present paper is to discuss the clinical presentation, pathophysiology, and treatment options in EGFRI-induced PPR.

## Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR/HER1/ErbB1) is a member of the type 1 receptor tyrosine kinase family. EGFR is physiologically expressed in cells of epithelial origin, especially in the undifferentiated, proliferating cells of the basal layer of the epidermis, outer root sheath of the hair follicle, epithelium of sebaceous and eccrine glands [1-3]. It is a 170-kD trans-membrane glycoprotein

composed of an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain [4]. Its natural ligands are the epidermal growth factor (EGF) and transforming growth factor–alpha (TGF-alpha). EGFR contributes to the homeostasis of epidermal cells, stimulating epidermal cell growth and division, inhibiting differentiation, protecting against ultraviolet induced cell damage, inhibiting inflammation, and accelerating wound healing [5-7].

EGFR overexpression is common in numerous solid cancers (65-75% of colorectal, 90% of head and neck, and 60-90% of lung carcinomas) [8, 9]. Dysregulated EGFR results in uncontrolled cell growth, proliferation, angiogenesis, cell migration, stromal invasion, and resistance to apoptosis and correlates with increased metastatic potential, reduced survival, poor response to chemotherapy and radiotherapy and a poor prognosis [7, 8, 10-12]. Therefore, EGFR represents an important therapeutic target.

## EGFR inhibitors

EGFR inhibitors (EGFRI) have proven efficient in the treatment of colorectal, head and neck, pancreatic, and non-small cell lung cancers (NSCLC) [11, 13-16]. Two classes of EGFRI are available: tyrosine kinase inhibitors that target the intracellular adenosine triphosphate binding domain (erlotinib and lapatinib) and monoclonal antibodies against the extracellular domain of the receptor that cause receptor internalization and thus prevent ligand binding: cetuximab, an immunoglobulin (Ig) G1 chimeric monoclonal antibody and panitumumab, an IgG2 humanized monoclonal antibody [11, 12].

Cetuximab is approved for EGFR-expressing, Kirsten rat sarcoma viral oncogene homolog (KRAS) wild type metastatic colorectal carcinoma as combination treatment with chemotherapy, or in monotherapy in patients who are refractory to oxaliplatin or irinotecan-based chemotherapy regimens or who do not tolerate irinotecan [17] and in advanced head and neck squamous cell carcinoma in association with radiotherapy and in recurrent or metastatic head and neck squamous cell carcinoma, as combination with platinum based chemotherapy. Erlotinib is approved for the treatment of advanced or metastatic non-small cell lung cancers in patients who have failed at least one prior chemotherapy regimen and in stage IV pancreatic cancer, in combination with gemcitabine or in monotherapy.

Although EGFRI have a much better tolerability profile compared with conventional cytotoxic drugs, [18] they are associated with significant skin toxicity. Considering EGFR function in normal skin development and function, the cutaneous adverse reactions of EGFRI are far from unexpected. More than 50% of patients receiving treatment with these antineoplastic agents' experience cutaneous side effects, [19] such as papulopustular reaction (PPR), xerosis, pruritus, telangectasias, hair growth disorders, and paronychia with pyogenic granuloma [20]. All these side effects are reversible and do not leave any sequels, but when severe, they may require dose modification or treatment discontinuation [21].

## Papulo-pustular rash induced by EGFRI

PPR is the most frequent dermatologic manifestation, occurring in up to 86% of patients treated with cetuximab [14, 22] and in 67-79% of patients receiving erlotinib [23, 24]. Grading of EGFR inhibitors induced PPR is performed by using one of two scoring systems: the oncological scoring system (the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0) or the dermatological skin score (WoMoScore) [25]. The latter is more sensitive and is preferred for long-term assessment of PPR. It ranges from 0 to 100 and is calculated based on body and facial involvement and severity of erythema, pustulation, scaling, and crusting [26]. PPR severity is dose-dependent [27] and in most cases, the intensity is mild (WoMoScore < 20) or moderate (WoMoScore 20-40). 5-18% of patients develop severe PPR (WoMoScore > 20), [14, 28] that alters the patient quality of life, predisposes to secondary infections, and often leads to dose reductions or discontinuation of therapy.

PPR usually involves the seborrheic areas of the face, neck, shoulders, upper trunk, and scalp, [5] but can extend to other areas of the body, the lower back, and abdomen, upper and lower limbs [29]. Palms and soles are generally spared [16, 30-35]. PPR appears 2-3 days after administration of the drug and evolves through several phases. During the first week, the patients experience erythema, oedema, and sensory disturbance in the affected area. In the second week, follicular papules appear, progressing to pustules. Untreated, the pustules may form lakes of pus. The rash reaches the maximum intensity after weeks 2-3 of evolution. Sun exposure can exacerbate the skin lesions [34]. By week 4, if anti-EGFR therapy is discontinued, crusting usually occurs and the eruption heals leaving the previously involved skin dry and slightly erythematous, sometimes with telangiectasias or hyperpigmented [16, 30-35]. Skin necrosis, ulceration and scarring have been reported [10, 16, 36, 37]. Pruritus may accompany the lesions. Delayed onset of PPR, 3 weeks after initiation of treatment with cetuximab, has been observed in 11% of the patients [29].

Although PPR usually gradually worsens if anti-EGFR therapy is continued, spontaneous improvement of skin lesions can take place [38]. Nevertheless, exacerbation of the rash occurs upon each drug administration [31]. In most cases, PPR is mild or moderate in severity. It tends to be more severe and widespread with monoclonal antibodies against EGFR compared to tyrosine kinase inhibitors [34]. 5-17% of patients treated with cetuximab develop severe PPR [29].

### Significance of the papulo-pustular rash induced by EGFRI

Interestingly, therapeutic response and progression-free survival are directly proportional to the intensity of the papulopustular rash [10, 21]. PPR is currently regarded as a surrogate marker for anti-EGFR treatment efficacy, reflecting receptor saturation by these therapeutic agents [14, 22, 23, 39, 40]. Thus, patients with severe PPR should not discontinue treatment as they are expected to have the best clinical outcome. Furthermore, studies that evaluate the benefit of individualized dose escalation in patients with no or mild skin rash at standard doses of EGFRI until the achievement of a desired severity level of PPR are ongoing and will help clarify the relationship between rash and response to treatment [41, 42].

### Pathogenesis of the papulo-pustular rash induced by EGFRI

The exact mechanism that leads to the appearance of PPR in patients treated with EGFRI is not completely elucidated.

A very important aspect is that the development of PPR is not related to pre-existing acne, a history of acne-prone skin or rosacea. PPR consists purely of inflammatory lesions, with no retentional lesions such as comedones or cysts, therefore the term "acneiform rash" is incorrect and should be avoided [30-35]. Microscopic examination of skin biopsy specimens also differentiates PPR from acne *vulgaris*. PPR is histopathologically characterized by the presence of a lymphocytic or mixed inflammatory infiltrate in the upper dermis, particularly involving the follicular *infundibulum*, follicular rupture and epithelial acantholysis [16, 30, 31, 34, 36, 43]. T-lymphocytes infiltrates predominate in the initial phases of the rash and are afterwards replaced by a neutrophilic suppurative infiltrate [16]. The pustules are sterile, but may become secondarily infected [31, 32].

Inhibition of EGFR causes growth arrest, premature epithelial differentiation and abnormal follicular keratinization. In addition, EGFR blockade increases expression of inflammatory chemokines with subsequent recruitment of inflammatory cells and release of cytokines and enzymes that produce keratinocyte apoptosis and tissue damage [36, 41, 44-46]. Thus, follicular occlusion and rupture occur. Moreover, bacterial overgrowth is promoted, aggravating skin lesions [47].

### Management of the papulo-pustular rash induced by EGFRI

Although not validated by randomized clinical trials, a series of consensus statements on the treatment of EGFRI - induced PPR have been published [10, 21, 48, 49]. Treatment goals are to prevent or reduce skin toxicity associated with anti EGFR agents, improve the patient's quality of life and avoid infectious complications, dose reduction or treatment discontinuation. Rigorous photo-protection, use of skin moisturizers, mild topical anti-inflammatory agents, topical antiseptics and antibiotics, and oral tetracyclines, particularly doxycycline and minocycline represent the main therapeutic measures employed in PPR induced by EGFRI [34, 35, 50].

Better understanding of the mechanisms involved in the development of skin toxicity of these agents has led to greater focus on preventive strategies. Results of two randomized double-blind clinical trials showed that prophylactic oral treatment with minocycline or tetracycline does not prevent PPR, but significantly reduces the severity of the rash [28, 51]. Recently, prophylactic and reactive treatments were compared in STEPP study (Skin Toxicity Evaluation Protocol with Panitumumab) [52] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2644628/-b36-co16-1-16 that concluded that pro-phylactic treatment reduces the incidence of moderate and severe cutaneous adverse effects by more than 50% and also delays the development of severe skin toxicities. The management of the rash is individualized and the treatment algorithms vary widely between medical centers. Mild PPR can be controlled by topical low-medium potency corticosteroids (1% hydrocortisone) or topical calcineurin inhibitors (pimecrolimus, tacrolimus), topical antiseptics and antibiotics (metronidazole, erythromycin or clindamycin 1-2% gel or lotion applied twice daily) [53, 54]. Topical 0.1% K1vitamin cream applied twice daily is also efficient not only in the treatment, but also in the prevention of PPR induced by EGFRI [55]. This is explained by K1 vitamin ability to activate EGFR signalling [56, 57]. In moderate and severe reactions, the association to the above mentioned local treatments of an oral semisynthetic tetracycline (doxycycline 100 mg daily or minocycline 100 mg daily for a minimum of 4 weeks) is generally recommended [28, 30, 31, 51]. Apart from their broad-spectrum antibacterial properties, oral tetracyclines exert anti-inflammatory

and immunomodulatory effects that render them efficient in this setting [58, 59]. Tetracyclines inhibit matrix metalloproteinases, influence mitogen-induced lymphocytic proliferation, [60, 61] inhibit neutrophilic chemotaxis, [62, 63] upregulate anti-inflammatory cytokines [64] and reduce production of proinflammatory cytokines [65]. However, the benefit associated with the prophylactic use of oral tetracyclines is maximum during the first month of treatment and diminishes by the end of the second month [28]. Therefore, continuing administration of oral tetracyclines beyond a 2-months period is not supported by the existing data.

In severe cases, a short course of oral cortico-therapy may also be administered, keeping in mind the possibility of interference with the antibody-dependent cytotoxic action of EGFR antibodies. In unresponsive patients, low dose oral isotretinoin therapy (10-20 mg daily) has been employed, [66, 67] but further studies are needed to determine its efficiency in EGFRI - induced PPR and its influence on the antitumoural effects of EGFRI. Topical retinoids like tazarotene did not prove efficient and can aggravate xerosis and induce local irritation. Oral antihistamines are used to reduce pruritus that may accompany the rash. If such treatments fail to improve the skin lesions, discontinuation of the anti-EGFR agent for 7–10 days and dose reduction upon reintroduction of the drug should be considered. Exceptionally rare extremely severe rashes should be treated in burn units and the administration of EGFRI should be permanently ceased.

## Conclusions

Skin toxicity represents a class effect of EGFRI, the most important dermatologic side effect of these agents being PPR. Although the severity of PPR is positively correlated to treatment response and progression - free survival, the discomfort associated with this rash, the negative impact on the patient's quality of life and the possible infectious complications are frequently the cause of dose reduction and treatment discontinuation. Prophylactic treatment or prompt interventions are essential for rash management and maintenance of patient tolerance and compliance. Oral tetracyclines efficiently control PPR induced by EGFRI and prevent severe exacerbations upon drug re-administration. Further studies are needed in order to establish evidence-based approach algorithms to the management of EGFRI - induced skin toxicity and to optimize the benefits of this antineoplastic therapy.

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