Erlotinib-related skin toxicities: Treatment strategies in patients with metastatic non-small cell lung cancer

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Skin toxicities are the most common side effects associated with the epidermal growth factor receptor inhibitor erlotinib, occurring in most patients receiving the drug. Clinical trials evaluating erlotinib for the treatment of non-small cell lung cancer have reported a range of skin disorders, the most common being acneiform rash, xeroderma (dry skin), pruritus, and paronychia. Although in the majority of cases these effects are mild and transient, they can have a considerable impact on a patient's quality of life and, if particularly severe and persistent, may necessitate treatment interruption or cessation and compromise treatment outcome. This coupled with recent evidence to suggest a positive correlation between the incidence and severity of rash and clinical outcome among erlotinib-treated patients with advanced or metastatic non-small cell lung cancer highlights the importance of adequately managing epidermal growth factor receptor inhibitor–related skin disorders. Clear treatment strategies are therefore necessary to ensure the prevention and optimal management of erlotinib-related skin toxicities thereby enabling patients to continue erlotinib treatment. In this review we present a practical approach for the treatment of erlotinib-related cutaneous side effects in Japanese patients with advanced non-small cell lung cancer providing details of specific treatment interventions, according to symptom severity, for each of the common skin disorders. In addition, the importance of preventive skin care measures—namely maintaining cleanliness, moisturization, and protection from external stimuli—in preventing the development of serious skin disorders is discussed and guidelines for the practice of proper skin care are presented. (J Am Acad Dermatol 2013;69:463-72.)

Key words: acneiform rash; cutaneous side effects; epidermal growth factor receptor inhibitor; erlotinib; Japanese patients; non-small cell lung cancer; prevention; skin toxicities.

In recent years, targeted therapy directed at the epidermal growth factor receptor (EGFR) has emerged as an important therapeutic option for the treatment of patients with a range of solid tumors including non-small cell lung cancer (NSCLC). Erlotinib is a highly selective oral tyrosine kinase inhibitor that targets EGFR to inhibit tumor cell growth and proliferation.[1] Based on the results of 1 international phase III study (BR.21) and 2 Japanese phase II studies, erlotinib monotherapy has received regulatory approval in Europe, the United States, and Japan for the treatment of patients

Abbreviations used:

ADL:	activities of daily living
AEs:	adverse events
BSA:	body surface area
CI:	confidence interval
CRC:	colorectal cancer
EGFR:	epidermal growth factor receptor
FTUs:	fingertip units
HR:	hazard ratio
NSCLC:	non-small cell lung cancer
OS:	overall survival
STEPP:	Skin Toxicity Evaluation Protocol with Panitumumab
UV:	ultraviolet

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with locally advanced or metastatic NSCLC who have failed at least 1 previous chemotherapy regimen.[2-4]

Dermatologic side effects are relatively common among patients treated with EGFR inhibitors.[5,6] These skin disorders are generally mild or moderate in severity and can be managed by appropriate interventions or by reducing or interrupting the erlotinib dose. Appropriate and timely management make it possible to continue a patient's quality of life and maintain compliance; however if these adverse events (AEs) are not managed appropriately, and become more severe, treatment cessation may be warranted compromising clinical outcome. Evidence has emerged in recent years to suggest that the incidence and severity of rash are positively correlated with treatment outcome among patients receiving erlotinib (Fig 1).[7-12] Strategies to improve the assessment and management of EGFR-related skin AEs are therefore essential to ensure compliance with anticancer therapy, thereby enabling patients to achieve optimal benefits. The purpose of this article is to describe the most common erlotinib-related skin disorders in patients with advanced/metastatic NSCLC and to provide treatment strategies for their management.

CAPSULE SUMMARY

- Skin toxicities are a common side effect of the epidermal growth factor receptor inhibitor erlotinib.
- We present a practical approach for the treatment of erlotinib-related cutaneous side effects including treatment interventions according to symptom severity and the importance of preventive measures.
- Skin toxicities impact quality of life and may necessitate treatment interruption. Ensuring the prevention and optimal management of erlotinib-related skin toxicities will enable erlotinib treatment continuation to gain the best outcome.

ERLOTINIB-RELATED SKIN DISORDERS: SYMPTOMS AND INCIDENCE

Common skin disorders with erlotinib

The most frequently occurring skin disorders reported with erlotinib are acneiform rash, xeroderma (dry skin), pruritus, and paronychia (periungual inflammation). Skin disorders have been generally categorized by the Common Terminology Criteria for AEs v4.0 (Table I), with special criteria for paronychia being adopted because there is no Common Terminology Criteria for AEs category for paronychia. Erlotinib-related acneiform rash typically manifests as red papules and/or pustules on the face, chest, abdomen, or thighs (Fig 2). Several features distinguish an acneiform rash from acne vulgaris, including the absence of bacterial infection.[13] Xeroderma is characterized by dryness and roughness of the skin, and scaling (Fig 2). The scales may be associated with inflammatory erythema or pigmentation. As the condition progresses, fissures appear and the skin becomes itchy and similar to pityriasis, resembling fish scales; the fissures can cause considerable pain. Pruritus, or skin itching, usually develops with xeroderma or dermatitis; it is unusual for a patient to present with pruritus without a rash. Pruritus may cause patients to scratch, resulting in scratch marks, lichenification, and eczematous inflammation with hyperpigmentation and/or secondary infection. Paronychia manifests as dusky erythema around several fingernails and toenails (Fig 3). This results in the formation of painful fissures, swelling, and noninfectious granulation. Bleeding or exudation can result in crust formation, which may be extremely painful and severely impact quality of life. Secondary infection arising from paronychia is also a common problem.

Incidence of the most common skin disorders

Data from a Japanese postmarketing surveillance study of erlotinib-treated patients with NSCLC (POLARSTAR; n = 3488) revealed a high incidence of rash (63%), with somewhat lower incidences for dry skin, pruritus, and paronychia (7.7%, 3.8%, and 6.0%, respectively).[14] The majority of the skin disorders were grade 1 (mild) or grade 2 (moderate) in severity; just 6.7% of rash cases were grade 3 or higher, and 0.2% of dry skin and pruritus episodes and 0.7% of paronychia cases were grade 3 or higher in the surveillance study (Table II).[14,15]

Time of onset typically varies according to the type of skin disorder. In the POLARSTAR study, median time to onset was shortest for rash (8 days, range 1-494) and longest for paronychia (32 days, range 2-558); median time to onset for dry skin and pruritus were 15 days and 11 days, respectively (Table II).[14] These findings are generally comparable with those from the 2 phase II studies for rash (median 6 days), pruritus (median 7 and 9 days), dry skin (12 and 23 days), and paronychia (41.5 and 49.5 days).[16]

TREATMENT STRATEGIES FOR ERLOTINIB-RELATED RASH

Published evidence

Few randomized controlled trials have been conducted in the management of EGFR-related skin disorders; 5 have been published to date although each study is small.[17-21] The studies were