Isotretinoin Plus Clindamycin Seem Highly Effective Against Severe Erlotinib-Induced Skin Rash in Advanced Non-small Cell Lung Cancer

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Introduction: Erlotinib is useful in advanced non-small cell lung cancer although compliance and efficacy are diminished by skin rash in a high proportion of patients, often necessitating dose reduction or drug withdrawal. No effective treatment for the rash is available.

Methods: We carried out a preliminary investigation on isotretinoin and clindamycin. Among 56 advanced lung cancer patients treated with erlotinib, 31 (53%) developed rash. Seven (35%) of the 20 G2/G3 cases agreed to treatment with clindamycin (450 mg/d, days 1–10; 300 mg/d, days 11–20) plus isotretinoin (20 mg/d, days 11–20) after being informed of the experimental nature of the combination.

Results: In 6 of 7 (86%) patients, the rash resolved (G1/G0) without dose reduction; in the other patient (G3), the erlotinib dose also had to be reduced. Median time to resolution was 14 days (range 7–20 days). No rash-treatment adverse events occurred during 20 days of administration.

Conclusions: Isotretinoin plus clindamycin promises to be the first effective treatment for erlotinib rash and is being tested further.

Key Words: Isotretinoin, Clindamycin, Erlotinib, Skin rash, Non-small cell lung cancer.

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Erlotinib is a selective inhibitor of the tyrosine kinase part of the epidermal growth factor receptor (EGFR) that has proved effective as second- or third-line therapy for non-small cell lung cancers (NSCLCs), 40 to 80% of which overexpress EGFR.[1] The most important erlotinib-related adverse event is an acne-like papulopustular skin rash mainly affecting the face, scalp, and upper torso.[2] Rash develops in approximately 60 to 80% of erlotinib-treated patients and is severe (G3–G4) in 5 to 20% of cases.[3]

Approximately 12% of patients require erlotinib dose reduction or complete drug withdrawal because of the rash.[1,4] In addition to intermittent or permanent erlotinib suspension and dose reduction, aspecific therapies are also applied including systemic and topical antibiotics, antihistamines, topical corticosteroids, and retinoids.[5–7] However, clinical trials on rash management have not been performed.

The antibiotic clindamycin is a common topical and systemic treatment for acne. Systemic clindamycin may potentiate polymorphonuclear leukocyte chemotaxis,[8] and when compared with tetracycline, clindamycin causes little resistance to *Staphylococcus aureus*.[9]

Retinoids, including isotretinoin, are also commonly used to treat acne. Isotretinoin has been used successfully to treat skin lesions induced by the EGFR-blocking agent cetuximab.[10,11] Isotretinoin may act by several mechanisms including a normalizing effect on epithelium and inflammatory mediators.[11]

We hypothesized that sequential use of clindamycin and isotretinoin might be effective in erlotinib-induced skin rash[12] and decided to try out the combination on NSCLC patients who developed skin rash.

METHODS

We treated 56 advanced NSCLC patients (stage III or IV, not suitable for surgery) from April 2008 to September 2009 with erlotinib (150 mg/d) after obtaining informed consent, mainly as second- or third-line therapy. Adverse events including rash were assessed according to Common Terminology Criteria for Adverse Events 3.0.[13]

Patients who developed G2/G3 skin rash were asked whether they wished to be treated for the rash with the experimental combination of clindamycin and isotretinoin after being informed of possible side effects of isotretinoin (particularly liver damage and photosensitivity).

Consenting patients were started on oral clindamycin (450 mg/d, days 1–10; 300 mg/d, days 11–20) plus oral isotretinoin (20 mg/d, days 11–20) and were examined clinically with photographic documentation on days 0, 15, and 30.

RESULTS

The most common side effect was cutaneous rash in 31 of 56 (53%) patients: G1 in 11 (19%), G2 in 12 (20%), and G3 in 8 (14%). Median time or rash onset was 14 days (range 5–60 days) from the start of erlotinib treatment.

Only 7 of 20 (35%) of the eligible (G2/G3) patients consented to receive clindamycin plus isotretinoin. The two-drug combination was effective in six (86%) of the seven

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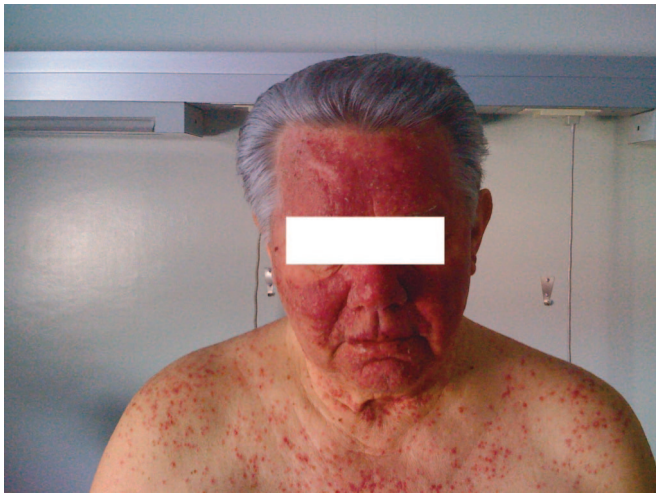

FIGURE 1. Day 0. Cutaneous rash after 15 days of erlotinib at 150 mg/d.

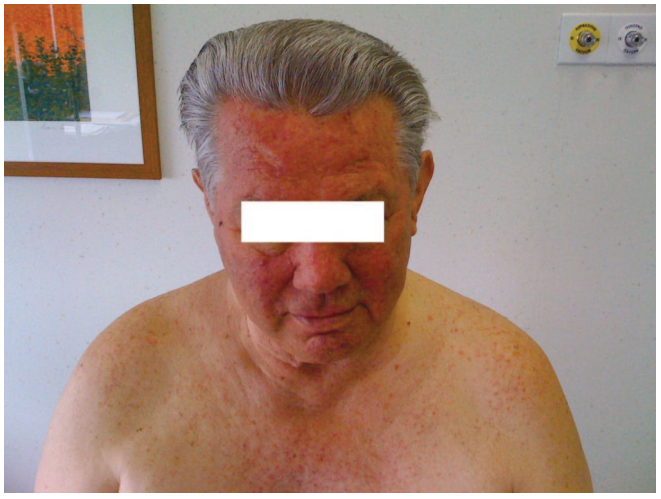

FIGURE 2. Day 15. Cutaneous rash after 30 days of erlotinib (150 mg/d) plus 15 days of therapy with clindamycin and isotretinoin.

treated patients, with resolution of rash to G1/G0; in the other patient (G3), it was necessary to reduce erlotinib to 100 mg/d. Median time to rash resolution was 14 days (range 7–20 days) in these seven patients. The Figures 1 and 2 show one patient before and after 15 days of clindamycin plus isotretinoin treatment. No adverse events associated with clindamycin or isotretinoin were observed during the 20 days of treatment. Of the 41 of 56 patients evaluable for erlotinib response, 9 (22%) had an objective response, whereas disease progression occurred in 25 (45%). Cutaneous rash (all grades) seemed related to erlotinib activity: 7 (78%) patients with response developed rash, whereas 13 (52%) patients with progressive disease did not develop rash.

DISCUSSION

Also being well tolerated, isotretinoin plus clindamycin did not seem to adversely affect the clinical activity of erlotinib. Thus, objective responses occurred in 44% of patients treated for cutaneous rash against 22% of the evaluable population; for stable disease and disease progression, the corresponding percentages were 28 versus 17% and 28 versus 61%, respectively. Although these percentages refer to very small numbers of patients and require verification, they are clinically impressive.

These findings and other data[14,15] suggest that rash could be a clinical marker predicting therapy success, further suggesting that dose reduction or drug withdrawal compromises the effectiveness of erlotinib.

To conclude, the results of this preliminary study indicate that sequential clindamycin and isotretinoin have promise as an effective means of managing erlotinib-induced skin rash, allowing maintenance of effective erlotinib dose and hence maximizing efficacy. A randomized phase II study to further explore efficacy is planned and will include a neutrophil chemotaxis assay on peripheral blood to further investigate the supposed rationale of the combination.

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