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Common and Uncommon Adverse Cutaneous Reactions to Erlotinib: A Study of 20 Chinese Patients with Cancer

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Abstract

Erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, is used for treating non-small cell lung cancers. It is frequently known to cause skin toxicities. Systemic toxicities and anaphylactic cutaneous reactions have been rarely mentioned. Adverse cutaneous reactions were reported in 20 patients, including 6 cases of anaphylactic dermatitis, 12 cases of acneiform rash, 9 cases of xerosis, 5 cases of nail changes, and 4 cases of hair changes. One case of anaphylactic dermatitis manifested as erythema with swelling on the face and neck, and others as erosive and scaly erythema on the fold of skin, or red macules, papules, plaques, and pigmentation on the whole body. Clinical details indicated anaphylactic reactions, including a high percentage of eosinophils in the peripheral blood, eosinophilic infiltration in the dermis layer, and good response to antihistamines and topical steroids. Systemic toxicities accompanied by cutaneous reactions occurred in five patients including one case of anaphylactic dermatitis and four cases of acneiform rash. Elevated hepatic enzymes were observed among all the patients with grade 3 or 4 acneiform rashes. One patient with anaphylactic dermatitis and one with acneiform rash discontinued erlotinib administration due to severe lesions, high fever, or severe elevation of hepatic enzymes.

Keywords: Erlotinib, adverse cutaneous reactions, anaphylactic cutaneous reactions, systemic toxicities.

Introduction

Erlotinib, an epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI), is approved for treating patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) ^[1]. The absence of systemic toxicities is one of the advantages compared with traditional antineoplastic agents ^[2]. However, patients treated with EGFR inhibitors are frequently known to develop skin toxicities. Common reactions include acneiform rash, dryness, hair changes and nail changes ^[3]. Intriguingly, the anaphylactic cutaneous reactions induced by erlotinib have been reported rarely. This study presented common lesions with systemic toxicities and uncommon adverse cutaneous reactions such as anaphylactic dermatitis in patients undergoing treatment with erlotinib for the benefit of practicing dermatologists and oncologists.

Case series

A total of 20 patients (10 males and 10 females) with a mean age of 60.8 years (39–79 years) diagnosed with NSCLC (in stage IIIb or IV), referred from the Department of Respiratory Medicine, were evaluated in the dermatology department from January 2015 to June 2016. The cutaneous symptoms developed after administering erlotinib (150 mg, once per day) in all patients.

Adverse cutaneous reactions in the patients included acneiform rash ($n = 12$, 60%), xerosis ($n = 9$, 45%), nail changes ($n = 5$, 25%), and hair changes ($n = 4$, 20%). Some patients also presented with anaphylactic dermatitis ($n = 6$, 30%).

One case of anaphylactic cutaneous reactions manifested as erythema with swelling associated with pruritus, which appeared on the face and neck, especially on the orbital regions and lips, just like angioneurotic edema (Figure 1). It coexisted with severe oral mucosal erosion and a high fever. Hematological testing in this acute patient showed abnormal results of hypersensitive C-reactive protein (hs-CRP, 116.02 mg/dL), complete blood count (proportion of eosinophil was 5.7%), and elevated hepatic enzymes (alanine transaminase, ALT: 48.5 U/L; aspartate transaminase, AST: 54.9 U/L), without detection of human herpesvirus-6 (HHV-6) and HHV-7. Pathological examination revealed spongiosis, vacuolar interface dermatitis,

dermal edema, and capillary dilation and congestion, with lymphocytic and eosinophilic infiltrates in the dermis (Figures 2 and 3). The diagnosis of drug hypersensitivity syndrome was ruled out according to two versions of criteria for the diagnosis of this syndrome^[4, 5]. This severe case was managed by interruption of erlotinib and treatment with systemic steroids and antihistamines.

The second case presented with erythema, erosion, and scales on the fold of skin (Figure 4), while four other cases of allergic dermatitis presented with red macules, papules, plaques, and crust on the whole body (Figure 5). Post-inflammatory brown residual pigmentation was noted. Complete blood counts indicated normal results except for a high percentage of eosinophils (7.6%–9%). Skin biopsies revealed parakeratosis, some serum in stratum corneum, acanthosis, and moderate perivascular lymphohistiocytic and eosinophilic infiltrates in the dermis layer (Figure 6). Antihistamines and topical steroids effectively relieved the symptoms.

Acneiform rash was seen in 12 patients with maculopapular lesions, inflammatory papules, and papulopustular eruptions, affecting the scalp, face, neck, presternal region, back, limbs, and also a suprapubic area (Figure 7). The rashes were accompanied by pain. Skin disorders were graded according to Common Terminology Criteria for Adverse Events v4.0^[6]. Among the 12 patients enrolled, 42% had grade 1, 25% had grade 2, 25% had grade 3, and 8% had grade 4 acneiform rash. High hs-CRP levels (5.89–46.588 mg/dL), high hemogram value (white blood cell count $10.31\text{--}13.47 \times 10^9/\text{L}$; high percentage of neutrophils, N%, 78.9%–90.1%), and elevated hepatic enzymes (ALT: 59–315 U/L; AST: 54.9–109 U/L) were noted among all the patients with grade 3 or 4 rashes. Histopathological studies indicated moderate acanthosis and neutrophilic infiltration in the epidermis and dermis, especially within the hyperkeratotic follicle, associated with minimal lymphocytes and histiocytes (Figure 8). The patient with grade 4 rashes, a high fever and severe elevation of hepatic enzymes (ALT: 315 U/L; AST: 109 U/L) was managed by the termination of erlotinib administration and conservative therapy for 2 weeks. Topical corticosteroids and antihistamines were found to be effective for grades 1 and 2 rashes. Grade 3 rashes were responsive to oral minocycline (100 mg, twice daily) combined with topical steroids, but drug withdrawal triggered a relapse.

The clinical features of the present case series are summarized in Table 1.

Discussion

Erlotinib is an orally administered EGFR-TKI. It is a targeted agent commonly used for treating advanced NSCLC (stage IIIB and IV) ^[1]. It is often associated with a peculiar spectrum of skin reactions, including acneiform rash, nail changes, regulatory changes in hair, and xerosis. Other reactions include telangiectasia, hyperpigmentation, enhancement of radiation dermatitis, oral aphthous ulcers, vasculitis, necrolytic migratory erythema, and transient acantholytic dermatosis ^[3, 7 and 8]. Acneiform rash is the most common adverse cutaneous reaction ^[3]. The other types of adverse cutaneous reactions are rare. This study reported acneiform rash consisting of most alterations of skin disorders; the other adverse cutaneous reactions such as xerosis and nail and hair changes were not infrequent. It was interesting that anaphylactic cutaneous reactions were observed in 6 out of 20 cases, and this clinical presentation was hitherto not described except for some lesions reported by Toshiyuki Yamamoto ^[9]. In 2013, he reported erlotinib-induced seborrheic dermatitis-like eruption on the face and trunk, superficial erosive lesions on the buttock or genital regions, erythema exclusively involving the umbilicus and prurigo nodules on the buttocks in Japan ^[9]. A parallel point existed in morphology between only one case of anaphylactic dermatitis presenting as erosive and scaly erythema (Figure 4) and seborrheic dermatitis-like eruption or superficial erosive erythema ^[9]. Other cases of anaphylactic dermatitis were different morphologically from those previously described ^[9]. The rash presenting like angioneurotic edema with severe oral mucosal erosion and a high fever in one of the patients (Figure 1) had never been mentioned earlier. Red macules, papules, plaques, and brown pigmentation on the whole body other than localized distribution (Figure 5) were characteristic and distinct morphologically compared with the lesions described as prurigo nodules. Moreover, clinical details in the present study indicated anaphylactic cutaneous reaction, including a high percentage of eosinophils in the peripheral blood, eosinophilic infiltration in the dermis layer, and good response to antihistamines and topical steroids, which were absent in the literature. The anaphylactic cutaneous reaction has been reported only in Japan and China hitherto. The speculation

regarding its susceptibility in Asian population needs to be confirmed by conducting further studies.

Skin disorders are generally mild or moderate in severity, but they are also the precise cause of discontinuation of erlotinib therapy in 1% of the patients^[6, 10]. Although systemic toxicities accompanied by cutaneous reactions are rarely mentioned, elevated hepatic enzymes were found in five patients. One patient with anaphylactic dermatitis and one with acneiform rash discontinued erlotinib administration due to severe lesions, high fever, or severe elevation of hepatic enzymes. The other three cases of acneiform rash rated grade 3 emerged with elevated hepatic enzymes. Systemic toxicities should be emphasized especially in cases with severe skin disorders. Timely detection and appropriate early intervention in patients who develop severe cutaneous reaction while on erlotinib therapy should be considered clinically.

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Table 1. Summary of clinical features among different types of adverse cutaneous reactions

Skin disorders	Cases, n= 20	Biospy cases, n = 18	Gender, n = 20		Ages (year)		Interval (day)		High level	High level	High level
			Male, n = 10	Female, n = 10	Mean	Range	Mean	Range	of	of	hepatic
									neutrophils, n = 4	eosinophils, n = 6	enzyme, n=5
Anaphylactic											
dermatitis	6	6	2	4	63	39–74	40.8	7-120	0	6	1
Acneiform											
rash	12	12	6	6	59	42–79	34.1	2-90	4	0	4
Xerosis	9	/	5	4	56.8	39–71	/	/	/	/	/
Nail changes	5	/	1	4	62.8	47–79	/	/	/	/	/
Hair changes	4	/	2	2	66.5	61–74	/	/	/	/	/

Legends To Figures:

Figure 1. Erythema with swelling on the neck, face, and lips.

Figure 2. Spongiosis, vacuolar interface dermatitis, dermal edema, and capillary dilation and congestion (H & E, × 40).

Figure 3. Eosinophilic infiltration in the dermis (H & E, × 100).

Figure 4. Red patches accompanied by erosion and scales on the neck.

Figure 5. Red and brown macules, papules, plaques, and pigmentation on the trunk.

Figure 6. Parakeratosis, some serum in stratum corneum, and acanthosis (H & E, × 40).

Figure 7. Inflammatory papules and papulopustular eruptions affecting the suprapubic area.

Figure 8. Acanthosis and periadnexal neutrophilic infiltration in the dermis (H & E, × 40).







