

CLINICAL REPORT

Cutaneous Side Effects in Non-Small Cell Lung Cancer Patients Treated with Iressa (ZD1839), an Inhibitor of Epidermal Growth Factor

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We report the cutaneous side effects of Iressa (ZD1839), a new anti-cancer agent that acts by inhibiting epidermal growth factor receptor signal transduction. The most common cutaneous adverse effect was the development of an acneiform eruption on the face, anterior trunk and back (39%). The second most common side effect was xerosis or desquamation of the face, body or distal parts of the fingers or toes (36%). Additional cutaneous side effects included multiple ingrown paronychia inflammation of the toes and fingers (6%), small ulcers of the oral mucosa or nasal mucosa, and urticaria. The cutaneous adverse effects of Iressa are similar to those of other epidermal growth factor receptor-targeted agents and result from direct interference with the functions of epidermal growth factor receptor signalling in the skin. Iressa-induced acne may be related to excessive follicular hyperkeratosis, follicular plugging, obstructions of the follicular ostium and alteration of hair cycle progression, which lead to an inflammatory response. Xerosis or desquamation reflects a disturbance of the equilibrium between proliferation and differentiation of epidermis. The mechanism by which Iressa leads to the development of paronychia and ingrown nail remains unclear. Key words: cutaneous side effects; epidermal growth factor receptor inhibitor; Iressa (ZD1839); non-small cell lung cancer.

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As non-small cell lung cancer (NSCLC) is usually asymptomatic in the early stages, many patients present initially with locally advanced or metastatic disease, which generally has a poor prognosis (1). Standard first-line treatment for patients with unresectable or metastatic NSCLC consists of platinum-based combination chemotherapy (1). However, these regimens have limited efficacy, with a number of combination therapies showing 2-year survival rates of less than

15%, and median survival times ranging from 7.4 to 8.5 months (1). At present, docetaxel is the only drug that is approved for use in advanced NSCLC following relapse after first-line platinum-based chemotherapy (2). There is a clear need for additional treatment strategies, calling for the development of more effective and less toxic treatments.

The epidermal growth factor receptor (EGFR) pathway, a key driver in the regulation of normal cell growth and differentiation of dependent tissues, also plays a role in promoting proliferation of malignant cells (1, 3, 4). The EGFR is expressed or highly expressed in a variety of human tumours of epithelial origin (1, 3, 4). Enhanced EGFR signalling seems to promote tumour growth by increasing proliferation, motility, adhesion and invasive capacity, and blocking apoptosis. EGFR expression is associated with metastasis, late-stage disease, resistance to therapy and poor prognosis (1, 3, 4). Consequently, EGFR is a promising target for cancer therapy. Iressa (ZD1839) is the first of a new class of EGFR-tyrosine kinase inhibitors (4). The result of a large phase II trial has shown that Iressa provides clinically significant symptom relief for many patients with solid tumours, in particular advanced NSCLC (5).

We studied the cutaneous side effects of patients with NSCLC who participated in a treatment protocol with Iressa as a single agent at our institute.

PATIENTS AND METHODS

A total of 79 patients took part in an expanded access programme (EAC) of Iressa at our institute. The main inclusion criteria were histologically/cytologically confirmed metastatic and advanced NSCLC (stage IV) not curable with standard therapy. The patients had received prior cancer therapies, including chemotherapy and radiotherapy. They were excluded if they showed evidence of another severe or uncontrolled systemic disease, unresolved toxicity from previous anti-cancer therapy, any history of significant corneal diseases and active dermatoses. None used other medications known to trigger or exacerbate acneiform eruptions, xerosis and paronychia. Iressa was administered as a single oral dose (250 mg day⁻¹) for at least 28 consecutive days. Fifteen patients did not complete 28 days of treatment because of disease progression or other medical problems. To assess the cutaneous reactions of Iressa, we

conducted a retrospective review of the case sheets of 64 patients (43 men and 21 women, mean age 57.3 years; range 33–77). The severity of the cutaneous adverse reactions was graded according to NCI toxicity criteria: grade 1, localized asymptomatic macular, papulopustular eruption or erythema; grade 2, macular, papulopustular eruption, erythema or desquamation with pruritus or other associated symptoms covering <50% of the body surface; grade 3, symptomatic generalized rash or desquamation covering \geq 50% of body surface area.

RESULTS

Skin adverse effects were reported in 34/64 patients (53%) included in this study. These events commonly consisted of acneiform eruption (25 patients, 39%), cutaneous dryness (23 patients, 36%), paronychia (4 patients, 6%), ulcer in the oral mucosa or nasal mucosa (3 patients, 6%) or urticarial rash (2 patients, 4%). There was no apparent association between occurrence of the cutaneous adverse effects and gender (Table I). Acneiform eruptions appeared between day 7 and day 14 of treatment, first on the nose or perioral area and spreading peripherally to the anterior chest, upper back, neck and, less frequently, limbs (Fig. 1). The lesions were small pustules, and none were cystic or nodular. Eight patients experienced grade 1 acneiform eruption localized to the face, and 17 had grade 2 eruption. The overwhelming majority of patients found that the skin reaction was tolerable, improved over time, or was manageable with the use of topical antibiotics (erythromycin or clindamycin) for pustular skin lesion. No patient was treated with oral antibiotics for acneiform eruptions. Fifteen patients developed seborrhoeic dermatitis on the face and acneiform eruption. Some grade of cutaneous dryness was noticed in 23 patients (36%). Seven had grade 1 cutaneous dryness and 16 experienced grade 2 eruption. Seborrhoeic dermatitis-like rash on the face, or xerosis on the whole body appeared. Desquamation on distal parts of the fingers or toes appeared in 10 patients (13%) (Fig. 2). The median time between onset of Iressa and appearance of xerosis was 20 days. Patients skin complaints were manageable with moisture lotion and topical steroid cream. None of the patients discontinued Iressa because of any of these events. Four patients presented pain, erythema and proliferation of granulation tissue around several finger and toe nails

Table I. Occurrence of cutaneous adverse effects according to gender

	Men (%)	Women (%)
Total no. of patients	43 (67)	21 (33)
Acneiform eruption	18 (72)	7 (28)
Xerosis	14 (61)	9 (39)
Paronychia	2	2
Urticaria	1	1

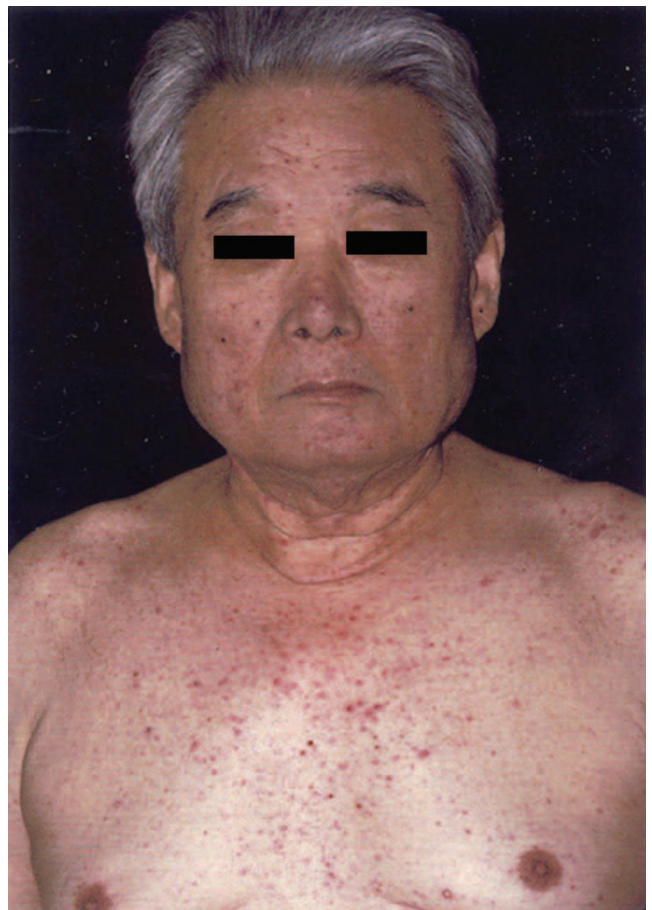


Fig. 1. Acneiform eruptions on the face and chest of a 65-year-old man treated with Iressa.

and ingrowth of the nails (Fig. 3). No prior episodes of psoriasis, paronychia, local trauma, ingrown nails, nail dystrophy or any other known risk factors for paronychia were known. Partial nail-plate excisions were performed in one patient and Iressa was briefly withdrawn (7 days). Other patients with paronychia



Fig. 2. Erythematous scales and exfoliation on the distal fingers of 55-year-old woman treated with Iressa.



Fig. 3. Periungual granulation tissue associated with lateral ingrowing of the toenails.

were treated with topical antiseptics (mupirocin ointment), improving the inflammation and pain. Cultures and biopsies were not performed. The median time between start of Iressa therapy and onset of the paronychia-ingrowing nails was 2 months. Additional cutaneous adverse effects included urticaria and small aphthous ulcers of the oral or nasal mucosa.

DISCUSSION

The epidermal growth factor receptor (EGFR) is a member of the *erbB* family of cell surface receptors (3, 4). This receptor family comprises 4 homologous receptors (*erbB-1*, *erbB-2*, *erbB-3* and *erbB-4*) (3, 4) composed of an extracellular ligand-binding domain, a lipophilic transmembrane domain and intracellular tyrosine kinase domain (3, 4). The EGFR can be activated by a variety of ligands, including EGF and transforming growth factor- α (TGF- α , amphiregulin and betacellulin) (3, 4). After ligand binding, receptor dimerization leads to tyrosine kinase activation and the recruitment and phosphorylation of intracellular substrates, leading to cell proliferation, motility, adhesion, invasion, survival and angiogenesis (3, 4). High EGFR expression has been associated with advanced tumour stage, resistance to standard therapies and, in some tumours, poor prognosis (3, 4). Following accelerated drug development programmes, phase III trials are now under way for a number of EGFR-targeted therapies, including the monoclonal antibody IMC-C225 (cetuximab), the EGFR-tyrosinase kinase inhibitor (Iressa, ZD1839) and OSI-774 (5, 6).

The cutaneous adverse effects associated with Iressa treatment probably reflect the significance of the EGFR signalling pathway in skin. In normal adult human skin, the EGFR is strongly expressed in keratinocytes, in cells of eccrine and sebaceous glands, in the outer root sheath of hair follicles, and in occasional endothelial cells (7).

The cutaneous eruptions in patients treated with

Iressa in our study consisted of acneiform eruption, seborrhoeic dermatitis-like rash on the face, xerosis on the body, desquamation of the distal parts of the extremities, paronychia-ingrown nails, ulcer of the oral or nasal mucosa, and urticaria. In a phase I trial of Iressa by Herbst et al. (8), acne-like rash (55%) was one of the most common adverse events. Baselga et al. (9) reported that the acne-like rash was observed in 65% and dry skin in 20% of the Iressa-treated patients with solid tumours. It has been reported that frequency of development of the acneiform eruption is dose-dependent. Thus the higher incidence of acneiform eruptions in previous studies may be related to the higher dose of Iressa (from 150 mg day⁻¹ to a maximum of 1000 mg day⁻¹) (8, 9). Baselga et al. (9) stated an acne rate of 65% at 150 to 400 mg day⁻¹ and 75% at 600 to 1000 mg day⁻¹.

Van Doorn et al. (10) reported histologic changes in three patients of Iressa-induced acneiform eruptions. The most striking histopathologic changes are prominent keratin plugs and microorganisms in dilated infundibula (11). The probable explanation of acneiform eruption may lie in the role of EGF in the normal differentiation and morphogenesis of hair follicles (11). EGFR functions to slow the growth and the differentiation of multiple cell types within the hair follicle, possibly directly in the cells of the outer root sheath (7, 10–13). *In vitro* models have demonstrated that EGF is involved in the switching from anagen to catagen (12). During normal hair follicle cycling, the lower portions of the hair follicle exist in an immune privileged site and do not express major histocompatibility complex (MHC) class 1 antigens (7, 12, 13). However, during the transition from anagen to catagen, MHC class 1 antigens are expressed in the lower follicle, macrophages infiltrate the area, and the lower portion of hair follicle degenerates (7, 12, 13). As EGFR null mice presumably lack EGF-induced suppression of oxygen radical production, which might be necessary for the resolution of inflammation, expression of MHC class 1 antigens in early catagen could trigger the destruction not only of the lower follicle but also of the entire organoid (7, 12, 13). Iressa-induced acne may be related to excessive follicular hyperkeratosis, follicular plugging, subsequent obstruction of the follicular ostium and alteration of hair cycle progression, which lead to follicle degeneration and destruction accompanied by a strong inflammatory response.

In keratinocytes, the expression of EGFR is highest in the basal layer of epidermis (7). In the epidermis, activation of EGFR reduces the terminal differentiation capacity of basal keratinocytes, but promotes differentiation of suprabasal keratinocytes (14). Inhibition of the EGFR-tyrosine kinase *in vitro* induces human keratinocyte growth arrest and terminal differentiation (14). The most striking histopathologic

changes on-treatment with Iressa were noted in the stratum corneum, which was markedly thinner and more compact, with a loss of its normal basket-weave pattern (11). The epidermal alterations reflect a disturbance of the equilibrium between proliferation and differentiation (11), which may be responsible for the xerosis and desquamation seen in some patients treated with Iressa.

Paronychia and ingrown nails have been reported during treatment with etretinate, indinavir, methotrexate and sulfonamide (15–19), but not with Iressa. It has been proposed that paronychia and ingrown nails as a result of etretinate may be a consequence of retinoid-induced skin fragility with penetration of nail fragments into the periungual tissues or desquamative dermatitis acting as a foreign body in the lateral nail groove (15). Indinavir, etretinate and Iressa have similar cutaneous side effects of xerosis and desquamative dermatitis. The mechanism by which Iressa leads to the development of paronychia and ingrown nails remains unclear, but it may be related to skin dryness caused by the medication. Recently, Busam et al. (20) reported paronychia in 5 of 10 patients treated with an anti-EGFR antibody, C225 (cetuximab). This report supports the notion that Iressa may play a role in the development of paronychia and ingrown nails. Iressa-induced paronychia may appear from 2 to 12 months after the beginning of treatment.

In summary, we describe the cutaneous adverse effects seen in 64 patients with NSCLC treated with Iressa. Further investigations about the EGFR pathway and cell cycle regulation in keratinocytes and hair follicle may be needed to extend the understanding of skin eruptions related to Iressa.

REFERENCES

- Salomon DS, Brandt R, Ciardiello F. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995; 19: 183–232.
- Magne N, Pivot X, Bensadoun RJ, Guardiola E, Poissonnet G, Dassonville O, et al. The relationship of epidermal growth factor receptor levels to the prognosis of unresectable pharyngeal cancer patients treated by chemoradiotherapy. *Eur J Cancer* 2001; 37: 2169–2177.
- Raymond E, Faivre S, Armand JP. Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy. *Drug* 2000; 60: 15–23.
- Baselga J, Averbuch SD. ZD1839 (Iressa) as an anti-cancer agent. *Drug* 2000; 60: 33–40.
- Fukuoka M, Yano S, Giaccone G. Final results from a phase II trial of ZD1839 (Iressa) for patients with advanced non-small-cell lung cancer (IDEAL 1). *Proc Am Soc Clin Oncol* 2002; 21: 298.
- Perez-Soler R, Chachoua A, Huberman M. A phase II trial of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ODI-774, following platinum-based chemotherapy, in patients with advanced, EGFR-expressing, non-small cell lung cancer (NSCLC). *Proceedings of the ASCO 2001*; 20 (Abstr. 1235).
- Nanney LB, Magid M, Stoscheck CM, King LE. Comparison of epidermal growth factor binding and receptor distribution in normal human epidermis and epidermal appendages. *J Invest Dermatol* 1984; 83: 385–393.
- Herbst RS, Marrie Maddox A, Rothenberg ML, Small EJ, Rubin EH, Baselga J, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol* 2002; 20: 3815–3825.
- Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* 2002; 20: 4292–4302.
- Van Doorn R, Kirtschig G, Scheffer E, Stoof TJ, Giaccone G. Follicular and epidermal alterations in patients treated with ZD1839 (Iressa), an inhibitor of the epidermal growth factor receptor. *Br J Dermatol* 2002; 147: 598–601.
- Albanell J, Rojo F, Averbuch S, Feyereislova A, Mascaro JM, Herbst R, et al. Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. *J Clin Oncol* 2001; 20: 110–124.
- Philpott MP, Kealey T. Effects of ECF on the morphology and patterns of DNA synthesis in isolated human hair follicles. *J Invest Dermatol* 1994; 102: 186–191.
- Hansen LA, Alexander N, Hogan ME, Sundberg JP, Dlugosz A, Threadgill DW, et al. Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development. *Am J Pathol* 1997; 150: 1959–1975.
- Peus D, Hamacher L, Pittelkow MR. EGF-receptor tyrosine kinase inhibition induces keratinocyte growth arrest and terminal differentiation. *J Invest Dermatol* 1997; 109: 751–756.
- Baran R. Etretinate and the nails (study of 130 cases) possible mechanisms of some side-effects. *Clin Exp Dermatol* 1986; 11: 148–152.
- Hodak E, David M, Feuerman EJ. Excessive granulation tissue during etretinate therapy. *J Am Acad Dermatol* 1984; 11: 1166–1167.
- Wantzin GL, Thomsen K. Acute paronychia after high-dose methotrexate therapy. *Arch Dermatol* 1983; 119: 623–624.
- Tosti A, Piraccini BM, D'Antuono A, Marzaduri S, Bettoli V. Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; 140: 1165–1168.
- Daniel CR, Scher RK. Nail changes secondary to systemic drugs and ingestants. *J Am Acad Dermatol* 1984; 10: 250–258.
- Busam KJ, Capodiceci P, Motzer R, Kiehn T, Phelan D, Halpern AC. Cutaneous side-effects in cancer patients treated with the epidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; 144: 1169–1176.