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Original Article

Cutaneous complications of erlotinib in the treatment of non-small cell lung cancer

以得舒緩治療非小細胞肺癌的皮膚併發症

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With the rapid expansion in knowledge concerning oncogenesis, targeted pharmacotherapies inhibiting tumour growth are emerging. This article aims to raise awareness of the dermatological side-effect profile of erlotinib. Erlotinib is a tyrosine kinase inhibitor of epidermal growth-factor receptor (EGFR) and is employed in the treatment of non-small cell lung cancer. We describe the dermatological side-effects of erlotinib, with particular attention to the clinical and histological features of its acne-like eruption. Patient comfort and compliance will be significantly enhanced by the early detection and treatment of side-effects from EGFR inhibitors.

隨著癌症發病原理知識的快速發展，分子標靶治療正興起。本文指出得舒緩於皮膚的副作用。得舒緩是表皮生長因子接受器的酪胺酸激酶抑制劑，用於治療非小細胞肺癌。得舒緩的皮膚副作用，特別是其痤瘡樣皮疹的臨床及組織學特點將予滿描述。早期發現及治療表皮生長因子接受器抑制劑的副作用有助患者的合作及舒適感。

Keywords: Acne-like, epithelial, neoplasia, paronychia, xerosis

關鍵詞：痤瘡樣，上皮，腫瘤，甲溝炎，乾燥病

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Introduction

Lung cancer is a leading cause of cancer mortality in both men and women. Its incidence is increasing in Asia due to cigarette smoking. With the rapid expansion of knowledge in areas concerning regulation of tumour growth and development, targeted pharmacotherapies inhibiting tumour growth are emerging. In this article, we aim at demonstrating the importance of recognition of dermatological side-effects of these increasingly used epithelial growth-factor receptor (EGFR)

blockers. Increased survival rates correlate with ongoing chemotherapy. Patients are able to continue with activities of daily living and work in a highly functional capacity. Effective management of side-effects is, therefore, of paramount importance.

Objective

To describe the muco-cutaneous side effects of erlotinib therapy in patients suffering from non-small cell lung cancer (NSCLC).

Methods

Three NSCLC patients having erlotinib chemotherapy were voluntarily recruited. They were regularly reviewed by their oncologists, as standardized for NSCLC patients. Due to the onset of dermatological side-effects, all three patients were referred to a dermatologist. Skin biopsies and clinical photos were taken. Patients were reviewed periodically by their dermatologists to assess progress and response to treatment.

Case report

We followed three patients over time and their clinical background was as follows:

Patient 1: A 41-year-old female was diagnosed to have adenocarcinoma of the lung after initial presentation with persistent hoarseness, cough and right upper lobe mass on chest X-ray. She was a non-smoker. Erlotinib was commenced as first-line chemotherapy.

Patient 2: A 77-year-old female was diagnosed to have adenocarcinoma of the lung after initial presentation with left arm pain and investigations revealed NSCLC with splenic metastases. She was a non-smoker. She was given carboplatin and gemcitabine followed by pemetrexed as first line chemotherapy, together with adjuvant radiotherapy. Remission was not achieved. Erlotinib was commenced as second-line chemotherapy 9 months post-diagnosis.

Patient 3: A 37-year-old female was diagnosed to have NSCLC after presenting with chest pain, fatigue and minimal weight loss for over 6 months. She was previously fit, well and was a non-smoker. Initial management consisted of left pneumonectomy, chemotherapy with carboplatin and paclitaxel for 6 weeks, followed by 29 sessions of radiotherapy over 9 weeks. Failing induction of remission, our patient was commenced on second-line erlotinib therapy 9 months post-diagnosis.

The demographic data, clinical details, side effect profile and treatment of our three cases were documented in Table 1.

Clinical features of acne-like eruption of erlotinib

They presented as papulopustular, acne-like eruption in the areas of sebaceous glands. This included the T-zone of the face, centering around the forehead, nose and chin (Figure 1).

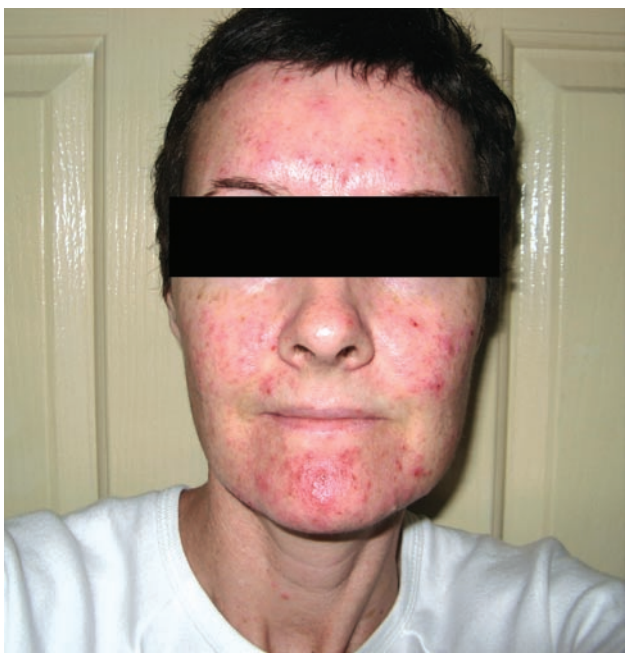

Figure 1. Clinical photo of case 3 showing erythematous papules with some excoriations distributed mainly on the T-zone of the face (forehead, cheeks and chin).

Table 1. Clinical details of 3 Australian patients with non-small cell lung cancer receiving erlotinib therapy

Patient no., Gender, Age, Ethnicity	Chemotherapy dosage	Timeline of side effects post commencement of erlotinib	Side effect management
1 Female 41 Greek	Erlotinib 150 mg daily only	Day 2-7: Scalp/hair neuralgia, acne like eruption on facial T-zone Day 11: Acne like eruption progressed over scalp, face, back, chest, anterior thighs Day 18: Distressing ongoing acne like eruption Day 24: Acne like eruption improved 12 months later: Ongoing acne like eruption with flares and regressions Xerosis (generalized) and pruritus Hair abnormalities: trichomegaly (long, curly eyelashes), hirsutism (generalized), scalp hair thinning Nail changes: paronychia, nail ridging, distal finger tuft fissuring	Erlotinib ceased 4/7 then resumed, topical clindamycin, vitamin supplements, cetaphil lotion, eyelash trimming, electrolysis/epilation
2 Female 77 Danish/Irish	Resistant to 1st line chemotherapy Erlotinib 150 mg daily Erlotinib 100 mg daily	Week 1-6: Painful acne like eruption, progressing in a craniocaudal distribution – face, neck, shoulders, forearms and knees Week 7-15: Ongoing acne like eruption, especially severe over facial T-zone, with nasal bacterial superinfection 4 months: Ongoing extensive painful debilitating acne like eruption with ulceration 5 months: Acne like eruption improved, nail ridging 15 months: Minimal acne like eruption	Mupirocin ointment, erlotinib ceased 3/52, wet dressings to ulcers, recommenced at 100 mg daily
3 Female 37 Anglo-Saxon	Refractory to surgery, 1st line chemotherapy/ radiotherapy Erlotinib 150 mg daily Erlotinib 100 mg daily	Day 2-7: Acne like eruption on facial T-zone, neck, chest, back, abdomen and legs Day 8: Ongoing less severe but significant generalized acne like eruption Day 21 onwards: Xerosis & desquamation, especially scalp 3 months: Marked brittle, wiry hair regrowth (post chemo- and radio-therapy) Hair abnormalities: trichomegaly of the eyelashes and hirsutism (generalized) Nail changes: paronychia – fingers on both hands and right big toe 4-5 months: Extensive acne like eruption: face, anterior chest, shoulders and back marked xerosis and pruritus 7 months: Significant improvement of acne like eruption after treatment by antibiotics	Decreased dose of erlotinib 100 mg daily Tetracycline for 3/52 switch to keflex & elidel Avoidance of dark clothing, open toed shoes Doxycycline, topical erythromycin

In addition, the back and chest were commonly involved. Associated erythema and pruritus could occur.

Histopathology

Histology was similar in all three patients. The pustular lesions showed a superficial and/or mid-dermal acute folliculitis. There was prominent neutrophilic exudate in the follicular lumen, associated with rupture and extension of intense neutrophilic infiltrate into the surrounding reticular dermis in addition to leukocytoclasis and some necrosis. No bacteria were identified. The superficial dermis contained a mild perivascular lymphocytic infiltrate. The epidermis had loss of the normal basket-weave orthokeratotic corneal layer, with a thinned compact orthokeratotic layer associated with hypogranulosis. There was no evidence of capillary dilatation or sebaceous gland hyperplasia (Figure 2).

We proposed a new severity grading system (Table 2, see discussion below). The relationship between erlotinib dosages and severity grading over time were illustrated in Figure 3 a, b and c.

Discussion

Mechanism of action of erlotinib

Abnormal EGFR expression occurs in several malignancies including head, neck, breast, lung, colorectal, ovarian, and bladder cancers.[1] The receptor function controls cellular processes linked to proliferation, survival, differentiation and angiogenesis. Deregulation can contribute to tumour progression.[2] Excessive expression of EGFR has been associated with chemoresistance and poor prognosis. Erlotinib inhibits the tyrosine kinase of the EGFR cascade with demonstrated antitumour activity alone or in combination with conventional chemotherapy.[1] EGFR is also present in the skin, particularly keratinocytes, follicular epithelium, capillaries of the epidermis, sebaceous and sweat glands. It is crucial for the normal development and physiology of the epidermis. Thus, not unexpectedly, adverse side effects of the EGFR inhibitors involve the skin and skin adnexae.[3]

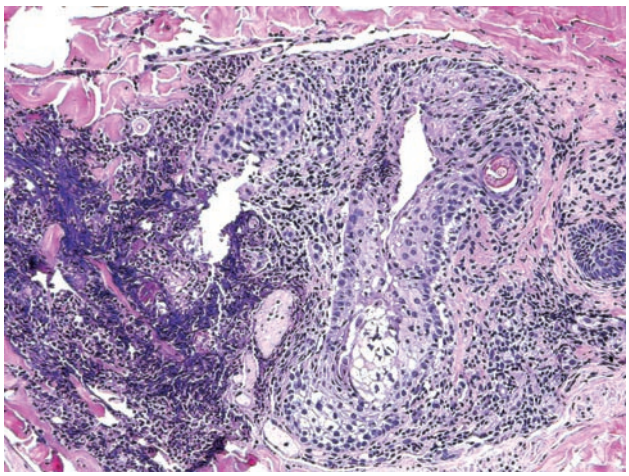

Figure 2. Photomicrograph of acne-like eruption, showing folliculitis with follicular rupture and extension of the inflammation into the adjacent dermis. (H&E stain, x 100 magnification)

Table 2. Grading severity of acne-like eruption based on symptoms and recommended therapy

Grade	Severity of skin lesion	Suggested therapy
Grade 1 Mild	Limited in extent Asymptomatic	Nil necessary
Grade 2 Moderate	Multifocal Symptomatic	Treatment usually necessary Topical +/- systemic antibiotics
Grade 3 Severe	Generalized Distressing extensive acne-like eruption	Systemic antibiotics +/- dose reduction/ cessation therapy

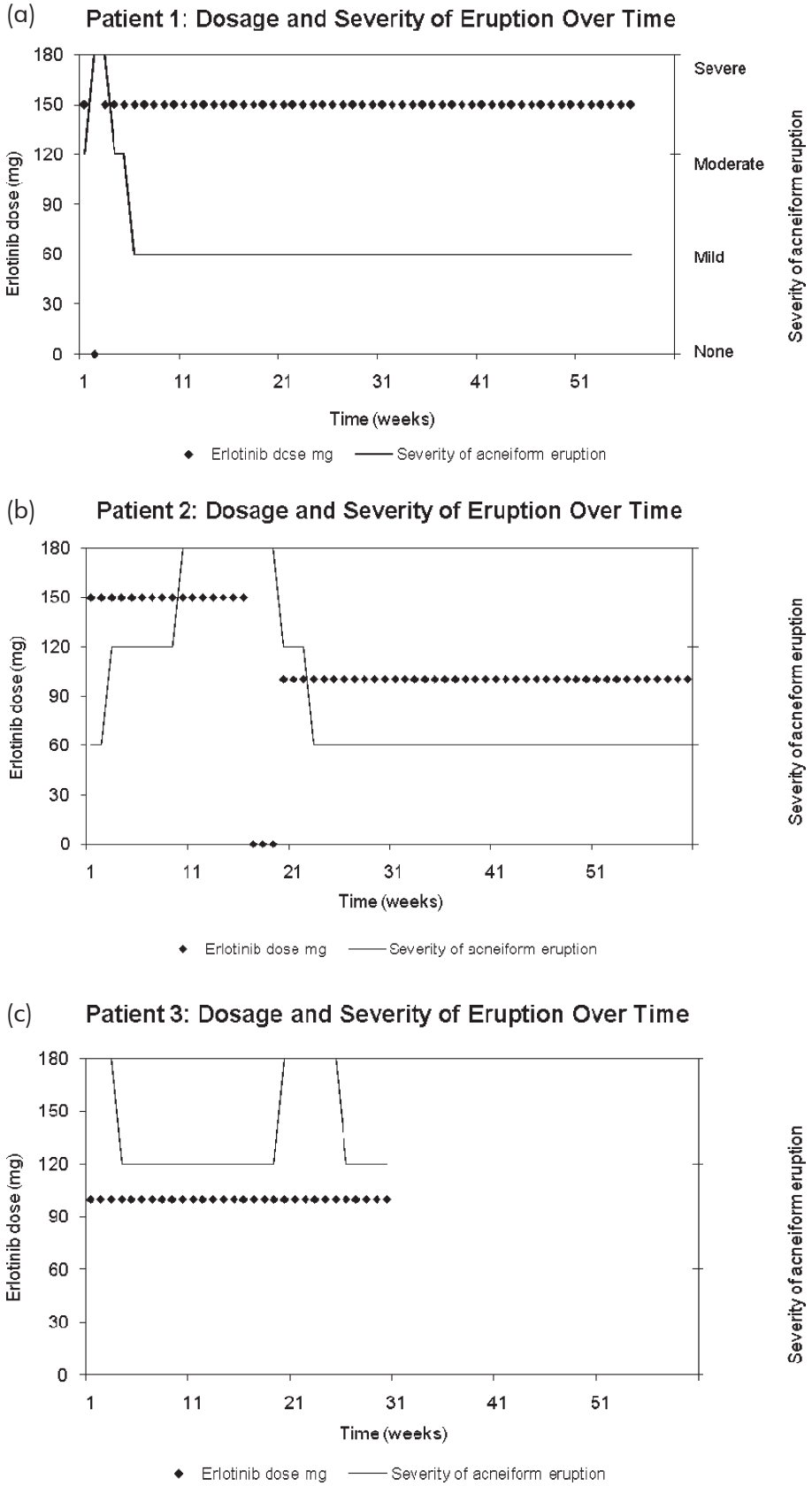

Figure 3. Relationship between erlotinib dosages and severity grading of acne-like eruption in three cases of the present report.

Skin and adnexal side-effects associated with tyrosine kinase inhibitors of the EGFR cascade include acne-like eruption, xerosis, pruritus, paronychia, pyogenic granuloma and hair changes. Our patients experienced cutaneous symptoms and signs consistent with those reported in the literature. Acne-like eruption was the most distressing and chronic. Although not fully characterized, there is a putative pathophysiological mechanism through which EGFR inhibitors cause cutaneous side effects. In experimental models, acne-like eruption is thought to be due to blockade of EGFR which profoundly modifies chemokines secretion, leading to leukocyte chemotaxis and infiltration in the follicles and finally skin inflammation.[4]

Defining the eruption – a new entity?

Until recently, the acne-like eruption has been referred to as "rash" by oncologists. This eruption appears to be a distinctive neutrophilic folliculitis unique to the EGFR inhibitors. It is the most common side effect recorded with EGFR inhibitors, occurring in 43-85% of patients taking these medications.[5-7] The severity of the eruption may have a positive association with treatment response and thus survival.[1]

Folliculitis, acneiform eruption,[1] pustular eruption,[8] acute generalized exanthematous pustulosis (AGEP)[9] are all terms used to describe the erythematous papulopustular eruption over the T-zone of the face, neck, retroauricular area, shoulders, chest, back, lower abdomen and thighs. We suggest the use of the term acne-like eruption because the other terms may confuse clinicians, potentially leading to inappropriate management. The use of the term AGEP is inappropriate due to the lack of the distinctive clinical picture of fever, leukocytosis and spontaneous resolution in approximately 14-21 days.[10] The changes of suppurative folliculitis in our three case are in keeping with those previously published in the literature describing the histopathology of follicular pustular lesions of EGFR inhibitor reactions.[6,8,11]

This "rash" distinguishes itself from acne by pruritus and the absence of open and closed comedones. Depending on the patient's age and history, acne vulgaris may be pre-existing or co-existing. This may complicate the clinical picture. The differential diagnosis includes acne vulgaris, acne rosacea, steroid folliculitis or drug-induced folliculitis.

We also propose a new severity grading system. Various severity grading systems have been used in the literature, including a generic National American Cancer Institute adverse event scale for acneiform eruptions.[12] Clinically there is a continuum of severity, both from the assessing clinician and the subjective patient experience. We find it more useful to use the following (Table 2). Grade 1 (mild): Acne-like eruption is an asymptomatic macular or papular erythematous eruption in an acneiform distribution which does not necessarily distress the patient to seek treatment. Grade 2 (moderate) is more florid. Grade 2 is multifocal in distribution and therapy is usually necessary. Grade 3 (severe) is generalized in distribution with confluent, painful lesions and/or ulceration, requiring systemic therapy.

Other side effects of erlotinib

Xerosis and pruritus

Xerosis, pruritus and desquamation was a side-effect experienced by all our patients. They developed fissures on their dry fingertips. Generalized body desquamation with prominent scalp involvement was also seen. The putative mechanism was the same as for acne-like eruption with disturbance in the suprabasal keratinocyte maturation.[13]

Hair changes

In our patients, several notable hair changes occurred after 2-3 months of therapy. These

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included hair texture alteration to fine, wiry/curly brittle hair, hirsutism, eyelash trichomegaly and gradual onset of androgen-like balding. Eyelash trichomegaly was particularly pronounced in patient 1, the mechanism for which is unknown. The androgen-like balding might be due to interactions between hormonal receptors and EGFR.[1]

Nail changes

They can present as debilitating paronychial inflammation with or without superinfection or friable pyogenic, granulomatous periungual tissue changes which can be a nuisance. Other nail changes include partial or complete loss of the nail, severe fissuring of the distal finger tufts, digital xerosis and desquamation or nail ridging and pitting. It is a delayed side-effect occurring weeks to months after therapy.[13]

Distinct from the putative mechanism of acne-like eruption, the pathophysiology mechanism of these nail changes is currently unknown. It is postulated to be due to disturbance in the nail matrix and epidermal keratinocytes, both being controlled by the same regulatory mechanisms.[13] The clinical picture of nail toxicity can be complicated by pre-existing or concomitant nail changes not related to erlotinib therapy, for example, concomitant nail disease in the diabetic population who are predisposed to nail changes.

Management of side effects of erlotinib

Acne-like eruption management varies according to the grade of severity (Table 2). Grade 1, which is mild, may not require any therapy, but this must be individualized to the patient. Over-the-counter non-soap based, cleansing face washes containing salicylic acid may be of use. For grade 2 (moderate) and grade 3 (severe), topical and or systemic management may be indicated. Topical therapies include erythromycin or clindamycin. Systemic options include tetracycline or erythromycin. Steroid use is inappropriate because of the risk of steroid induced acne. Oral isoretinoin is controversial and we do not recommend its use.[14] Dose reduction or cessation of erlotinib may be required in severe or refractory cases.

Management of associated xerosis and pruritus encompasses general measures. This includes minimization of skin heat exposure and the use of non-soap based products. Fragrance-free low irritant moisturisers and fish oil supplements may be useful. The clinical scenario can be complicated by coexisting xerotic skin conditions, for example if the patient has a background history of asteatotic eczema, then dermatological review is essential.

Erlotinib hair toxicities are variable and hirsutism is by far the most distressing to female patients. Temporary measures of epilation and waxing are often helpful for avoidance of social embarrassment. The clinical context of the patient is again important, particularly in the setting of erlotinib-associated hirsutism on a background of cystic acne. This scenario may warrant anti-androgen consideration but again dermatological review is indicated. Eyelash trichomegaly is often quite pronounced but can be managed with simple trimming.

The management of nail and periungual side effects includes preventive measures of avoidance of trauma and frequent water immersion or contact with harsh chemicals. Meticulous care with frequent application of topical petrolatum emollient is recommended.[13] Early treatment is best as paronychia with or without infection is painful and often debilitating. It responds well to topical kenacomb ointment twice daily for a few weeks. If secondary infection occurs, then appropriate systemic antimicrobials are indicated. Pyogenic granuloma is bothersome to patients because minor physical trauma or trivial irritation may induce bleeding. Early treatment of pyogenic granuloma with topical steroids and plastic occlusion may be all that is necessary. Difficult cases may need intralesional steroids or excision by a dermatologist.

Why treat?

Erlotinib is a targeted chemotherapy with low systemic toxicity and high specificity. Unlike currently used first-line cytotoxics, EGFR blockers do not cause significant nausea, vomiting, alopecia, myelosuppression or neuropathy.[15] However, due to their site of action on the EGFR, florid cutaneous side effects may occur. These can be uncomfortable, psychologically distressing, disfiguring and socially debilitating.

The impact of these dermatological side effects is significantly increased because successful therapy is ongoing and currently the optimal duration of chemotherapy is unknown. Management is essential because the side effects can impinge on functional quality of life and potentially compromise compliance to chemotherapy.[16,17] In addition, the evolving documentation of side effects in the literature leads to wider recognition, greater research and debate for best management of an important developing entity.[18]

All three of our patients experienced cutaneous side-effects, the most distressing being acne-like eruption. The literature to date has attached importance to this as a marker of positive therapy response. The significance of severe acneiform eruption and positive clinical outcome does however require further research.[1,13,19] At a doctor-patient level, this population requires specialist management of their side-effects. Drug information prior to the start of therapy can prepare patients for expected side-effects. Regular surveillance, timely intervention and follow-up is then required. Ongoing collaboration between dermatologists and medical oncologists for optimal patient care is essential.

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