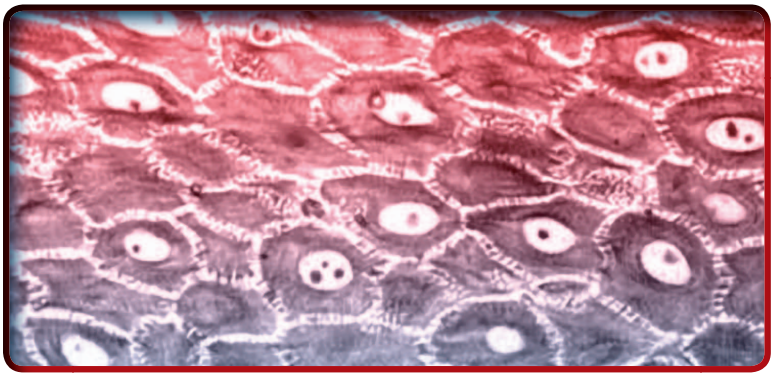
EDUCATIONAL REVIEW

Management of
Epidermal Growth Factor Receptor Inhibitor-Induced Dermatologic Toxicity



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The epidermal growth factor receptor (EGFR) is 1 of 4 types of human epidermal receptors that are found primarily on cells of epithelial origin and have a vital role in cellular growth, proliferation, and migration.[1-3] Abnormal activity at the EGFR receptor has been implicated in many types of solid tumors, including colorectal, non-small cell lung, head and neck, and pancreatic cancers.

Two distinct drug categories have been developed to inhibit tumor growth and proliferation that results from dysregulated EGFR activity. The small molecule inhibitors, also known as tyrosine kinase inhibitors (TKIs), enter the cell and inhibit signaling pathways by binding to the adenosine triphosphate binding site. The monoclonal antibodies do not enter the cell but rather bind to the extracellular receptor, resulting in inactivation of the receptor. Table 1 lists the FDA-approved EGFR inhibitors and their indications.[4-9] Other TKIs and monoclonal antibodies that affect receptors other than EGFR are available but will not be discussed in this review.

One benefit of the EGFR inhibitors is that they are devoid of traditional systemic chemotherapeutic adverse effects. Their use, however, is associated with dermatologic toxicity.[2,3,10,11] Skin rash is the most commonly reported dermatologic adverse effect, but other toxicities include pruritus and xerosis, as well as nail and hair changes. The mechanism of this toxicity appears to be related to the inhibition of EGFR in the skin. EGFR is highly expressed in keratinocytes, the major cellular component of epidermal tissue, in the basal layer of the epidermis. Keratinocytes undergo a highly regulated process of differentiation as they move from the basal layer of the epidermis to the skin surface. EGFR inhibitors interfere with this regulation, thus compromising the skin's integrity.[2,12-14]

Dermatologic Toxicities

Rash

The rash that occurs with EGFR inhibitors often is described as papular, pustular, or papulopustular, with a follicular distribution; it most commonly occurs on the scalp, face, and upper trunk.[14,15] The rash generally appears within 1 to 2 weeks of treatment and evolves from edema and erythema to pustular eruptions.[2,14,16] Rash symptoms usually dissipate within 1 month of EGFR inhibitor discontinuation and often will improve even with continued EGFR inhibitor therapy. Some patients with rash will not require intervention, but others will be bothered by the skin dryness and itching and will need treatment.

Although the terms *acne-like* or *acneiform* frequently are used to describe the rash, this is discouraged because of the differences in the pathologic processes of acne and EGFR-inhibitor rash.[17] The severity of the EGFR-induced rash has been graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), initially version 3.0 and more recently version 4.0 (Table 2).[18,19] However, it has been suggested that NCI-CTCAE criteria do not adequately address adverse events associated with the EGFR inhibitors, prompting a Multinational Association of Supportive Care in Cancer expert group to propose a new scale (Table 3).[20]

Rash has been reported to be more severe and to occur more frequently in patients treated with the monoclonal antibodies compared with those treated with TKIs.[2,10,14] The reason for this is not fully described, and multiple theories have been proposed. Li and colleagues proposed that the monoclonal antibodies suppress EGFR signaling more, resulting in greater toxicity.[2] Eaby and colleagues suggested that higher peak concentrations are reached with the monoclonal antibodies due to their intermittent administration, versus the daily administration of TKIs, resulting in greater toxicity.[10]

The incidence of EGFR inhibitor-induced rash is difficult to determine due to differences in categorization and reporting.[10] Jatoi and colleagues reviewed clinical trials of cetuximab (Erbitux, ImClone/Bristol Myers Squibb), panitumumab (Vectibix, Amgen), and erlotinib (Tarceva, Genentech) and found that, in general, rash occurred in more than 50% of patients.[21] A recent meta-analysis of patients receiving cetuximab revealed that the incidence of reported rash was 88.2% (81.6% follicular-pustular).[22] A small number of patients (6.5%) had rash that was grade 3 or higher.

Xerosis

Xerosis is dry, itchy skin that occurs in up to 35% of patients who receive EGFR inhibitors.[14,23] Xerosis can occur in areas of the face and trunk but also frequently presents on the extremities after several weeks of EGFR inhibitor therapy. Patients who are older, have a history of atopic dermatitis, or have had previous cytotoxic chemotherapy are at greater risk for xerosis.[24] Hyperpigmentation of the skin may occur in patients with

Table 1. EGFR Inhibitors

EGFR Inhibitor	Receptor(s)	Indications
Monoclonal Antibodies		
Cetuximab (Erbitux, ImClone/ Bristol-Myers Squibb)	EGFR	*Colorectal cancer* • As a single agent for the treatment of EGFR-expressing metastatic colorectal cancer after failure of irinotecan- and oxaliplatin-based regimens or in patients who are intolerant of irinotecan regimens • In combination with irinotecan in patients with EGFR-expressing metastatic cancer who are refractory to irinotecan-based therapy *Head and neck cancer* • In combination with radiation therapy for locally or regionally advanced squamous cell carcinoma of the head and neck • As monotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy
Panitumumab (Vectibix, Amgen)	EGFR	*Colorectal cancer* • As a single agent for the treatment of EGFR-expressing metastatic colorectal cancer with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens
Tyrosine Kinase Inhibitors		
Erlotinib (Tarceva, Genentech)	EGFR	*Pancreatic cancer* • First-line for patients with locally advanced, unresectable, or metastatic pancreatic cancer in combination with gemcitabine *Non-small cell lung cancer* • Treatment of locally advanced or metastatic disease after failure of 1 or more chemotherapy regimens
Gefitinib (Iressa, AstraZeneca)	EGFR	*Non-small cell lung cancer* • Monotherapy for patients with locally advanced or metastatic cancer after failure of both platinum-based and docetaxel chemotherapies
Lapatinib (Tykerb, GlaxoSmith-Kline)	EGFR, HER2	*Breast cancer* • In combination with capecitabine for patients with advanced or metastatic disease whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab • In combination with letrozole for treatment of postmenopausal women with hormone receptor-positive metastatic cancer who overexpress the HER2 receptor for whom hormonal therapy is indicated

EGFR, epidermal growth factor receptor; **HER2,** human epidermal receptor type 2

Based on references 4-9.

rash or xerosis and may not reverse with treatment discontinuation.

Nail Changes

Nail changes including cracking, discoloration, pitting, paronychia (inflammation of the lateral nail bed), and nail loss have been described.[2,14,23,25] These changes are reported to occur in approximately 10% to 20% of patients. Paronychia is the most well-described nail change and is believed to result from skin thinning.[14] Paronychia typically occurs on the thumbs and great toes, with a delayed onset of at least 1 month from the start of treatment and a duration that can persist months beyond discontinuation of EGFR inhibitor therapy.[2,14] Patients with paronychia are predisposed to secondary infections.

Hair Changes

Changes in hair growth, texture, or thickness have been reported in up to 15% of patients taking EGFR inhibitors.[2,23,25] Infrequently, trichomegaly (excess eyelash growth) has been reported. These alterations tend to be more delayed than other EGFR-related dermatologic adverse effects, generally occurring after 2 or more months of therapy. Hair changes typically resolve within weeks or months after therapy discontinuation.[2]

Rash and Survival

The presence of rash from EGFR inhibitors has been correlated with increased response to EGFR inhibitor therapy and improved survival.[26-28] It has been proposed that dermatologic toxicity may be a marker for full EGFR receptor inhibition. However, results from studies that dose EGFR inhibitors until the presence of rash occurs are preliminary and have been conflicting.[29,30] Further research in this area is necessary.

Management

There are no well-established guidelines for the prevention or treatment of EGFR inhibitor-induced dermatologic changes. Treatment is largely based on anecdotal data from case reports, cases series, and expert opinion.

Rash Prophylaxis

General nonpharmacologic prophylactic recommendations are shown in Table 4. In addition to these measures, the use of oral antibiotics for prophylaxis has been studied in 2 randomized controlled trials.[31,32] Tetracycline and its derivatives have been the primary antibiotics studied because of their anti-inflammatory effects. Scope and colleagues randomly assigned 48 cetuximab-treated patients to receive 100 mg of minocycline or placebo daily.[31] All patients also received topical tazarotene 0.05% (Tazorac, Allergan) to be applied to one side of the face twice daily. Prophylactic therapy was initiated on the same day as cetuximab therapy and continued for 8 weeks. Patients in the minocycline group had a significantly reduced log lesion count at 4 weeks compared with placebo (P=0.005); however, by 8 weeks there was no significant difference between the groups. The proportion of patients with moderate to severe rash and itching was somewhat improved with minocycline at 4 weeks, but again, the difference between the groups was minimal by 8 weeks. Almost one-third of patients discontinued tazarotene due to skin dryness or irritation, and there appeared to be little beneficial effect with this treatment. In a second study, tetracycline (500 mg twice daily) was compared with placebo for rash prevention in patients receiving EGFR inhibitors.[32] Tetracycline was initiated within 14 days of EGFR initiation and continued for 4 weeks. Although there was little difference in overall rash incidence, the tetracycline-treated patients had a lower incidence of physician-reported grade 2 or higher skin toxicity at week 4 (17% vs 55%; P=0.04). At week 8, the incidence of moderate to severe skin toxicity remained lower in the tetracycline group (27% vs 47%), but it was not significantly different.

Rash Prophylaxis Versus Treatment

Recently, Lacouture et al published the first trial comparing preemptive therapy (given at the start of EGFR inhibitor therapy) with reactive therapy (treatment after the development of a rash).[33] All 95 patients were being treated with panitumumab for colorectal cancer. Preemptive therapy consisted of a morning application of moisturizer, sunscreen prior to going outdoors, 1% hydrocortisone cream at bedtime, and 100 mg of doxycycline twice daily. Reactive treatment was at the discretion of the investigator and was prescribed at any point during weeks 1 to 6 of the study. Patients in the preemptive therapy group had fewer grade 2 or higher skin toxicities (29% vs 62%) during the 6-week treatment period.

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Based on these results, it appears that preventive therapies for rash should be further studied; however, the presence of rash has been correlated with survival, and there is concern that preventive therapy reduces the appearance of this marker of efficacy.[14]

Rash Treatment

Table 5 summarizes several expert recommendations for the treatment of EGFR inhibitor-induced rash.[10,11,17] A number of authors also have published recommendations based on their personal practice.[15,34] Treatment recommendations typically include topical therapy for mild symptoms with progression to systemic antibiotics and corticosteroids for more severe rashes.

Topical agents. Topical corticosteroids, antibiotics, and immunosuppressants frequently are recommended. Use of topical antiseptics, fusidic acid, econazole, and benzoyl peroxide also have been reported without obvious benefit.[35]

Pimecrolimus (Elidel, Novartis), a topical immunosuppressant, was evaluated in a small trial (N=24) of patients receiving cetuximab.[36] Pimecrolimus applied to one side of the face for 5 weeks reduced the lesion count on the treated side at both 2 and 5 weeks compared with the non-treated side. Additionally, patients reported decreases in burning, itching, dryness, and redness. However, the authors reported that the results did not show a clinically significant benefit, and thus they call into question the role of pimecrolimus.

The use of topical corticosteroids is also controversial. Li and colleagues reported that corticosteroids may potentiate EGFR toxicity and recommend that these agents be avoided.[2] Lynch and colleagues recommend topical steroids be applied for 7 days beyond resolution of symptoms but not for more than 14 consecutive days.[3] One author recommends use of topical corticosteroids for a maculopapular rash but recommends clindamycin gel if the rash has pustular characteristics.[15] It is possible that topical steroids are most effective early in rash treatment.[26]

In addition to clindamycin, other topical antibiotics that have been used include erythromycin, fusidic acid, and metronidazole. Topical clindamycin appears most frequently in the literature and seems effective, particularly for pustular rash.[15,37]

Topical retinoids have been recommended by some authors, but many reports suggest they should be avoided because of their drying effects.[38] In the prevention study by Scope and colleagues, tazarotene cream resulted in significant skin irritation.[31] The Erlotinib Expert Panel suggests that further study of topical retinoids is necessary because one case report suggests positive results.[17]

Regenecare, a wound gel with lidocaine, aloe vera, collagen, and sodium alginate, is being evaluated for its efficacy in improving itching and pain in patients receiving EGFR inhibitors.[2] A pilot study revealed that a small number of patients with grade 2 rash applying the gel to affected areas had less itching and pain.[39]

Menadione (vitamin K_3), has been shown to reverse the effects of EGFR inhibitors in the skin and is the first proposed treatment to reverse the EGFR inhibition process.[40] A topical formulation is in Phase I clinical trials.

Oral agents. The mechanism of oral antibiotics has been reported to be primarily anti-inflammatory rather than antibacterial; thus, tetracycline and its derivatives are the most widely recommended agents.[17] Although minocycline and tetracycline were not dramatically successful when given as preventive agents, their use did improve rash severity.[31,32] These data combined with success in case reports make them a reasonable option for rash treatment. Oral corticosteroids also are frequently recommended. Oishi suggests that

Table 2. NCI Grading Criteria for EGFR Inhibitor-Induced Rash

Source	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NCI-CTCAE v3.0	Rash (acneiform)	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	Not available	Death
NCI-CTCAE v4.0	Rash (acneiform)	Papules and/or pustules covering <10% BSA that may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10% to 30% BSA that may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA that may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection requiring oral antibiotics	Papules and/or pustules covering any percentage of BSA that may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection requiring IV antibiotics; life-threatening consequences	Death
NCI-CTCAE v4.0	Rash (maculo-papular)	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10% to 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA, with or without associated symptoms; limiting self-care ADL	Not available	Not available

ADL, activities of daily living; **BSA,** body surface area; **NCI-CTCAE,** National Cancer Institute Common Terminology Criteria for Adverse Events
Based on references 18 and 19.

Table 3. Suggested Grading Criteria for EGFR Inhibitor-Induced Rash

Source	Adverse Event	Grade 1A	Grade 1B	Grade 2A	Grade 2B	Grade 3A	Grade 3B
Lacouture 2010	Papulo-pustular eruption	<5 papules or pustules *OR* 1 area of erythema or edema <1 cm	<5 papules or pustules *OR* 1 area of erythema or edema <1 cm *AND* pain or pruritus	6-20 papules or pustules; *OR* 2 to 5 areas of erythema or edema <1 cm	6-20 papules or pustules *OR* 2 to 5 areas of erythema or edema <1 cm *AND* pain, pruritus, or effect on emotions or functioning	>20 papules or pustules *OR* >5 areas of erythema or edema <1 cm	>20 papules or pustules *OR* >5 areas of erythema or edema <1 cm *AND* pain, pruritus, or effect on emotions or functioning

Based on reference 20.

corticosteroids are a good option for a rash that has progressed but is not pustular.[15] Several authors recommend the use of antihistamines for itching.[10,15,38]

Xerosis Management

Little information has been published on the management of xerosis associated with EGFR inhibitors. Emollient use is generally recommended.[37] The emollient for the face and upper trunk should be an oil-in-water–based cream because greasy ointments could worsen the papulopustular rash; however, if the limbs are affected, a water-in-oil cream or ointment may be used.[24] Low-dose corticosteroids can be used if eczema develops. Secondary infections should be treated appropriately.

Treatment of Nail and Hair Changes

Li and colleagues recommend the use of topical steroids and antiseptic soaks for paronychia.[2] Segaert and colleagues suggest that a potent topical steroid applied to the nail bed at symptom onset may prevent worsening of the paronychia.[24] Suh and colleagues reported a case of paronychia that failed to respond to oral cephalexin and topical mupirocin but did respond to doxycycline 100 mg twice daily. Therapy was continued for 6 weeks, with full symptom resolution.[41]

The hair changes that can occur in patients treated with EGFR inhibitors often do not require intervention,[2] but if trichomegaly occurs, an ophthalmologic examination may be indicated and the patient's eyelashes may need to be cut.

Conclusion

Although dermatologic reactions are common with EGFR inhibitors, treatments for these reactions have not been fully evaluated in clinical trials. Recent data suggest that preventive regimens may be valuable, but further research in this area is necessary before widespread use is recommended. Rash management will be necessary for some patients. Patients with mild to moderate symptoms may improve with topical therapy; however, patients with more severe rash will likely require oral therapy with antibiotics or possibly systemic corticosteroids. Typically, discontinuing or reducing doses of EGFR inhibitors is avoided unless a severe reaction occurs.

Patients undergoing treatment with EGFR inhibitors should be

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Table 4. Basic Measures To Prevent EGFR Inhibitor-Induced Toxicities

Sun exposure	• Avoid the sun when possible • Use sunscreen (preferably containing zinc oxide or titanium dioxide)
Skin care	• Use alcohol-free emollients to prevent dry skin • Avoid dyes and perfumes • Use mild body wash • Take cool or lukewarm baths (rather than hot showers) • Apply hypoallergenic makeup for covering rash • Avoid over-the-counter acne products
Nail care	• Keep nails clean and trimmed • Avoid activities that could cause nail bed trauma (eg, wearing tight-fitting shoes)

Based on references 2, 3, 10, 15, and 38.

Table 5. Recommendations for the Treatment of EGFR Inhibitor-Induced Rash

Expert Group	Recommendations
Erlotinib Expert Panel Recommendations[17]	*Grade 1* • Treatment with topical agents is optional (topical antibiotics, 2% sulfosalicylic creams) • No dose reduction or treatment interruption *Grade 2* • Topical treatment as in Grade 1, with controversial recommendation for topical corticosteroids; patients with more severe symptoms could add oral therapy with tetracyclines and corticosteroids; antihistamines for pruritus • No dose reduction or treatment interruption; for very distressing symptoms, erlotinib may be interrupted for 3 to 5 days (restart at full dose; if rash recurs within 15 days, a dose reduction to 100 mg can be considered) *Grade 3* • Topical agents, tetracycline, and oral corticosteroids can be used; tetracycline may be considered for a short duration to prevent future episodes after resolution of event • EGFR therapy should be interrupted until rash improves to Grade 2; restart at 100 mg/day; discontinue therapy if rash recurs with the reduced dose *Grade 4* • Refer to burn unit for intensive care • Discontinue therapy indefinitely
Canadian Panel Recommendations for Monoclonal Antibodies in Gastrointestinal Malignancies[11]	*Mild (Grade 1)* • Topical corticosteroid (hydrocortisone 1%) and clindamycin 2% twice daily until resolution *Moderate (Grade 2)* • Topical treatment as above until rash improves to Grade 1 plus oral antibiotics (minocycline 100 mg twice daily or doxycycline 100 mg once or twice daily) for at least 4 weeks and as long as symptoms of rash are present • For scalp lesions, use topical clindamycin plus triamcinolone acetonide 0.1% in equal parts propylene glycol and water until resolved *Severe (Grade 3)* • Panitumumab: hold treatment until toxicity is Grade 2 or less • Cetuximab: hold treatment for 1 week • THEN follow Grade 2 recommendations; treatment can be continued if symptoms improve (follow dose escalation as recommended by manufacturer); treatment should be discontinued if no improvement is seen
2006 EGFR Inhibitor Dermatologic Toxicity Forum[3,10]	*Mild* • No treatment OR topical hydrocortisone (1% or 2.5%) and/or clindamycin 1% gel for 2 weeks (no alteration in EGFR inhibitor regimen); proceed to moderate treatment if no improvement or worsening reaction *Moderate* • Either topical hydrocortisone 2.5% cream, clindamycin 1% gel, or pimecrolimus 1% cream AND doxycycline or minocycline 100 mg twice daily for 2 weeks (no alteration in EGFR inhibitor regimen); proceed to severe treatment if no improvement or worsening reaction *Severe* • Add oral corticosteroid to moderate regimen and reduce EGFR inhibitor dose for 2 weeks; EGFR inhibitor may be interrupted or discontinued if symptoms worsen

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educated about the common dermatologic toxicities, especially skin rash. Techniques for skin care, rash prevention, and potential management strategies should be thoroughly discussed. Oncologists, dermatologists, nurses, and pharmacists should remain vigilant for EGFR inhibitor-induced dermatologic toxicities, and multidisciplinary care should be instituted for patients who develop these toxicities.

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