

NCCN Task Force Report: Management of Dermatologic and Other Toxicities Associated With EGFR Inhibition in Patients With Cancer

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Key Words

Dermatologic toxicities, ocular toxicities, rash, acne-like rash, papulopustular rash, dry eye, paronychia, radiation dermatitis, epidermal growth factor receptor, EGFR, EGFR inhibitor, tyrosine kinase inhibitors, TKI, cetuximab, panitumumab, erlotinib, gefitinib, colorectal cancer, head and neck cancer, non-small cell lung cancer

Abstract

This NCCN Task Force Report describes the management of dermatologic and ocular toxicities that occur in patients treated with epidermal growth factor receptor (EGFR) inhibitors. Task force members are from NCCN member institutions and include oncologists, dermatologists, an ophthalmologist, and a mid-level oncology provider. This report describes commonly used therapies that the task force agreed are appropriate standards of care for dermatologic and ophthalmologic toxicities associated with EGFR inhibitors, which generally are supported only by anecdotal evidence. Few recommendations are evidence based; however, some commonly used therapies have data supporting their use. Conclusions from completed clinical trials are generally limited by the small numbers of patients enrolled. The information in this report is based on available published data on treating toxicities associated with EGFR inhibitors, data from treatment of clinically similar toxicities from different etiologies, and expert opinion among the NCCN Task Force members. (*JNCCN* 2009;7[Suppl 1]:5–21)

Indications for Epidermal Growth Factor Receptor Inhibitor Therapy

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor from a larger family of ErbB receptors that mediate cell survival, proliferation, angiogenesis, and invasiveness; thus, EGFR is associated with many carcinogenic processes.¹ Inhibitors of EGFR increase overall survival in patients with colorectal, head and neck, pancreatic, and non-small cell lung cancers (NSCLC) and are under investigation in other tumor

types. Classes of EGFR inhibitors include monoclonal antibodies, such as cetuximab and panitumumab, and small molecular weight tyrosine kinase inhibitors, such as erlotinib, gefitinib, and lapatinib (which is a dual EGFR and human epidermal growth factor receptor 2 [HER2] inhibitor).² The monoclonal antibodies target the extracellular domain of EGFR and are given intravenously. The small molecule inhibitors of EGFR inhibit the ATP-binding site of the kinase domain and are given orally. These EGFR inhibitors are currently approved by the FDA for certain types of metastatic cancer, such as breast, colon, head and neck, NSCLC, and pancreatic cancers. In addition, clinical trials are in progress for EGFR inhibitors in patients with skin cancer and other solid tumors.³

Cetuximab is used for metastatic colorectal cancer in patients with wild-type K-ras tumors either as monotherapy or combined with irinotecan.^{4–7} In selected patients, cetuximab is also indicated for advanced NSCLC when combined with cisplatin and vinorelbine,⁸ and for advanced or metastatic/recurrent head and neck cancer.^{9,10} Panitumumab is indicated for metastatic, chemotherapy-refractory colorectal cancer in patients with wild-type K-ras tumors.^{11,12} Determination of K-ras mutational status is important in colorectal cancer because patients with mutated activated K-ras do not respond to treatment with cetuximab or panitumumab.^{12,13}

Erlotinib is indicated as second- and third-line therapy for patients with recurrent or metastatic NSCLC. Patients with NSCLC who have adenocarcinoma histology and never smoked often benefit from erlotinib therapy, because many of these patients have EGFR mutations (e.g., exon-19 deletion) that are associated with sensitivity to erlotinib or gefitinib.¹⁴

Patients who have NSCLC with an exon-19 deletion and are treated with erlotinib have a 1-year survival rate of 80% and a median survival of 34 months.¹⁴ Thus, molecular selection can be used to determine which patients with NSCLC will benefit from therapy with erlotinib and exclude those with little chance of benefit. Erlotinib in combination with gemcitabine is also indicated for patients with pancreatic cancer.¹⁵ Gefitinib is indicated for patients with metastatic NSCLC who benefit from this therapy.^{16,17} Lapatinib in combination with capecitabine is indicated for patients with HER2-positive advanced breast cancer.^{18–20}

EGFR inhibitors are associated with reproducible side effects, including dermatologic toxicities (e.g., skin rash, xerosis, paronychia), mucositis, stomatitis, diarrhea, infusion reactions, ocular abnormalities, and hypomagnesemia.²¹ Skin rash is one of the most frequently occurring side effects and occurs with many EGFR inhibitors, including cetuximab, panitumumab, erlotinib, and gefitinib, whether the agent is a monoclonal antibody or small molecule; therefore, skin rash seems to be a class effect.

Skin rash caused by cetuximab, panitumumab, and erlotinib is associated with a higher response rate and increased survival;^{5,22–24} severity of the skin rash is directly related to increasing survival.^{23,25,26} For example, patients treated with cetuximab and radiation therapy (RT) for head and neck cancer with a more prominent skin rash have longer median survival compared with those who have a less prominent rash (56.7 vs. 24.4 months; $P = .02$).²⁶ Patients treated with erlotinib for NSCLC who have a grade 2 or higher rash have a median survival of 11.1 months compared with 3.3 months for those with no rash ($P < .001$).²³ The association between skin rash and response/survival observed in the erlotinib trials suggests that administering this agent at its highest tolerated dose may improve the possibility of a clinical response. Several studies are investigating the feasibility of escalating the dose of EGFR inhibitors until a tolerable rash occurs in patients with various malignancies.

Oncologists sometimes discontinue therapy or reduce the dose of EGFR inhibitor because the rash is disfiguring or painful.²⁷ Because of the association between rash and survival, current recommendations favor treating the rash over dose reduction, whenever possible.²⁸ Although the rash can be an

impediment to EGFR inhibitor use, familiarity with management strategies to avoid dose reduction may be beneficial. NCCN convened a task force of experts in EGFR inhibitors and their associated toxicities to assess the biomedical literature and clinical experience in managing these toxicities. This report presents the conclusions.

Dermatologic Toxicities

EGFR inhibitors are associated with dermatologic toxicities, such as skin rash, paronychia (suppurative inflammation around the nails), dry skin (xerosis), dry mucus membranes, pruritus, urticaria, superinfection of the skin, increased growth of eyelashes (trichomegaly), facial hirsutism, and alopecia.²⁹ Some patients experience mucositis, which rarely includes aphthous ulcers. Some patients treated with gefitinib experience a purpuric drug reaction and necrolytic migratory erythema-like lesions.

Skin Rash

The skin rash associated with EGFR inhibitors occurs more often than other dermatologic toxicities and may be severe; it affects mainly the face, scalp, neck, upper chest, and back. Patients often refer to the rash as acne, and the term *acneiform* was used for initial descriptions of the rash. However, the EGFR inhibitor-associated skin rash is actually a papulopustular rash distinct from acne, but is often referred to as an acne-like or acneiform rash because of the inflammatory follicular appearance of the lesions.^{5,30,31} Although the EGFR inhibitor-associated skin rash has the papules and pustules of acne vulgaris, it lacks comedones, which are the primary lesions of classic acne. Despite a similar appearance to acne vulgaris, however, the etiology, pathophysiology, and therapeutic approaches to EGFR inhibitor-associated exanthems are entirely different. More recently, the rash has been described as follicular rash, folliculitis, macular/papular eruption, pustular eruption, and monomorphic pustular lesions.^{30,32}

Quality-of-life assessments using the Skindex-16 score have shown that this skin rash has a significant negative emotional component.³³ Patients also state that the skin rash causes irritation, burning, and stinging. In a survey conducted among oncology providers, 80% indicated that patients complain of pruritus, 57% said patients also complain of tenderness, and 32% had to prescribe pain medications for the skin rash.²⁷

The skin rash typically begins within 8 to 10 days after initiation of EGFR therapy, peaks at approximately 2 weeks, and often tapers within 8 weeks of therapy cessation. If patients continue receiving EGFR inhibitors, the skin rash persists; however, its severity often waxes and wanes over time. Postinflammatory side effects, such as telangiectasias, erythema, and hyperpigmentation, tend to occur 5 to 9 weeks after initiation of EGFR inhibitor therapy.³⁴ This section discusses biopsy findings, incidence, grading, and description of skin rash (including in-field toxicity) associated with EGFR inhibitors; management is discussed later.

Biopsy Findings: The papulopustular rash mainly occurs in areas with many sebaceous glands and follicles, such as the face, neck, shoulders, upper trunk, and scalp.³⁵ Histopathologic findings also indicate that the papulopustular rash is a suppurative inflammation and not acne vulgaris, because no comedones or other signs of classic acne are present. The rash is presumed to occur because inhibition of EGFR signaling affects the epithelium, hair follicles, and sebaceous glands. The initial skin rash is caused by inflammation, although infection can occur later (*Staphylococcus aureus* is typically found).^{30,36} In patients with papulopustular rash, the lesions initially show a T-lymphocyte infiltrate followed by a neutrophilic inflammatory infiltrate. Skin biopsies from day 8 show a dermal inflammatory cell infiltrate around follicular infundibula and a suppurative folliculitis with rupture of the epithelial lining.³⁶

EGFR is expressed in the basal layer of keratinocytes in the epithelium, follicles, and sebaceous glands.^{37,38} Inhibition of EGFR decreases cell growth and alters differentiation of keratinocytes in the epithelium and hair follicle.^{39,40} The abnormal epidermal differentiation leads to follicular obstruction and subsequent inflammation. The epidermis becomes thin (leading to xerosis), and the skin becomes fragile.⁴¹

Incidence: Approximately 90% of patients treated with cetuximab or panitumumab will experience skin toxicity.²⁷ The papulopustular rash occurs in 67% to 75% of patients treated with erlotinib.^{27,42} Patients treated with cetuximab, panitumumab, erlotinib, or gefitinib are more likely to have a rash than those receiving lapatinib.⁴³ The severity of the skin rash also varies depending on the patient and type of EGFR inhibitor used. Patients treated with

monoclonal antibodies, such as cetuximab, often have a more severe skin reaction on the face.^{9,44} In addition, patients with a better performance status or a more robust immune system may experience a more severe rash. However, in patients with breast cancer treated with lapatinib (the dual HER2 and EGFR inhibitor), the skin rash is typically only mild to moderate in severity and occurs mainly on the upper chest, not face; many patients do not develop any rash.^{43,45}

Ultraviolet light seems to trigger the rash in some patients perhaps by inducing EGFR expression and activation in the skin; thus, patients treated with EGFR inhibitors should consider protecting their skin from the sun by using sunscreen.^{46,47} Although both fair- and dark-skinned patients experience the rash, it is more likely to be severe in those with fair skin.⁴⁸ A retrospective review of 42 patients treated with erlotinib found that 63% of patients (n = 16) with fair skin (a lower Fitzpatrick skin phototype [I/II]) experienced a more severe rash (grade 3–4) than those (n = 7) with darker skin (higher phototype [V/VII]), who did not have severe rash (P = .0006).⁴⁸ African-American and Hispanic patients also experience skin rash (see Figure 1).

Grading: The severity of the acne/acneiform rash, rash/desquamation, and dermatitis associated with radiation can be graded using the National Cancer Institute's (NCI) common terminology criteria for adverse events ([CTCAE] see version 3).^{31,49} Adverse events are graded on a scale of 1 to 5, with grade 1 being the mildest and least symptomatic. A grade 3 acneiform rash is defined as a "symptomatic and disfiguring" rash, which can be interpreted differently by various researchers. Thus, comparing the severity of rash among different studies is difficult, because it is difficult to accurately grade. The NCI's CTCAE (see version 3) does not adequately reflect the potential for dose limitation that can arise from skin rash associated with EGFR inhibitors.⁵⁰ The rash typically occurs on a limited extent of skin but may be dose-limiting when painful, confluent, or superinfected. The NCI's CTCAE can also be used to grade other dermatologic problems that may occur with EGFR inhibitors (e.g., hair loss/alopecia, dry skin, nail changes, pruritus/itching, telangiectasias).

Description: Patients experience the rash as follows: during the first week of EGFR inhibitor therapy, some patients may have a sensation of erythema and



Figure 1 Skin rash associated with epidermal growth factor receptor (EGFR) inhibitor therapy. (Top) Rash associated with cetuximab. (Bottom) Rash associated with panitumumab. Courtesy of Patricia L. Myskowski, MD.

edema on the central face with a sensation of sunburn (termed *sensory disturbance*). During the second week of therapy, many patients have a papulopustular eruption that eventually dries out and forms crusts, which are not always indicative of infection (see Figure 2). Later, patients may develop telangiectasias and diffuse erythema on areas previously affected by the skin rash.

Although the pustules are usually sterile, some patients may develop a secondary bacterial infection at the site of the dermatologic toxicity (i.e., face, nail bed).^{30,51-53} For example, of 231 patients treated with EGFR inhibitors, 36% had infections.⁵⁴ These superinfections can be bacterial, fungal, or viral. Thus, it is important to culture suspicious lesions (e.g., those with purulent drainage) so that patients can undergo early treatment and sensitivity-directed antibiotic therapy.

In-Field Toxicity: Distinguishing in-field from systemic skin toxicity is important in patients undergoing external-beam RT together with an EGFR inhibitor. Curative doses of ionizing radiation used for head and neck cancer result in a high incidence of grade 3 and 4 in-field skin injury, including radiation dermatitis, mucositis and hemorrhagic mucositis, severe pain, dysphagia, and odynophagia.^{9,55-57} A few case reports indicate that patients irradiated 6 months to 1 year before the administration of EGFR inhibitors (e.g., erlotinib), may have sparing of skin rash in the site that was previously irradiated (Figure 3).⁵⁸⁻⁶⁰ However, in patients treated simultaneously with EGFR inhibitors and RT, a more confluent area of the papulopustules may occur in the irradiated area; the worsening of in-field toxicity may be a higher grade of dermatitis/mucositis (see Figure 3).⁶¹ A recent meta-analysis showed that patients (most with head and neck cancer) treated with EGFR inhibitors combined with RT have an increased risk for radiation dermatitis, skin rash, and mucositis compared with those just receiving RT.⁶² The radiation dermatitis can be severe (see Figure 4).

A recent survey by the EORTC of 125 patients with head and neck cancer from 15 institutions found that grade 3 to 4 dermatitis occurs in approximately 49% of patients treated with cetuximab and concurrent RT.⁵⁷ In another group of 14 patients with head and neck cancer treated with cetuximab and concurrent RT, 5 developed grade 3 to 4 dermatitis, and 10 (71%) also developed superinfection with *S aureus*.⁵³ Grade 4 dermatitis has also been described when cetuximab is administered in the setting of reirradiation, when using radiation to a recurrence or second primary within a previously radiated field.^{63,64} In 5 patients who were reirradiated, 2 experienced complete necrosis of the skin in the area of radiation. In the histologic specimen, complete apoptosis of the keratinocytes throughout the epidermis and evidence of superinfection were seen.^{63,65} In patients who must undergo reirradiation in the same field, whether they can also receive concurrent EGFR inhibitors is not currently clear. A phase I study of reirradiation and erlotinib has been completed recently.

Xerosis and Pruritus

Xerosis may be observed in patients treated with EGFR inhibitors.³⁰ Histologic specimens from patients with xerosis show miniaturized sweat (eccrine) glands and a compacted stratum corneum.^{66,67} Pa-

Dermatologic Toxicities

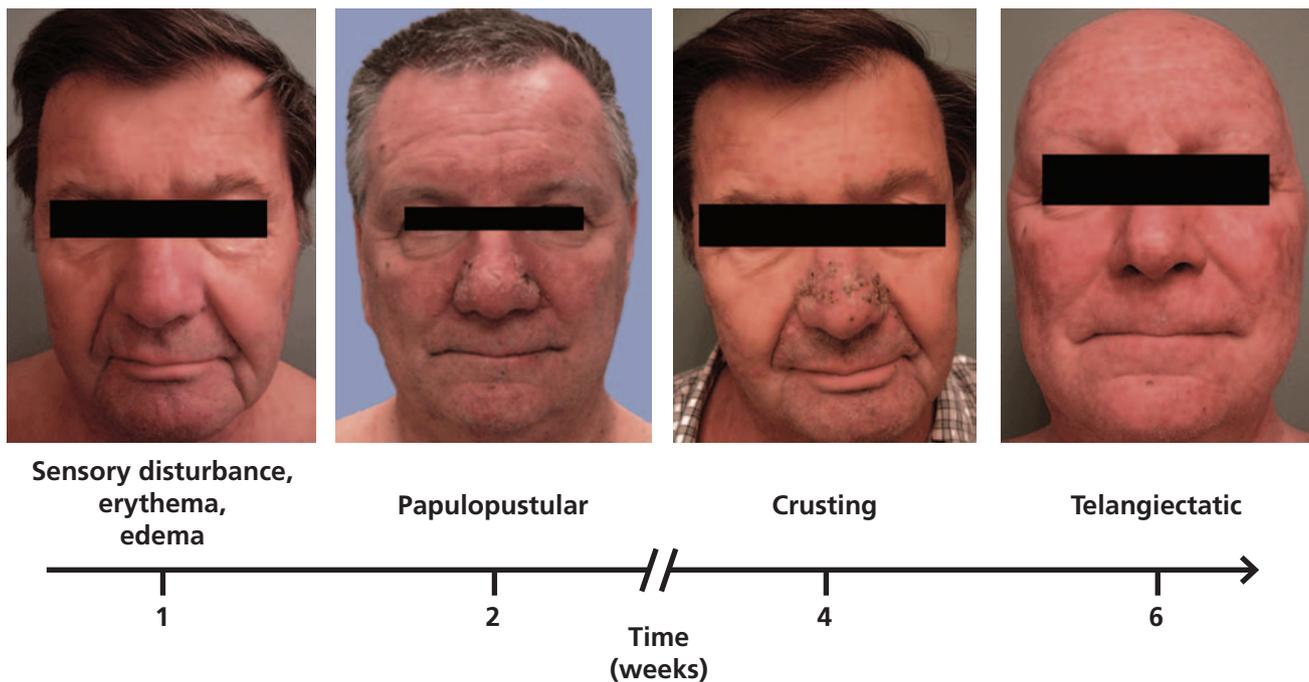


Figure 2 Phases of the skin reaction after initiation of epidermal growth factor receptor inhibitor therapy. From Lacouture ME, Cotliar J, Mitchell EP. Clinical management of EGFR dermatologic toxicities: US perspective. *Oncology (Wiliston Park)* 2007;21(11 Suppl 5):17–21; with permission.

tients may also have desquamation of the epidermis. The dry skin may manifest as painful fissures on the tips of fingers or on heels.

Patients receiving EGFR inhibitors may experience pruritus (10%–52%), which may interfere with sleep. The itching can occur in the papulopustules and areas of xerosis. The risk for superinfection (e.g., with *S aureus*) may be increased by scratching. Cultures should be obtained from suspicious lesions (e.g., those with purulent drainage); if pathogenic bacteria are found, patients should be treated appropriately.

Nail Involvement

Clinically significant changes in the nails may occur in patients taking EGFR inhibitors, including painful paronychia (12%–16%), periungual pyogenic granuloma-like inflammation, swelling and fissuring of the lateral nail folds and distal finger tufts, and cracking of the nails and cuticles (see Figure 5). Nail changes have been reported with all EGFR inhibitors.⁵² Paronychia affects fingernails and toenails (mainly the thumb and big toe) and is associated with tenderness, which impairs daily activities. Patients may find the toe in-

volvement more distressing than involvement of the fingers.⁵² Pyogenic granulomata are often associated with the paronychia. Paronychia usually occurs later than the skin rash (after 20 days to 6 months of treatment with EGFR inhibitors). Initially, paronychia



Figure 3 Effect of radiation on the skin rash associated with erlotinib. (Left) Prior radiation (rectangle) spares the skin from rash. (From Mitra SS, Simcock R. Erlotinib induced skin rash spares skin in previous radiotherapy field. *J Clin Oncol* 2006;24:e28–29; with permission.) (Right) Concurrent radiation intensifies the skin rash. (From Lacouture ME, Hwang C, Marymont MH, Patel J. Temporal dependence of the effect of radiation on erlotinib-induced skin rash. *J Clin Oncol* 2007;25:2140; author reply 2141; with permission.)



Figure 4 Severe radiation dermatitis associated with epidermal growth factor receptor (EGFR) inhibitor therapy. Courtesy of Mario E. Lacouture, MD.

appears predominantly inflammatory, with soft tissue edema visible on MRI; the late course is often complicated by superinfection.^{52,68} Inflamed tissue may be colonized with bacteria, leading to positive wound cultures even in the absence of clinically significant infection. The presence of purulent discharge or collection in association with paronychia may indicate a clinically relevant infection. Although some believe very heavily colonized skin will not heal, others believe that the presence of certain pathogens is a more



Figure 5 Tender paronychia and friable pyogenic granuloma-like lesion of fingernail after cetuximab therapy. Courtesy of Patricia L. Myskowski, MD.

important factor in the prevention of healing.^{69–71} Patients with paronychia can be infected with *S aureus*, methicillin-resistant *S aureus* (MRSA), *Enterococcus*, and *Pseudomonas*.⁵² Paronychia may wax and wane in intensity during therapy or in response to dose interruption or reduction of EGFR inhibitors.

Hair Abnormalities

EGFR inhibitors affect the skin and hair, because EGFR is highly expressed in the basal and suprabasal layers of keratinocytes in the epidermis and in the outer root sheath of the hair follicle, and is implicated in differentiation and regulation of skin, nail, and hair follicle development. Treatment with EGFR inhibitors results in hair changes that vary with the type and location of the hair, and among individuals. After about 100 days of treatment with EGFR inhibitors, approximately 30% of patients report hair abnormalities, including scalp and body alopecia; conversely, patients may also experience increased hair growth along with hair curling after erlotinib.^{30,67} Patients often report a change in hair texture (curlier, finer, and brittle), which may reverse after treatment. Men have slower growth of their beards and androgenic-pattern alopecia; however, increased growth of the eyelashes has been reported.^{30,67} After prolonged therapy on cetuximab, some patients have very thin, sparse eyebrows and brittle hair.

Skin lesions on the scalp can be associated with inflammation and alopecia.⁷² In areas with significant inflammation and consequent scarring, the hair may not grow back (termed *scarring alopecia*).⁷³ Thus, it is important to treat scalp inflammation promptly to avoid permanent hair loss. Non-scarring alopecia can develop after 2 to 3 months of treatment; the hair that eventually grows back can be brittle and curly.⁷⁴ Approximately 20% of patients have facial hypertrichosis and trichomegaly.^{67,75} The eyelashes grow long and curly, and may turn inward.^{76,77} During treatment with EGFR inhibitors, hyperpigmentation of the hair (yielding very black hair) has been described in a small number of patients.

Other Toxicities

Ocular Changes

EGFR is widely distributed on the eye surface in the conjunctival and corneal epithelium; it is also present in the eyelid skin, lash follicles, tear glands, and

sebaceous and sweat glands.⁷⁸ Inhibitors of EGFR are known to have ocular side effects, such as dry eye, inflammation of the lid margin (blepharitis), dysfunction of the sebaceous glands of the eyelid (meibomitis), long eyelashes (trichomegaly), corneal erosion, and inversion or eversion of the eyelid margin (entropion or ectropion).⁷⁹ Most ocular side effects are not vision-threatening; however, many require prompt examination by an ophthalmologist to quickly treat the sometimes severe discomfort and prevent ocular injury. Many ocular symptoms resolve with discontinuation of the EGFR inhibitor, but symptomatic management of ocular toxicity, or dose reduction or interruption, may be preferable to discontinuation in patients who are deriving clinical benefit from the treatment.

Ocular side effects encompass 1) changes in the tear film, 2) changes in the eyelid, and 3) other miscellaneous eye conditions. Tear film changes cause dysfunctional tear syndrome, which is the most common ocular symptom in patients taking EGFR inhibitors.⁷⁹ Eyelid changes include blepharitis, meibomitis, and changes to the eyelashes (including trichomegaly, patchy eyelash loss, and misdirected, thickened, or hyperpigmented eyelashes). Miscellaneous changes include corneal epithelial defects and ectropion or entropion.^{80,81}

Dysfunctional tear syndrome is frequently associated with decreased tear production that leads to keratitis sicca; patients complain of burning or grittiness in their eyes, red eye, and vision fluctuation with blinking. The tears may also have altered composition in patients with blepharitis and meibomitis, who can have symptoms similar to patients with decreased tear production. The onset of dry eye may occur within a week or less of EGFR inhibitor initiation. Dysfunctional tear syndrome is easily treated (see section on "Management of Ocular Toxicities").⁷⁹

The diagnosis and management of blepharitis are straightforward. Patients taking EGFR inhibitors report that their eyelids become sore and irritated, and the discomfort can be severe. The changes to the eyelid margin range from mild redness to significant edema and soreness of the eyelid margin, with small pustules at the base of the eyelashes.⁷⁹ Crusts of debris (crusting) can also collect at the base of the eyelashes. Matting of eyelashes and crusting are especially evident on waking. Because severe blepharitis can affect the tear film, these patients may also note visual fluctuation. Chronic blepharitis can cause ectropion

or entropion of the eyelid margin, thus causing misdirected eyelashes, which are associated with red eye, irritation, and abrasion. If inflammation of the eyelid margin is adequately treated, eyelash orientation may normalize. Patients with meibomitis typically complain of discomfort, burning, and visual fluctuation. Although these symptoms can all resemble blepharitis, meibomitis does not cause crusts on the eyelid margin; meibomitis causes pouting meibomian gland orifices with thick secretions.⁷⁹

Trichomegaly sometimes occurs after months of exposure to an EGFR inhibitor. The long eyelashes may brush the cornea, leading to corneal erosions; these microabrasions of the cornea can lead to vision-threatening conditions, such as corneal ulceration and vision loss.⁸² The eyelashes of patients who are taking EGFR inhibitors long-term may also be excessively thick and hyperpigmented and may fall out or become brittle and break.

The package inserts for several EGFR inhibitors report a low incidence of eye symptoms, principally conjunctivitis (cetuximab, 7%–15% of patients; erlotinib, 12%; panitumumab, 4%). Gefitinib is associated with eye pain, corneal erosion or ulcer, and aberrant eyelash growth, and rarely with ocular ischemia or hemorrhage (see package insert). In 20% of patients treated with gefitinib, eye symptoms have been reported (including conjunctivitis, blepharitis, dry eye, corneal erosion, trichiasis).^{83,84} Recent data from the SERIES (Skin and Eye Reactions to Inhibitors of EGFR and Kinases) clinic indicate a higher incidence of ocular events than previously reported, with ocular symptoms occurring in at least one third of patients.⁸² The origin of ocular inflammation in patients treated with EGFR inhibitors is not well established but may, to some extent, result from dysfunctional tear syndrome and abrasions from misdirected eyelash growth. The incidence of infectious conjunctivitis is actually less than 5% of patients with conjunctivitis taking EGFR inhibitors.

Symptoms that require prompt referral to an ophthalmologist include 1) sustained eye pain and/or loss of vision; 2) severe eye redness and/or sensitivity to light; 3) no response within 1 week of initiation of treatment for squamous blepharitis, meibomitis, or dysfunctional tear syndrome; and 4) misdirected eyelashes, especially recurrent misdirected eyelashes. In addition, if a topical steroid eye drop is used to treat ocular inflammation, ophthalmologic examination is

indicated to rule out an infectious cause and to monitor intraocular pressure in patients expected to have long-term survival.

Management of Skin Toxicities

This section describes commonly used therapies that task force members agreed are appropriate approaches to care. Given the paucity of prospective data on managing skin and ocular toxicity associated with EGFR inhibitors, no evidence-based standards can be strongly recommended. Conclusions from completed clinical trials are limited by the small numbers of patients enrolled.

Before treating the patient, what side effects are bothering the patient the most must be determined. Some patients may be very distressed because the rash affects their appearance, whereas others may be more concerned about the painful paronychia affecting fingers and toes, limiting their mobility. The experience of the task force members is that reducing the dose of EGFR inhibitors is required more commonly for paronychia than for skin rash. Some patients may have pain, some may have pruritis, and others inflammation. Task force members recommend initiating treatment for mild or moderate side effects, lest they become dose-limiting. Table 1 provides a summary of the management for toxicities associated with EGFR inhibitor therapy.

In many cases, the patient's symptoms and side effects are managed by mid-level practitioners. Practitioners caring for these patients must be aware of these expected toxicities and appropriate management options and must provide extensive patient teaching. Many of the current treatment options are based on anecdotal rather than evidence-based medicine. Further clinical trials are needed to better define the best treatment options for managing these toxicities. Given their integral role in managing these patients, mid-level practitioners should be directly involved in clinical trials and educational efforts to better manage the toxicities associated with EGFR inhibitors.

Modifying EGFR Inhibitor Therapy

Brief dosing interruptions can be helpful in managing high-grade EGFR inhibitor-associated skin and ocular toxicities. These toxicities may lessen over the course of 1 to 2 weeks, and then reintroduction of the EGFR inhibitor (without a repeat loading dose

in the case of monoclonal antibodies) is often feasible. The role of dose reduction remains uncertain. Pivotal trials of cetuximab used dose modification for managing high-grade skin rash. However, the reproducible relationship between rash and survival for all EGFR antagonists suggests, but does not prove, that maintaining full dose in patients with rash may be beneficial. Until clinical trials with improved patient selection prospectively test the role of higher dose, maintaining full dose seems preferable but should be guided by the patient's tolerance of skin rash. Treatment of skin and ocular toxicities reduces the need for dose modification.

Treatment of Skin Toxicity

Much of the information about management of the papulopustular rash associated with EGFR inhibitor therapy in the biomedical literature is anecdotal.^{49,85} In addition, treatment varies in different countries.⁸⁵⁻⁸⁷ Because the skin rash waxes and wanes (over weeks or months), whether therapies are efficacious has been difficult to determine. Some studies of topical agents use a split-face application to allow for intrapatient control.⁸⁸

Commonly Used Topical Therapies: Initial clinical descriptions of the skin eruption caused by EGFR inhibitors compared it to acne. Biopsy and culture data show that the skin eruption is an inflammatory process completely distinct from acne.^{35,36} Most conventional topical antiacne medications, including topical retinoids and benzoyl peroxide, are not indicated to treat the papulopustular skin rash resulting from EGFR inhibitors.^{49,51} These agents are drying and can increase the sensations of burning and irritation, and no reports suggest they improve either rash or symptoms.^{44,89} A small randomized trial of tazarotene (a topical retinoid) showed that it had no clinical benefit in treating cetuximab-related skin rash.⁸⁸ A recent split-face study assessing topical pimecrolimus (a calcineurin inhibitor with anti-inflammatory properties) for cetuximab-related skin rash found that it did not improve patients' assessments of their symptoms, and dermatologists agreed that it did not improve symptoms.⁹⁰

Topical steroids and antibiotics (e.g., clindamycin, erythromycin) may be useful for treating the papulopustular skin rash.^{44,49,85,91-93} Some task force members routinely use low-strength topical steroids on the face, or medium-strength topical steroids on the body, if the patient is symptomatic (see Figure 6).⁴⁴ However, the use of topical steroids and anti-

Dermatologic Toxicities

Table 1 Management of Toxicities Associated With Epidermal Growth Factor Receptor Inhibitor Therapy

Trichomegaly with Eye Irritation	<ul style="list-style-type: none"> • Referral to ophthalmologist because of risk for trichiasis • Clip long eyelashes
Paronychia	<ul style="list-style-type: none"> • Bacterial and fungal culture; appropriate oral antibiotics • Monsel's (ferric subsulfate) solution or silver nitrate applied to bleeding overgrown tissue • 4% thymol in alcohol, aluminum acetate (Burrows solution) soaks, white vinegar soaks (1:10), bleach soaks (1/4 cup bleach:3 gallons water) • Topical steroids for noninfected paronychia • Nail clipping or possible removal of nail plate
Fissuring	<ul style="list-style-type: none"> • Monsel's solution, zinc oxide cream • Protective coverings, cyanoacrylate glue to fissures to relieve pain and promote healing
Desquamation	<ul style="list-style-type: none"> • Petroleum jelly, other thick emollients (e.g., Bag Balm) • Mild (neutral pH) soap • 12% ammonium lactate, 6% salicylic acid, 20% urea
Pruritus	<ul style="list-style-type: none"> • Cool compresses, sedating antihistamines at evening/bedtime, topical steroids, topical menthol lotions • Gabapentin or pregabalin

Courtesy of Patricia L. Myskowski, MD.

biotics to treat skin rash is based on expert preference and clinical experience rather than data from randomized clinical trials. Severe skin rash may be associated with extensive formation of yellow crusts and debris. These may be removed with petrolatum jelly, ammonium lactate, or dilute hydrogen peroxide soaks and with gentle débridement. However, hydrogen peroxide should be avoided or used cautiously in areas with hair because of possible bleaching.

Some patients may develop culture-positive infections at the site of the dermatologic toxicity (i.e., face, nail bed).^{30,51} If superinfection is suspected (because of the extent of inflammation and edema, the presence of a dominant lesion that appears larger and more inflamed than the remainder of the lesions, or purulent drainage), the site should be cultured to determine the organism and sensitivity, particularly if the patient has already been treated with topical or oral antibiotics.³⁰ Long-term prophylactic topical mupirocin ointment can be used in the nose to prevent *S aureus* colonization, especially for patients with recurrent infection.⁵¹

Most skin rashes related to EGFR inhibitors do not cause scarring after treatment, but telangiectasias (dilated blood vessels) and postinflammatory hyperpigmentation may occur. African-Americans may be especially prone to postinflammatory hyper-

pigmentation after EGFR inhibitors, which may resolve or significantly improve within 3 months after treatment is discontinued. Patients who develop significant skin rashes during EGFR inhibitor therapy may be more sensitive to sunlight after treatment.

Based on experience treating telangiectasias from other etiologies, the pulsed dye laser and intense pulsed light may effectively decrease the erythema and prominence of telangiectatic vessels. Postinflammatory hyperpigmentation, again based on treating the condition resulting from other etiologies, may fade through the use of hydroquinone, azelaic acid, topical retinoids, or laser-based therapies.

Commonly Used Systemic Therapies: Systemic therapy is an option for skin rash associated with EGFR inhibitors in certain settings, including 1) severe rash (grade 3 or 4), 2) rash shown to be or looks infected, 3) rash refractory to topical agents, or 4) rash that is recurrent despite dose modification (see Table 2). Although systemic steroids are not typically used to treat skin rash associated with EGFR inhibitors, published case reports suggest they may be appropriate in some settings with careful supervision, usually in the inpatient setting.

Oral Antibiotics: Oral antibiotics for skin rash include tetracycline, doxycycline, or minocycline.^{35,91} As previously described, oral antibiotics have been



Figure 6 Treatment of skin rash associated with cetuximab. (Left) Rash before treatment. (Right) Appearance 1 week after débridement and treatment with 0.2% hydrocortisone valerate on the right side of the face and with 0.1% tazarotene on the left side of the face. The forehead was not treated with either the topical steroid or retinoid. From Moss JE, Burtness B. Cetuximab-associated acneiform eruption. *N Engl J Med* 2005;353:e17; with permission.

studied in small trials of prophylaxis against the emergence of rash associated with EGFR inhibition. The enteric-coated form of doxycycline is less toxic to the gastrointestinal tract. If suspicious skin lesions yield positive cultures (which are caused by infection and not simply colonization), treatment according to standard of care is appropriate.

Oral Retinoids: Isolated case reports suggest a limited role for oral retinoids in patients with high-grade dermatologic toxicity from EGFR inhibitors.^{94–96} In patients with skin rash from erlotinib, low doses of

oral acitretin (10 mg/d) were used and the skin rash improved after 4 weeks.⁹⁶ Whether this improvement was related to the cyclical nature of this rash or reflected a therapeutic effect is unclear.

Oral retinoids have anti-inflammatory effects and improve cellular differentiation. However, mucocutaneous dryness (especially lip dryness) is a problem with patients receiving oral retinoids (especially isotretinoin) at higher doses, and this may exacerbate the xerosis caused by EGFR inhibitors. Higher doses of oral retinoids are associated with desquamation and paronychia inflammation after longer durations of therapy, which also occur with EGFR inhibitors.⁵² In addition, because retinoids are photosensitizing, the concern exists that if patients are on concomitant radiation, the skin rash may worsen if they are also on retinoids. Thus, when oral retinoids are used, the lowest dose should be prescribed. However, the relative worth of this strategy, compared with dose modification or interruption, is not known.

Novel Treatments: Topical Menadione: A topical vitamin K3 analog, menadione, is being investigated in a phase I trial for use in reducing the skin rash associated with EGFR inhibitors. Menadione inhibits phosphatases that would usually inactivate EGFR in the skin. In vitro experiments suggest that menadione maintains or even increases EGFR phosphorylation and activity in the skin. It is hypothesized that menadione may reverse skin changes caused by systemic EGFR inhibitors.^{97,98}

In-Field Toxicity: In-field skin toxicity can occur when EGFR inhibitors are given concurrent with RT; it requires management of the radiation dermatitis component. Randomized clinical trials have shown a benefit for using topical mometasone to treat in-field radiation dermatitis.⁹⁹ For patients with radiation dermatitis who are also superinfected, both topical antibiotics and steroids can be used (e.g., topical antibiotic to the eroded area and a topical steroid to the noneroded, but still-inflamed, areas). Oral antibiotics and topical steroids can also be used in this setting. Some have suggested that systemic doxycycline should not be used in patients with grade 2 to 3 radiation dermatitis (e.g., in patients undergoing RT with cetuximab for head and neck squamous cell cancer); however, no data are available for or against using systemic doxycycline in this setting.¹⁰⁰

Grade 4 in-field dermatologic toxicity, with extensive desquamation, has been described with con-

Table 2 Systemic Therapies for Rash Associated With Epidermal Growth Factor Receptor Inhibitor Therapy

Prophylactic/Mitigating Treatments (i.e., to decrease severity of rash)

- Tetracycline, minocycline, doxycycline

Reactive Treatments (based on anecdotal or nonrandomized studies)

- Tetracyclines: minocycline, doxycycline, tetracycline
- Retinoids: isotretinoin (problem with paronychia), acitretin

Reactive Treatment for Infection

- Importance of bacterial culture, especially around nose, abscesses, pustules on body
- Anti-Staphylococcal antibiotics: cephalexin, dicloxacillin
- Anti-methicillin-resistant *Staphylococcus aureus* antibiotics: sulfamethoxazole/trimethoprim, linezolid

Courtesy of Patricia L. Myskowski, MD.

current cetuximab and radiation; this is often an indication for discontinuing the EGFR inhibitor and/or interrupting the radiation course. Hospitalization is sometimes indicated for pain management, hydration, and wound care. Cautious and supervised use of potent topical steroids (e.g., clobetasol ointment) can be effective. Systemic steroids are not typically used to treat skin rash associated with EGFR inhibitors; however, they may be appropriate for severe radiation dermatitis with careful supervision (usually inpatient). If indicated, a prednisone-equivalent dose of 40 mg daily tapered slowly over 1 to 2 weeks is usually sufficient to calm a severe flare. Surveillance for possible superinfection has been discussed but requires increased vigilance during systemic immunosuppressive therapy.

Prophylactic Approaches: Prophylactic oral tetracyclines (e.g., minocycline, doxycycline) may be useful for decreasing the severity of the skin rash. A recent randomized trial of 48 patients showed that prophylaxis with oral minocycline (100 mg daily) diminished the severity of the cetuximab-related cutaneous adverse effects during the first month of cetuximab treatment; facial lesions and moderate-to-severe itching were significantly decreased with minocycline prophylaxis (lesion count with placebo = 110 vs. minocycline = 61; $P = .008$).⁸⁸ Another recent placebo-controlled, double-blind study in 61 patients found that prophylactic oral tetracycline (500 mg, twice daily) did not prevent skin rash in patients taking EGFR inhibitors.¹⁰¹ However, tetracycline seemed to decrease severity of the skin rash and improve quality of life, because patients had less burning and itching. At 4 weeks (but not 8 weeks), fewer patients treated with tetracycline had moderate-severe skin rash (\geq grade 2) compared with those treated with placebo (4 vs. 16 patients; $P = .04$). Using a less-photosensitizing agent (e.g., minocycline) may be prudent in certain settings (e.g., EGFR inhibitor combined with RT), although no studies have compared tetracycline antibiotics in this setting.

A randomized study (Skin Toxicity Evaluation Protocol with Panitumumab [STEPP]) of 95 patients found that multiagent prophylactic skin treatment, involving oral doxycycline (100 mg, twice daily), topical corticosteroids (1% hydrocortisone), skin moisturizer, and sunscreen, decreased (from 62% to 29%) the incidence of skin toxicities (\geq grade 2) compared with reactive skin treatment, which also used the same regimen during the first 6 weeks based on investigator assessment of skin toxicity.¹⁰² Pa-

tients were instructed to use the topical steroid and doxycycline rigorously, and the sunscreen and moisturizer as they saw fit for dry areas.

When used prophylactically, a randomized study showed that topical steroids were beneficial in decreasing, but not preventing, radiation dermatitis.¹⁰³ Results of 2 large randomized studies using an oil-in-water topical trolamine emulsion to prevent radiation dermatitis have been negative.^{104,105}

Ultraviolet radiation has been reported to trigger the rash in some cases; thus, patients treated with EGFR inhibitors should consider using sunscreen.⁴⁷ Non-alcohol-based sunscreens will be less irritating. In general, the task force members suggest using physical sunblocks (e.g., zinc oxide, titanium dioxide) with 30 SPF that block UVA and UVB and applying them thickly.

Management of Other Dermatologic Problems

In addition to the skin rash, patients being treated with EGFR inhibitors can have other dermatologic side effects, such as xerosis, pruritus, paronychia, fissuring, desquamation, and hair abnormalities. A management summary for these cutaneous problems is shown in Table 1. Brief dosing interruption of EGFR inhibitors may be necessary, but dose modification or cessation of therapy should be avoided if possible (see “Modifying EGFR Inhibitor Therapy”).

Xerosis and Fissures

Treatment for xerosis relies on the use of emollients, such as zinc oxide (30%), petroleum jelly, and other thick emollients (e.g., Aquaphor, Aveeno, Bag Balm, Cetaphil, Cutemol, Eucerin, Vanicream).^{106,107} Alcohol-based lotions, antibacterial soaps, and long, hot showers should be avoided.

Fissures on the heels and fingertips can be treated with Monsel's solution (ferric subsulfate), silver nitrate, aluminum chloride solution, zinc oxide (20%–30%), or cyanoacrylate glue (Krazy Glue, Super Glue).¹⁰⁸ Ferric subsulfate solution does not sting or stain as much as silver nitrate, is hemostatic, shrinks excess vascular tissue, and does not support the growth of bacteria.^{109,110} However, some task force members believe that ferric subsulfate solution increases the size of the fissures and stains tissue. Ferric subsulfate solution should not be used on the face. Bleach soaks (10 min/d) are especially useful to

prevent infection; an effective dilution is one-quarter cup of bleach in 3 gallons of water.

Cyanoacrylate preparations relieve pain and promote healing. Some patients and health care providers prefer cyanoacrylate glue, because liquid cyanoacrylate coverings may increase the sensation of burning and delay healing. In Europe, clinicians use 50% propylene glycol in an aqueous solution. Preparations of 10% salicylic acid with cyanoacrylate have also been used.

Pruritus

Pruritus associated with xerosis or papulopustular rash can be distressing and interfere with sleep. Every effort should be made to maximize therapy for xerosis. Many dry skin care measures (i.e., minimizing the use of soap, increased use of emollients, avoiding alcohol-based agents) and topical antipruritics (e.g., Aveeno Anti-Itch, Sarna Ultra) are helpful, cheap, easy to use, and simple. Topical agents for the scalp include fluocinonide 0.05%, clobetasol foam, or steroid shampoo.¹⁰⁶ To decrease itching at night, cold compresses and antihistamines with sedative effects (e.g., diphenhydramine) can be used in the evening and at bedtime. Some clinicians expressed concern that antihistamines are not useful when the itch is mediated by nonhistamine pathways. Because patients with pruritus often scratch, vigilance for evidence of superinfection is important.

Pregabalin (100 mg, twice daily) has been reported to be useful for pruritus caused by cetuximab in patients for whom antihistamine and topical anti-inflammatory therapy failed.¹¹¹ Pregabalin inhibits the release of calcitonin gene-related peptide, which mediates itching through increase in gamma-aminobutyric acid. For patients with intractable itch, pregabalin seems to be more useful than antihistamines.¹¹² Ongoing clinical trials of interventions for pruritus in this population include 1) topical lidocaine, 2) fusidic acid combined with erythromycin, and 3) 1% metronidazole cream.

Paronychia

To prevent paronychia, patients taking EGFR inhibitors should avoid frequent water immersion or contact with harsh chemicals, and should apply petroleum jelly to the periungual soft tissue frequently. Patients with paronychia may be superinfected with *S aureus*, MRSA, *Enterococcus*, and *Pseudomonas*.⁵² Therefore, suspicious sites should be cultured and infections treated with appropriate oral antibiotics.¹¹³ Yeast (e.g., *Candida* sp.) can occur on the finger and toe nails.

Patients with recurrent infections of the same strain should be urged to dispose of old slippers or shoes because of the risk for reinfection from fomites. Trauma may play a role, especially in the paronychia of the great toes; patients may have neuropathy from other chemotherapy drugs and should be counseled to wear well-fitting shoes or sandals that minimize further trauma. Lesions may persist despite antibiotics. Healing may take as long as several months after EGFR inhibitor treatment is stopped.

Silver nitrate or ferric subsulfate solution can be used to treat paronychia. Silver nitrate is hemostatic and is especially useful for patients with potential bleeding problems (i.e., those on anticoagulants or aspirin). Nails can be clipped (embedded nails can be removed) and cellulose sponge (Surgifoam) can be packed in the area. Paper tape (not Band-Aids) should be used to hold the cellulose sponge in. The nail should be kept clean and dry so it can grow out.

Patients with paronychia can also use daily soaks and cushioning to provide symptomatic relief.^{30,36,52} White vinegar soaks (1:10) are especially good for *Pseudomonas*. Other topical agents include aluminum acetate (Burrows solution) soaks, silver nitrate (which stains around the nails), intralesional triamcinolone, 4% thymol in alcohol, or bleach soaks (see Table 1).^{52,67} Bleach soaks (10 min/d) are especially useful to prevent infection (¼ cup of bleach:3 gallons of water). Some task force members recommend topical corticosteroid cream (e.g., methylprednisolone) for inflammatory paronychia.^{52,114} Because isotretinoin is associated with desquamation, xerosis, and paronychial inflammation, it should be avoided in patients with paronychia.⁵²

Skin Lesions in Areas with Hair

Scarring alopecia can develop in patients taking EGFR inhibitors.¹¹⁵ Thus, skin lesions in the scalp, beard, or chest must be treated to avoid permanent hair loss. Patients can be treated with 0.2% hydrocortisone valerate, steroid shampoos (e.g., fluocinolone acetonide), or class 1 topical steroid lotions or solutions (e.g., clobetasol, betamethasone dipropionate). However, patients prefer not to use ointments or creams in these areas.⁸⁵

Management of Ocular Toxicities

The most common eye condition seen in patients who are on EGFR inhibitors is a dysfunctional tear syndrome leading to dry eye, sensation of grittiness,

and complaints of vision fluctuation. Artificial tears may relieve these symptoms; however, many patients will not experience relief with artificial tears alone. A 2-week course of topical loteprednol or fluorometholone, under the supervision of an ophthalmologist, can help resolve these symptoms. Topical cyclosporine drops can be started concurrently with steroid drops, and cyclosporine can be continued alone after the steroid drops are discontinued.

Blepharitis can be managed with warm compresses and careful eyelid hygiene using an eyelid cleanser. The eyelid cleanser cleans the eyelid margin, softening the crusts and making it easy to remove them from the base of the eyelid margins. Anti-inflammatory eye ointment is often necessary in patients with an inflamed eyelid margin. A combination of a topical steroid and an antibiotic eye ointment can be used initially (especially if pustules are present) and, after the first week, the steroid (e.g., fluorometholone ophthalmic ointment) can be used alone if necessary or to prevent recurrent symptoms. Patients taking topical ophthalmic steroids who are expected to have long-term survival must have their intraocular pressure measured by an ophthalmologist to assess for glaucoma.⁷⁹ Meibomitis is managed with hot compresses to the eyelid margin (twice daily with a clean wash cloth). Severe meibomitis may respond to systemic doxycycline (100 mg/d for 6 weeks).

Patients with misdirected eyelashes are at risk for microabrasions on the surface of the cornea, which can become infected. Thus, it is important to clip long eyelashes or remove the misdirected eyelashes before they scratch the cornea.^{76,77} Patients whose eyelashes need clipping may prefer to have this done by an ophthalmologist, although self-care or help from a caregiver is also an option; patients should keep their eyes closed during this procedure. In patients with recurrent misdirected eyelashes, referral to an ophthalmologist for diathermy in a focal manner at the base of the eyelashes can be considered as a means to permanently remove the misdirected lashes.⁷⁹

Future Directions

Patients who are potential candidates for EGFR inhibitor therapy should be tested to confirm they have appropriate biomarkers (e.g., EGFR, K-Ras) so patients who will not benefit from therapy are not exposed to the discomforts of the skin toxicity.¹²⁻¹⁴

If biomarkers are developed that indicate which patients are likely to get a skin rash, then prophylactic approaches to prevent rash will be more attractive.⁸⁸ Clinical trials assessing different treatments for dermatologic toxicities have been underpowered; therefore, future trials must have larger sample sizes.^{99,101} Patients undergoing topical therapy must be carefully followed to determine whether they experience any systemic effects from these agents. In addition, it is essential to ascertain that novel interventions for dermatologic toxicities do not interfere with the anticancer efficacy of the EGFR inhibitors.

Conclusions

EGFR inhibitors have been shown to increase overall survival in patients with many types of cancer; however, toxicity can limit their use. Therefore, clinicians must manage these side effects in an appropriate and timely manner to avoid discontinuation and dosage reduction of EGFR inhibitors. Many of the current treatment options for toxicity associated with EGFR inhibitors are based on anecdotal rather than evidence-based medicine. Further clinical trials are needed to better define the best treatment options for managing these toxicities.

Symptom-guided management with topical agents is generally appropriate for the papulopustular eruption associated with EGFR inhibitors. Recommendations are largely based on the experience of the task force members and case reports because this area has not been studied extensively. Topical steroids reduce inflammation in many patients; topical clindamycin and erythromycin may have similar effects, albeit sometimes with more irritation.

Providers should remain vigilant for evidence of superinfection, particularly purulent drainage, dominant lesions, or excessive induration and erythema. Positive cultures may be evidence of infection or colonization, and clinical judgment is required in evaluating culture results.

Systemic therapy is an option for skin rash associated with EGFR inhibitors in certain settings, including severe, infected, refractory, or recurrent rash. Prophylactic oral tetracyclines may reduce the severity of rash, based on small randomized trials. The use of systemic steroids is reserved for grade 4 rash and in-field toxicity and requires careful supervision, usually in an inpatient setting.

To prevent paronychia and xerosis, patients

taking EGFR inhibitors should avoid frequent water immersion or contact with harsh chemicals, and should apply petrolatum ointment frequently. Ferric subsulfate solution or silver nitrate can be used to treat the paronychia. Infections should be treated with appropriate oral antibiotics. Soaks and cushioning can provide symptomatic relief.^{30,36,52} Topical agents include aluminum acetate (Burrows solution) soaks, silver nitrate, intralesional triamcinolone, 4% thymol in alcohol, or white vinegar or bleach soaks. Topical corticosteroid cream (e.g., methylprednisolone) may be useful for inflammatory paronychia.^{52,114}

Xerosis can be treated with zinc oxide (30%), ammonium lactate, petroleum jelly, and other thick emollients. Alcohol-based lotions, antibacterial soaps, and long hot showers should be avoided. To treat pruritus, many dry skin care measures (e.g., less soap, more emollients) and topical antipruritics are very helpful. Skin lesions in areas with hair can be treated with 2% hydrocortisone valerate, steroid shampoos (e.g., fluocinonone acetone), or topical steroid lotions or solutions.

Fissures on the heels and fingertips can be treated with ferric subsulfate solution, silver nitrate, aluminum chloride solution, or zinc oxide (30%). Many task force members recommend cyanoacrylate glue, because it is inexpensive, relieves pain, and seems to permit healing. Oral antibiotics (e.g., doxycycline) are useful for infected fissures.

Artificial tears can be used to treat dry eye, which is the most common eye condition in patients taking EGFR inhibitors. However, many patients with dry eye will not experience relief with artificial tears alone. Topical cyclosporine and loteprednol or fluorometholone can help resolve these symptoms.

Blepharitis can be managed using warm compresses, careful eyelid hygiene using an eyelid cleanser, and anti-inflammatory eye ointment. A combination of an antibiotic eye ointment and/or a topical steroid can be used. Patients must be assessed for eye infection and those who are on topical steroids need to be assessed for glaucoma.⁷⁹ Long eyelashes must be clipped or misdirected eyelashes removed before they scratch the cornea.^{76,77}

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