

CASE REPORT

Cutaneous Side-Effects of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (TKI) In the Treatment of Lung Cancer: Description and Its Management

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SUMMARY

Epidermal growth factor receptor (EGFR) - Tyrosine Kinase inhibitors (TKI) like erlotinib and gefitinib have been approved as monotherapy for the treatment of patients with locally advanced or metastatic non small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. The use of EGFR-TKI is associated with unique and dramatic dermatologic side effects. We report 2 patients with NSCLC developing a typical acneiform (papulo-pustular) eruption shortly after initiation of EGFR-TKI.

KEY WORDS:

Epidermal growth factor receptor – tyrosine kinase inhibitors; Non small cell lung cancer; Acneiform eruption

INTRODUCTION

Epidermal growth factor receptor (EGFR) - Tyrosine Kinase inhibitors (TKI) like erlotinib and gefitinib have been approved as monotherapy for the treatment of patients with locally advanced or metastatic non small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. It acts by inhibiting intracellular phosphorylation of the tyrosine kinase associated with the EGFR. EGFR is also an important regulator of growth and differentiation in the skin

and hair. Therefore, the use of EGFR-TKI is associated with unique and dramatic dermatologic side effects^{1,2} including follicular acneiform eruptions, seborrhoeic dermatitis, xerosis and chronic paronychia.

CASE REPORTS

Case 1

A 60 year old Chinese lady was diagnosed to have advanced adenocarcinoma of the right lung with osseous metastases; for which she was given radiotherapy and chemotherapy. Oral erlotinib was started when her disease progressed despite on chemotherapy. She developed acneiform eruption over the face and upper trunk 10 days after commencement of erlotinib (Grade 2 rash) followed by alopecia, paronychia, seborrhoeic dermatitis and xerosis. The rash improved with oral doxycycline and topical treatment of fucidin and benzoyl peroxide.

Case 2

A 43 year old Malay man presented with recurrent adenocarcinoma of the right lung (Stage IIIB). He was given radiotherapy followed by oral gefitinib. He was noted to have acneiform lesion over upper trunk and face (Grade 2 rash) after 2 weeks of gefitinib treatment. The rash improved with topical benzoyl peroxide and oral doxycycline.

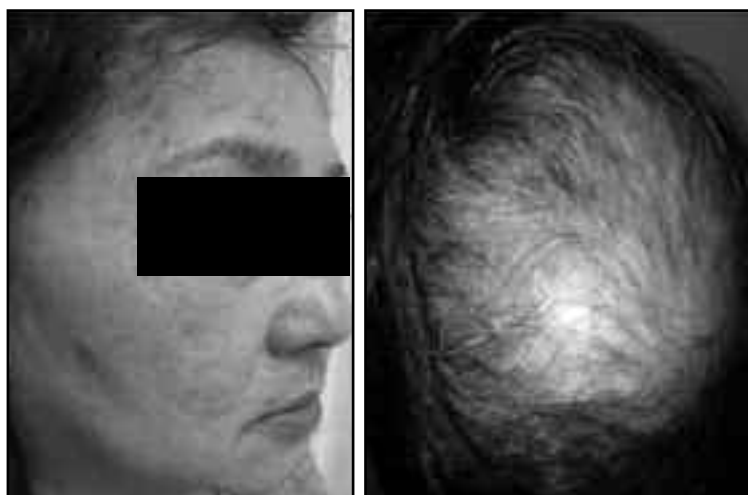


Fig. 1a & 1b: Papulo-pustular eruption involving face, neck and scalp and diffuse alopecia secondary to Erlotinib.

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Table I: Dermatological side effect with anti-EGFR therapies (*Reported with single agent therapy)

EGFR-TKI	Any Grade (%)	Grade 3 / 4 (%)
Erlotinib2	75-79	5-10
Gefitinib1	62-75	Up to 4

Table II: Spectrum of dermatological side effect

Adverse Event	Description	Frequency	Time Course
Rash	Monomorphous erythematous maculo-papular, follicular or pustular lesions +/- pruritus	60% - 80%	Onset: Between 1 and 3 week of treatment Resolution: Within 4 weeks after withdrawal of treatment but may wax and wane
Paronychia & Fissuring	Painful periungual granulation, associated with erythema, swelling and fissure of lateral nailfolds +/- distal finger tufts	6% - 12%	Onset: After 2 -4 months of treatment Resolution: Persistent, several months after withdrawal
Hair Changes	Hair loss or excessive hair growth (Curlier, finer and more brittle hair)	Isolated reports	Variable onset, usually after 7 to 10 weeks to many months
Dry Skin	Diffuse fine scaling	4% - 35%	Usually after appearance of rash
Hypersensitivity Reaction	Flushing, urticaria and anaphylaxis	2% - 3%	Occurs on first day of initial dosing

DISCUSSION

The recent improvement in the understanding of the processes that regulate tumour growth and development has led to the development of novel biologically targeted therapies as a potential treatment options for patients refractory or intolerant to chemotherapy.

Rash is a common side-effect of all EGFR-TKI^{1,2}. (Refer Table I) The precise mechanism for development of rash is not well defined. It is postulated to be caused by the inhibition of EGFR-signalling pathways in the skin³. In adults, the EGFR is expressed in the skin, primarily in proliferating, undifferentiated keratinocytes of the basal layers of the epidermis and the outer root sheath of the hair follicles⁴. For this reasons, these new drugs lead to the development of cutaneous side effects.

EGFR-TKIs are responsible for an entirely unique constellation of class-specific side effects on the skin occurring in most patients. Briefly, EGFR-TKI-induced skin side effect consists of an acneiform eruption, skin dryness leading to eczema and fissures, nail changes, hair changes, telangiectasia, hyperpigmentation and mucosal changes⁵ (Table II).

It is interesting to note that both of our cases showed papulo-pustular eruption sparing the area of previous radiotherapy. This sparing of irradiated skin from EGFR-TKI related acneiform eruption seems to be caused by radiation induced follicular loss⁵.

As evidence-based controlled trials are still very sparse, treatment of EGFR-TKI skin side effects mainly relies on case series and recommendations from expert. Proper grading of rash is an essential step toward determining what management strategies are most appropriate for patients. The severity of skin side effect is graded according to National Cancer Institute Common Terminology.

Patients with mild to moderate skin side effects are recommended to continue treatment without dose modification. When intervention is indicated, patients have been treated empirically with varying response by: topical antiseptics, topical antibiotics (clindamycin, fusidic acid), systemic antibiotics (tetracycline, minocycline, erythromycin), topical retinoids, topical immunomodulatory agents and short-term topical steroids or systemic retinoid / steroids for the more intense reactions⁶.

With the widespread use of EGFR-TKI in the metastatic setting of cancers, it will be important to provide supportive and adequate treatment for the majority of patients experiencing skin side effects.

CONCLUSION

Although these new targeted therapies have low systemic toxicity, cutaneous side effects are common and can be troublesome. Proper pre-treatment counseling and management will improve the treatment compliance and avoid unnecessary interruption of the TKI use.

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