

ORIGINAL ARTICLES

Adverse Cutaneous Reactions to Erlotinib

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Abstract. *Introduction.* Erlotinib is an inhibitor of human epidermal growth factor approved for treating non-small cell lung cancer. The aim of this prospective observational study was to determine the prevalence of adverse cutaneous reactions caused by erlotinib and assess the management of such effects.

Methods. Eleven patients with lung cancer and 1 with ovarian cancer received erlotinib at a dose of 150 mg/d. The prevalence, severity, and time course of the adverse cutaneous reactions were assessed.

Results. The most frequent cutaneous reaction was acneiform eruption (10 cases). The patients were treated with topical erythromycin and clindamycin, or with doxycycline. Also reported were seborrheic dermatitis (5), paronychia (4), xerosis (3), mouth blisters (3), blepharitis (2), cheilitis (1), and fissures on the hands and feet (1). The first reactions to appear were seborrheic dermatitis (9.8 days until onset) and acneiform eruption (11.8 days), whereas the paronychia presented latest (65.3 days). One patient with acneiform eruption and another with paronychia suspended treatment until the lesions improved. *Conclusions.* Erlotinib induces adverse effects in most patients treated. Acneiform eruption, seborrheic dermatitis, and paronychia are the most frequently reported reactions and can lead to temporary suspension of erlotinib administration.

Key words: erlotinib, epidermal growth factor receptor, acneiform, seborrheic dermatitis, paronychia.

EFFECTOS CUTÁNEOS ADVERSOS CAUSADOS POR ERLOTINIB

Resumen. *Introducción.* El erlotinib es un inhibidor del factor de crecimiento epidérmico humano aprobado en el tratamiento del cáncer de pulmón no microcítico. El objetivo de este estudio prospectivo y observacional es determinar la prevalencia de los efectos cutáneos adversos por erlotinib y su manejo.

Métodos. Once pacientes con cáncer de pulmón y una con cáncer de ovario fueron tratados con erlotinib en dosis de 150 mg diarios. Se evaluó la prevalencia, la intensidad y la cronología de los efectos cutáneos adversos.

Resultados. La reacción cutánea más frecuente fue la erupción acneiforme (10 casos). Los pacientes fueron tratados con eritromicina o clindamicina tópicas, o con doxicilina. Los pacientes también desarrollaron dermatitis seborreica (5), paroniquia (4), xerosis (3), aftas orales (3), blefaritis (2), queilitis (1) y fisuras en manos y pies (1). Los efectos adversos más precoces fueron la dermatitis seborreica (9,8 días hasta la aparición) y la erupción acneiforme (11,8 días), mientras que la paroniquia fue el efecto más tardío (65,3 días). Un paciente con erupción acneiforme y otro con paroniquia suspendieron el tratamiento con erlotinib hasta la mejoría de las lesiones.

Conclusiones. El erlotinib produce efectos cutáneos adversos en la gran mayoría de los pacientes tratados. La erupción acneiforme, la dermatitis seborreica y la paroniquia son los efectos más frecuentes, que pueden llevar a interrumpir temporalmente la administración de erlotinib.

Palabras clave: erlotinib, receptor de factor de crecimiento epidérmico, acneiforme, dermatitis seborreica, paroniquia.

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Introduction

Recent years have seen the development of novel molecular entities for treating cancer. Several of the resulting new drugs inhibit the activity of epidermal growth factor (EGF), whose concentrations are increased in some solid tumors thereby activating an autocrine loop.¹ EGF activity can be

inhibited either by directly blocking its receptor (EGFR) with monoclonal antibodies such as cetuximab (Erbix),² or by using EGFR-tyrosine kinase inhibitors such as gefitinib (Iressa), erlotinib (Tarceva),³⁻⁵ and lapatinib.⁶ Drugs that block EGF activity have a better safety profile than standard chemotherapy agents and have no adverse effects on blood cell counts. The most frequently reported adverse effects associated with EGFR inhibitors are diarrhea and skin reactions, in particular localized papules and pustules that appear on the face and in the midchest region after the first week of treatment.⁷

Skin reactions associated with cetuximab and gefitinib have been studied in detail.⁸⁻¹⁷ Erlotinib was approved by the European Medicines Agency and the Spanish Agency of Medicines and Healthcare Products for the treatment of locally advanced or metastatic non-small cell cancer in patients unsuccessfully treated with at least one chemotherapy regimen. Erlotinib has been approved relatively recently and has a seemingly similar safety profile to that of other EGFR inhibitors. The aim of this study was to determine the frequency, time course, and severity of adverse skin reactions associated with the use of erlotinib.

Patients and Methods

Twelve patients were started on erlotinib treatment at the Oncology Department of the Consorci Hospital General Universitari in Valencia, Spain. The group included 9 women and 3 men aged between 29 and 67 years (mean age, 52.9 years). One of the patients had ovarian cancer and the others all had stage III or IV lung cancer that had not responded to conventional chemotherapy. None of the patients were receiving other drugs that could have been involved in causing the skin reactions observed. Erlotinib

was administered orally, as a single dose of 150 mg/d. All the patients were visited at least twice by a dermatologist. The first visit was made 2 weeks after treatment, and the remaining visits were made at 4-week intervals to check for the appearance of delayed skin reactions and to evaluate response to dermatological treatment. At each visit, patients underwent a complete skin examination that included nails, mouth, and scalp. The attending dermatologists recorded the location, time to onset after starting erlotinib therapy, and severity of the lesions. Severity was measured in accordance with the reporting guidelines described in the Common Terminology Criteria for Adverse Events, version 3.0 (Publish Date August 9, 2006), published by the National Cancer Institute and available at <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.

Results

All the patients but one developed adverse skin reactions; these consisted of acneiform eruption, development or exacerbation of seborrheic dermatitis, paronychia, dry skin, mouth ulcers, heel, toe, and finger fissures, blepharitis, and angular cheilitis (Table 1). No other mucocutaneous changes associated with the use of erlotinib were detected and none of the adverse events observed were grade 4 or 5.

Acneiform eruption presented as inflammatory papules and pustules, which, in all patients, were located on the top part of the nose and in the nasolabial creases (Figure 1). In many patients, the lesions also affected other parts of the face (notably the forehead and the chin), the scalp, the neck, and presternal and interscapular regions (Figure 2). In the most severe case of acneiform eruption, hemorrhagic crusts formed on the pustules on the nose; treatment with erlotinib was suspended until the lesions improved. When the treatment was reinstated 2 weeks later, the acneiform lesions

Tabla. Adverse Mucocutaneous Effects Due to Erlotinib

Adverse effect	Patient, No.	Average Time to Onset, d	Toxicity Grade		
			1	2	3
Acneiform eruption	10	11.8	1	6	3
Seborrheic dermatitis	5	9.8	1	4	0
Paronychia	4	65.3	1	2	1
Mouth ulcers	3	24	0	3	0
Xerosis	3	32	2	1	0
Blepharitis	2	30	1	1	0
Fissures	1	30	0	1	0
Angular cheilitis	1	20	0	1	0



Figure 1. Papules and pustules in seborrheic areas of the face.



Figure 2. Confluent papules and pustules in the presternal region.

returned but they were considerably less severe. Patients with grade 2 acneiform eruption confined to the face were treated with topical erythromycin or clindamycin, while those with grade 2 or 3 lesions were given 100 mg of doxycycline daily for 2 weeks or until the lesions resolved. The development of acneiform lesions did not seem to be associated with a greater frequency or severity of other adverse skin events associated with EGFR inhibitors.

A punch biopsy of the acneiform lesions was performed in 2 patients. The first biopsy revealed a notable subcorneal pustule containing neutrophils, as well as reduced thickness of the corneal layer, reduction of the granular layer, dilated capillary blood vessels, and a predominantly lymphocytic perivascular inflammatory infiltrate containing neutrophils and extravasated red blood cells. The second biopsy revealed a lymphohistiocytic infiltrate surrounding the pilosebaceous units and granulomas with multinucleated giant cells (Figure 3).

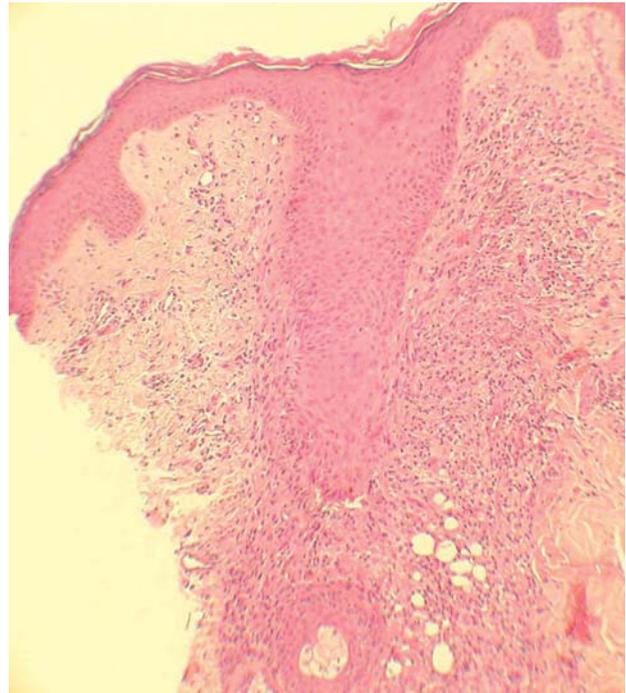


Figure 3. Granulomatous inflammation around a hair follicle (hematoxylin–eosin, original magnification $\times 40$).

The second most common skin reaction in our group of patients was an eruption similar to seborrheic dermatitis. In most cases, these lesions appeared on the head, in the nasolabial creases, between the eyebrows, and behind the ears (Figure 4). One patient with a history of mild seborrheic dermatitis confined to the face developed presternal lesions. Many patients with seborrheic dermatitis also had acneiform lesions, although the predominance of one condition over the other was very variable. Patients with clearly predominant seborrheic dermatitis were treated with an emulsion of hydrocortisone and ketoconazole.

Paronychia affected both fingers and toes; some patients developed inflammation in just one finger or toe, others in several, and involvement was both simultaneous and consecutive. The nail folds were inflamed and most patients also developed pyogenic granulomas (Figure 5). One patient developed extremely painful exudative lesions, which led to the temporary interruption of erlotinib. Culture of the exudate revealed *Staphylococcus aureus*. The patients were treated with astringent washes, topical antibiotics, and oral antibiotics in the case of persistent suppurative lesions that did not respond to topical antibiotics. Silver nitrate was applied to reduce excessive tissue.

The mouth ulcers measured approximately 2 mm in diameter and had a whitish background. Although painful, the ulcers were not very symptomatic (Figure 6). They appeared on the buccal mucosa and the tongue but not on the nasal mucosa. Xerosis presented as asteatotic eczema

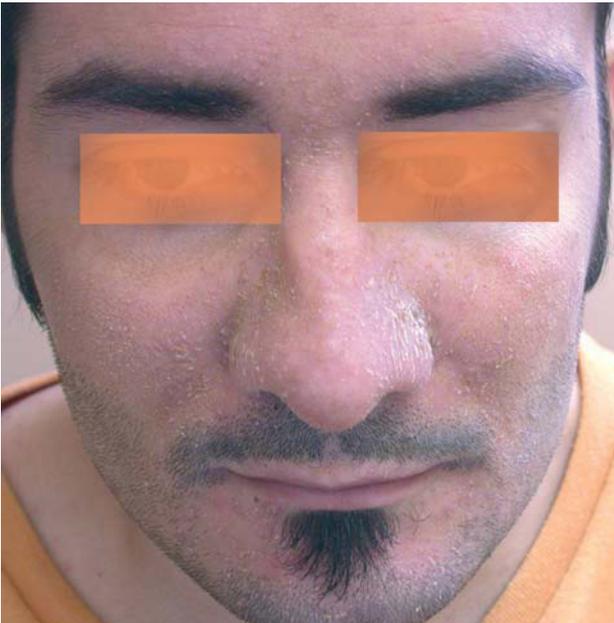


Figure 4. Facial erythema and yellowish scales in the nasolabial creases and between the eyebrows.

and generalized dry skin. One patient developed painful fissures on her heels and the interphalangeal joints of the hands (Figure 7). Blepharitis only occurred in patients with acneiform eruption and onset was simultaneous.

There were no reports of hair growth disorders or decreased hair quality. The one patient who did not develop adverse effects due to the use of erlotinib developed metastatic squamous cell lung cancer of the skin, detected by the attending dermatologist at week 8 week of treatment.

Discussion

The most common adverse effects associated with EGFR inhibitors are skin reactions, which, together with diarrhea, are severe enough to be dose limiting.¹⁸ It is essential to treat these adverse reactions adequately to ensure improved quality of life, greater acceptance of treatment, and the use of higher doses for longer periods of time. The effectiveness of the strategies used to manage these adverse effects, however, has not been studied, and the literature contains descriptions of cases involving just small numbers of patients. The fact that the skin lesions caused by EGFR inhibitors tend to resolve spontaneously makes it even more difficult to evaluate treatment efficacy.

Acneiform eruption is the most frequently reported adverse skin reaction associated with EGFR inhibitors, and within this group of drugs, erlotinib is the most common cause of adverse skin reactions because it is used at the maximum tolerated dose.¹⁹ In one study involving 485



Figure 5. Paronychia with granulated tissue build-up.



Figure 6. Punctiform ulcers on the tongue.



Figure 7. Fissures and paronychia on fingers.

patients with non-small cell lung cancer treated with erlotinib, 75% of patients developed a skin eruption; 6% of these required a dose reduction and 1% required treatment discontinuation.¹⁹ Skin eruptions of this type have attracted strong interest from oncologists as it is believed that their severity might be related to improved tumor response and increased survival.^{2,4,20,21} Several authors have suggested that severity indicators could be used to tailor EGFR inhibitor dosage to achieve maximum tumor response.²¹⁻²³ The cause of acneiform eruption is unknown although it could be due to EGFR inhibition in the epidermis and hair follicle. EGFR is preferentially expressed in the basal cell layer of the epidermis and in the outer sheath of the hair follicle, where it contributes to follicle differentiation and development.²⁴ Acne induced by EGFR inhibitors could be associated with follicular hyperkeratosis, follicular plugging, obstruction of the follicular ostium, and alteration of the hair growth cycle, leading to follicular degeneration and destruction and a severe inflammatory response.⁸ There is no evidence to support that the pustules seen in patients treated with erlotinib are of infectious origin.^{9,14}

Exanthema clearly predominates in seborrheic areas such as the face (particularly the nasolabial creases and the nose and chin), the scalp, the neck, and the shoulders and chest (mostly presternal and interscapular regions). Affected patients develop follicular papules and pustules, which are often itchy. Some patients develop erythema similar to rosacea in addition to papules and pustules, while others experience flaky/scaling skin that is evocative of seborrheic dermatitis. In more severe cases, hemorrhagic crusts may form on the pustules.¹³ The lesions appear in the week following treatment and reach maximum severity at week 2 or 3, after which they gradually and spontaneously disappear.^{3,19} Both the severity of the lesions and the speed with which they appear are directly related to dose.²⁵ Most patients who develop acneiform eruption due to EGFR inhibitors have grade 1 or 2 toxicity; only 3% develop grade 3 toxicity, and, notably, there have been no reports of life-threatening cases.²⁶ Despite its most commonly used name, acneiform eruption, numerous factors (absence of comedones, monomorphic appearance of lesions, absence of cysts and nodules, complete resolution of depressed scarring, and intense itching that sometimes occurs) differentiate this pustulous reaction from true acne.

The histopathological findings for lesions due to erlotinib, gefitinib, and cetuximab are the same. According to the literature, there is a predominantly neutrophilic infiltrate in the dermis and around the follicular infundibulum. The corneal layer is thin and compact and loses its characteristic basket-weave appearance. There have been several reports of a lichenoid reaction with keratinocyte apoptosis, vacuolar degeneration of the basal cell layer, and a mononuclear infiltrate. Other findings include acantholysis, parakeratosis,

and extravasated red blood cells. Sweat and sebaceous glands are unremarkable.^{8-10,12-15,2}

Treatments described in the literature include topical antibiotics and antiseptics such as erythromycin, clindamycin, fusidic acid, tretinoin cream, ketoconazole and econazole cream, benzoyl peroxide gel, topical corticosteroids, iodine povidone solution, hexamidine solution, and oral antibiotics such as minocycline and fusidic acid.^{8,12,13,15} It is preferable to avoid retinoid and salicylic acid and gels and solutions in patients with xerosis and flaky/scaling skin. One group of authors reported the gradual spontaneous disappearance of lesions despite continued administration of the EGFR inhibitor at the same dose.¹³ In the same study, patients administered oral fusidic acid and erythromycin emulsion from the moment they received the first dose of cetuximab did not develop either papules or pustules. Oral isotretinoin is not recommended as it can exacerbate xerosis and paronychia. Antihistamines can help when acneiform eruption is accompanied by itching.

Acneiform eruption was the most common adverse effect in our series of patients, and the use of antibiotics in solution (erythromycin or clindamycin) did not seem to be effective. Patients treated with doxycycline, in contrast, improved considerably, probably more as a result of its antiinflammatory action than its antibiotic action.²⁸

Although seborrheic dermatitis was very common in our series of patients, very little emphasis has been made of this condition in previous studies. Seemingly, the patients in our group who developed diffuse grade 2 or 3 eruption had a history of mild or moderate seborrheic dermatitis, indicating, perhaps, that erlotinib might exacerbate this condition in predisposed individuals. The fact that seborrheic and acneiform lesions had a similar time to onset and distribution in certain patients suggests that the conditions share the same pathogenic mechanism, in all likelihood related to EGFR expression in the pilosebaceous unit.^{29,30} In our case, we decided to treat seborrheic dermatitis as a separate entity as in certain patients it was clearly distinguishable from acneiform eruption, although it is possible that the 2 conditions (and also very possibly blepharitis) were opposing manifestations of the same adverse effect. Patients with clearly predominant seborrheic dermatitis component in the eruption received rapid relief following administration of hydrocortisone and ketoconazole in emulsion. We do not know, however, if the beneficial effect observed was due exclusively to the active ingredients or also to the vehicle used.

EGFR inhibitors can cause dry skin with diffuse flaking or scaling evocative of atopic dermatitis; this adverse effect is more common in elderly patients who have previously undergone chemotherapy.^{8,15,30}

The literature also contains anecdotal reports of hair growth disorders such as slow beard growth, trichomegaly, and fine, brittle hair following the use of gefitinib.^{11,15,31} We

observed no hair disorders in our patients, probably because our series was small, but also possibly because different tyrosine kinase inhibitors can cause different adverse effects.

Paronychia is a painful condition characterized by erythema and excessive granulation tissue around several finger and/or toe nails. Affected nails have the appearance of ingrown nails. The time to onset with gefitinib ranges from 4 weeks to over 12 months⁸ and superinfection is common.³² Treatments reported in the literature include antiseptic and astringent washes, topical and systemic antibiotics, and even the partial excision of the nail plate.^{8,33,34} In our patients, the application of silver nitrate helped to reduce excessive granulation tissue. It may be necessary to temporarily suspend treatment in these patients because of the intense pain and subsequent difficulty walking.

Conclusions

Although acneiform eruption is the most common and well-known adverse effect associated with erlotinib, other skin reactions capable of affecting patients' quality of life can also occur. Despite the small size of our series, our findings coincide with those of other studies of EGFR inhibitors in that the most common manifestations were acneiform eruption, paronychia, and xerosis. It is difficult to compare the prevalence of seborrheic dermatitis with that in other studies as some authors treat it as a component of acneiform eruption. Both acneiform eruption and paronychia may require dose reduction or temporary interruption of treatment. The appropriate management of adverse skin reactions clearly improves quality of life. It is particularly important to note that improved tolerance to erlotinib would allow the use of higher doses aimed at improving tumor response and increasing survival. Further studies involving greater numbers of patients are required to determine the incidence, time course, and response to treatment of the adverse effects associated with erlotinib.

Conflicts of Interest

The authors declare no conflicts of interest.

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