Management of dermatological toxicities in patients receiving EGFR inhibitors

Kathy Lynch, RN

Hematology Oncology Associates of Northern New Jersey, Morristown

Patients receiving treatment with epidermal growth factor receptor inhibitors often experience dermatological toxicities. The majority of patients develop skin rash, and may also experience adverse nail and periungual alterations. EGFR inhibitors have become part of the standard of care for several solid tumors, including metastatic colorectal cancer, cancers of the head and neck, and non–small-cell lung cancer, thus adequate management of these side effects is necessary to ensure patient compliance to therapy, as well as to maximize patient comfort and quality of life. Although the clinical onset and the course of these events are generally predictable, proper management of these dermatological effects is challenged by a lack of widely accepted, adequate grading scales, and by chronic underreporting, often hampered by subjective perceptions. Consequently, no uniform standardized methodology to grade and manage symptoms is available. This review presents a protocol our center optimized to successfully manage cetuximab-associated acneiform rash and nail toxicities. Our practice emphasizes the importance of taking pre-emptive measures, and implements a multimodal approach to control symptoms upon onset. This management strategy may effectively reduce toxicity and symptom severity, enabling patients to complete their antitumor regimen as scheduled and maintain ability to carry out daily life activities.

The epidermal growth factor receptor (EGFR) is a transmembrane protein that regulates multiple cellular processes, including proliferation, differentiation, and survival, and is overexpressed in a variety of cancerous solid tumors.[1-3] The EGFR inhibitor class of targeted antitumor agents is designed to bind to the EGFR, thereby preventing its activation and downstream signaling cascade.[4] EGFR inhibitors have emerged as a therapeutic standard against multiple malignancies, including colorectal cancer, squamous cell carcinoma of the head and neck (SCCHN), non–small-cell lung cancer (NSCLC), and metastatic breast cancer; and use of these agents is becoming increasingly widespread.[5]

Members of this drug class with a current Food and Drug Administration (FDA)-approved indication include the monoclonal antibodies cetuximab and panitumumab, and the small molecule tyrosine kinase inhibitors (TKIs) erlotinib and lapatinib.[5] Additional EGFR-targeted agents are currently in mature stages of clinical development with promising outcomes.[5-8] The antitumor activity of EGFR inhibitor agents as a class is primarily through blockade of the EGFR signaling pathway.[4] TKIs bind the receptor intracellulary and block its activity at the kinase domain; monoclonal antibodies interact with the extracellular portion of the receptor and block its ligands from binding, precluding receptor activation. Among the currently available agents, cetuximab is the only monoclonal antibody from the IgG1 subtype that can also elicit antitumor activity via modulation of certain immune responses known as antibody-dependent cellular cytotoxicity (ADCC).[9,10]

Although the toxicity profile of EGFR inhibitors is generally favorable, patients receiving these agents are often affected by dermatologic toxicities, namely acneiform (papulopustular) rash and, less commonly, nail changes, and/or paronychia.[11] Patients may also experience xerosis, pruritus, flushing, telangiectasias, mucositis, and changes in hair growth.[12] These dermatological toxicities are an agent classwide phenomenon[4] and warrant attention because they can have an impact on patient quality of life (QoL) and daily functioning owing to physical pain, discomfort, and psychological stress.[13-15] Proper toxicity management is crucial to maintain patient QoL and, importantly, treatment compliance to maximize therapeutic benefit and minimize toxicity-driven treatment interruptions. The need for effective toxicity management is growing as EGFR-inhibitor use is expanding across tumor types and disease settings;

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Correspondence: Kathy Lynch, RN, RCCA-Morristown Division, 100 Madison Avenue, Carol G. Simon Cancer Center, Morristown, NJ 07962 (kathyl217@yahoo.com).
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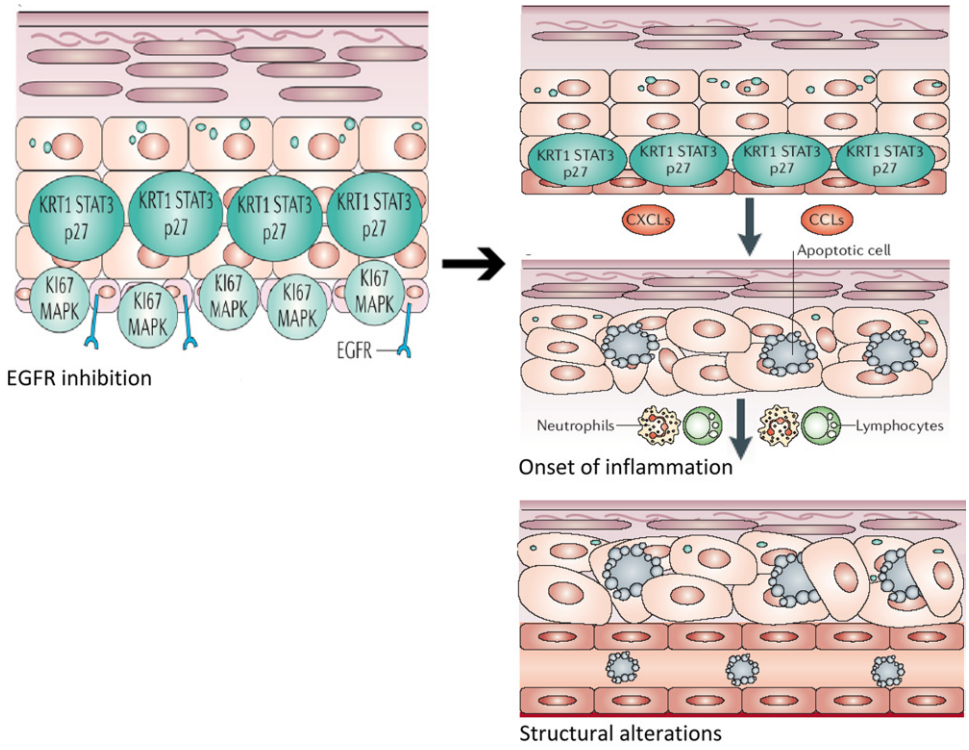

FIGURE 1 Mechanism of EGFR inhibitor-induced dermatological toxicity.[11]

and these agents are being increasingly incorporated into various and multimodal treatment regimens.

Several randomized trials evaluating the effects of various EGFR-inhibitor dermatologic toxicity treatment approaches have yielded mixed results[16-21] suggesting that a multimodal management approach is optimal. Although management must be tailored to the individual patient according to the severity of toxicity as well as her or his lifestyle habits and potential economic burden,[22] there are several general approaches found to be effective. This report presents one such successful multimodal approach for managing acneiform rash and nail changes in patients treated with cetuximab. This protocol emphasizes taking pre-emptive measures and uses a combination of topical and systemic agents based on individual patient need.

Mechanisms of EGFR inhibitor-associated dermatological toxicities

In addition to high expression levels of EGFR in certain tumors, expression has been detected in multiple normal organ systems, such as the digestive tract, eyes, thymus, skin, and respiratory, urogenital, and endocrine systems.[4] In adults, the highest EGFR expression levels are found primarily on rapidly dividing epithelial cells, namely in the basal keratinocyte layer of the epidermis (Figure 1).[4] The EGFR controls normal skin growth by regulating keratinocyte maturation, apoptosis, and hair follicle growth and development.[4] The dermatological events experienced with EGFR inhibitor therapy are believed to be the direct result of the EGFR signaling blockade in the skin resulting in impaired growth and migration, increased apoptosis of keratinocytes, and enhanced inflammatory chemokine expression by these cells.[11] These EGFR inhibitor-induced alterations in keratinocyte development lead to tissue damage and reduced epidermal thickness,[11] and a secondary inflammatory response.[11] Although not an intrinsically infectious process, this disruption of the epidermis may also render the cells susceptible to secondary bacterial and fungal infection.[23]

Following from this etiology, it is possible to hypothesize that development of skin toxicity may be a surrogate marker of activity at the tumor level via either effective EGFR inhibition or an immune-based local inflammatory reaction.[24] In fact, heightened interest in EGFR inhibitor-associated skin rash has emerged from reports correlating its development with clinical efficacy in patients.[25-29] However, the basis for this association remains uncertain and whether skin rash is a true early indicator of EGFR inhibitor agent efficacy, and not just prognostic, remains to be prospectively validated.[30]

TABLE 1 The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading scale (general and specific for acneiform rash)[48]

Grade	General	Acneiform rash[a]
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b]	Papules and/or pustules covering 10%-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[c]	Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated
4	Life-threatening consequences; urgent intervention indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences
5	Death related to AE	Death

Abbreviations: AE, adverse event; ADL, activities of daily living; BSA, body surface area.
[a] A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back; [b] Preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc; [c] Bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Rash

Clinical onset and presentation

Acneiform rash, also referred to as acne-like rash, rash, skin rash, or papulopustular rash,[31] presents in the majority of patients receiving anti-EGFR therapy (cetuximab and panitumumab: 69%-90%; erlotinib: 49%-75%), though few experience severe toxicity (NCI-CTCAE [National Cancer Institute Common Terminology Criteria for Adverse Events]scale grade 3 or 4, 1%-25%; Table 1).[32-35] The onset and presentation of dermatological toxicities is predictable and appears to be dose-dependent.[12,15,36,37] Onset of these events occurs sequentially, responding to the different timing of the underlying biological events (Figure 2).[11] Onset of rash typically occurs within the first 2 weeks of treatment,[15,32] and resolves in the majority of the patients after treatment cessation, although in some cases, the event may continue beyond 2 to 3 weeks.[32]

Rash severity may be influenced by the type of therapeutic regimen and by certain patient characteristics. For instance, a recent meta-analysis of 5,333 patients reported that the addition of cytotoxic chemotherapy agents to cetuximab significantly increased the risk of high-grade acneiform rash when compared with cetuximab monotherapy ($P < .01$).[33] However, it is unclear whether this increase was exclusively due to intrinsic exacerbation by cytotoxic agents or to the lengthened time on cetuximab for patients who receive it in combination (patients tend to have longer times to progression). The use of other

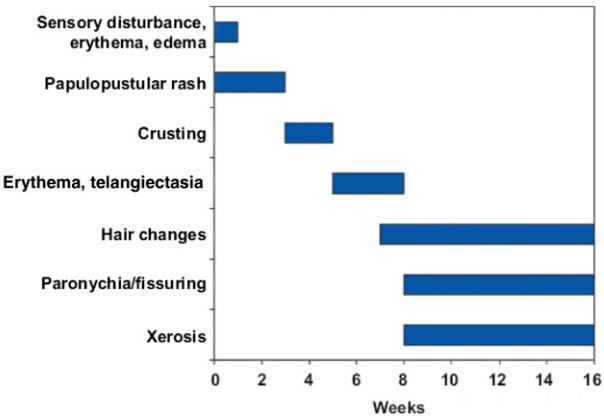

FIGURE 2 Onset and presentation of dermatological toxicities upon initiation of EGFR inhibitor treatment.[15]

EGFR inhibitors in combination is less common, so the impact of combination regimens with erlotinib or panitumumab on the risk of experiencing rash has not been fully explored. In addition, heterogeneity in management strategies may account for differences seen in rash development and severity, as well as certain patient characteristics that have been associated with increased incidence or severity of rash, including male gender, age of < 70 years, low performance status (0-1), a never or former smoker status, and lower skin phototype (fairer skin).[38-40] Patients with paler skin have increased sensitivity to the damaging effects of ultraviolet (UV) radiation and are more susceptible to developing severe EGFR inhibitor-

TABLE 2 Recommended cetuximab dose modifications for severe (NCI-CTCAE grade 3 or 4) acneiform rash[32]

Occurrence	Treatment modification	Outcome	Subsequent dosage modification
1st	Delay infusion 1-2 wk	Improvement	Continue at 250 mg/m^2
		No improvement	Discontinue
2nd	Delay infusion 1-2 wk	Improvement	Reduce dose to 200 mg/m^2
		No improvement	Discontinue
3rd	Delay infusion 1-2 wk	Improvement	Reduce dose to 150 mg/m^2
		No improvement	Discontinue
4th	Discontinue		

Abbreviation: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

associated skin rash than are patients with darker skin types.[41] This correlation supports laboratory research showing that UV radiation exposure following EGFR signaling inhibition results in epidermal cell death and decreased skin thickness.[42,43]

EGFR inhibitor-associated skin rash develops as a typical papulopustular rash on the face (most commonly the nose and cheeks) and may also spread to the chest and back and, less commonly, to the arms, legs, and scalp.[23,36] Although the rash may appear similar to acne vulgaris, thus the common nomenclature used (acneiform, acne-like), it is not acne and has a distinct etiology.[11] Unlike acne, EGFR inhibitor-associated rash does not always present with comedones, can be accompanied by pruritus, and is responsive to anti-inflammatory agents and not anti-acne agents.[11]

Symptoms are usually mild-to-moderate, usually resulting in discomfort or itching. Severe manifestations such as disfigurement or permanent scarring do not typically occur, although residual skin darkening may remain after the rash resolves in some cases.[36-44] Dry skin may follow the initial rash manifestations while nail changes and fissures typically appear after longer treatment periods (two to four months).[37] The presentation of skin rash appears to be multiphasal,[23] and its intensity and severity has been observed to wax and wane and symptoms may improve spontaneously.[36,37] These fluctuations may be a result of the natural clinical course of the rash, but in our experience patient behaviors (sometimes hard to characterize in detail before the initiation of therapy) may also affect severity.

Challenges in patient evaluation

Successful management of cetuximab-associated dermatological toxicity is challenged by the chronic underreporting and subjective nature of these events as well as by a paucity of evidence-based treatment guidelines.[45-47] Furthermore, there are no standardized grading scales that adequately assess dermatologic toxicities specific to EGFR inhibitors. The widely used grading scale offered in the NCI-CTCAE version 4 may be inadequate in this setting,[48] and other groups have proposed alternate grading scales and management protocols specific to toxicities associated with EGFR inhibitors.[37,49-51] Thus far, none of these improved grading scales have become uniformly adapted. One of the challenges may be standardizing a grading scale to provide adequate balance to the severity of the symptoms versus the extent of body surface affected. Nevertheless, this gap poses an obstacle for health care providers trying to reach a consensus in reporting these dermatological events, particularly in light of the subjective nature of the symptom assessment. Improvements in toxicity grading scales will hopefully minimize disparity of toxicity evaluation between patients and facilitate event reporting.

Management

In general, antitumor treatment can continue unmodified in patients experiencing mild or moderate rash, however, if a patient experiences severe rash (grade 3 or 4), adjustments should be made as exemplified by cetuximab guidelines shown in Table 2.[32] A major objective of rash management is to ensure that therapy administration continues as scheduled (unmodified) so as not to jeopardize or compromise clinical benefit.

To achieve this goal, pre-emptive measures, including applying sunscreen, avoiding sun exposure, and keeping skin clean and hydrated with mild soaps and moisturizers have proven effective in some prospective studies,[49] but not in others.[17] Similarly, studies evaluating prophylactic systemic antibiotic administration have yielded mixed results. The randomized Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial in patients receiving panitumumab evaluated whether a pre-emptive skin

TABLE 3 Management of skin rash and nail/periungual toxicities

Prophylactic and general care
Counsel patient and provide educational materials to take home.
Cleanse skin with a gentle, moisturizing soap. *Examples: Dove (Sensitive Skin Unscented), Head & Shoulders (be sure to rinse off completely), Aveeno Moisturizing Bar*
Avoid alcohol-containing and other drying soaps and cleansers.
Moisturize skin twice per day with a perfume-free emollient. *Examples: Nivea, Aquafor, Aveeno*
Avoid excess sun exposure and wear sunscreen (SPF ≥ 15), preferably one containing titanium dioxide or zinc oxide. *Examples: Banana Boat Kids Tear Free Sunblock, Neutrogena Sensitive Skin Sunblock Lotion, Kiss My Face 100% Paraben-free Sunscreen*
Avoid chemical irritants such as solvents, polishes, and chlorine.
Avoid putting pressure on the nail folds.
Avoid tight-fitting shoes
Provide patient with prescription for an oral tetracycline antibiotic (doxycycline 100 mg PO BID).
Acneiform rash
Begin course of tetracycline antibiotic (doxycycline).
Consider clindamycin topical cream applied to affected area BID.
Consider a methylprednisolone dose pack if patient is symptomatic.
For severe (grade 3/4) rash, delay cetuximab infusion until rash clears (see Table 2).
Nail changes and paronychia
Cushion affected area.
Apply tea tree oil to affected area.
Daily 5-minute soaks with 1:10 vinegar: water solution.
Apply frequent petroleum jelly emollient. *Example: vitamin A&D ointment.*
Consider applying Flurandrenolide tape to inflamed, cracked areas.
Consider Metronidazole 1% topical gel, applied once or twice daily.
For severe symptoms affecting activities of daily life, delay cetuximab infusion.

toxicity management approach, which included use of skin moisturizers, sunscreen, topical steroid and systemic doxycycline, reduced rash severity compared with a reactive (after skin toxicity developed) management approach.[49] The study reported a more than 50% reduction in the incidence of specific grade 2 or higher skin toxicities during the specified skin treatment period in the pre-emptive group compared with the reactive group. Furthermore, patients in the pre-emptive group reported less QoL impairment than patients in the reactive group.[49] In contrast, several studies specifically evaluating effects of pre-emptive systemic antibiotics reported no benefit in preventing outbreak of rash by prophylactic administration,[16,20,21] however, they seemed to reduce the rash severity once onset.[20,21]

After evaluating available topical and systemic agents for rash symptom relief, our treatment center has formulated and implemented an optimized management protocol outlined in Table 3, which is generally consistent with previously published strategies.[51,52] We have found that taking proactive skin care measures is effective in minimizing rash severity and duration, improves patient comfort, and is generally a well-accepted approach. Protecting skin from excess UV radiation exposure is critical and, therefore, sunscreens containing titanium dioxide or zinc oxide are preferable[14] especially for patients with fair skin.

A list of recommended topical skin care products to be used both prior to and during cetuximab therapy is provided in Table 3.

Our center recommends that oral doxycycline 100 mg be administered twice daily for at least 6 to 8 weeks once a patient develops skin rash (beginning at rash onset). We suggest providing the patient with a prescription prior to rash onset and instruction to start doxycycline at first sign of rash eruption to minimize time lapse to systemic antibiotic treatment. Additionally, clindamycin topical cream may be applied to affected areas twice daily. Systemic and topical antibiotics can reduce rash severity through their anti-inflammatory properties as well as by eradicating a possible bacterial infection.[23,53] Since the etiology is not infectious, early-stage rash generally does not involve bacterial infection; but later-stage rash, once epidermal cell integrity has been compromised, has been reported to be a secondarily infectious process with patients testing positive for *Staphylococcus aureu.*[23]

A methylprednisolone dose pack can also be considered to reduce inflammation if the patient is symptomatic, however, the use of systemic and topical steroids is not generally recommended in this setting due to conflicting evidence regarding its beneficial effects.[54] Use of retinoids and antiseptics is not recommended in the treatment of skin rash. Retinoids likely interfere in the EGFR signaling pathway and may be of concern in the realm of cetuximab treatment,[55] and antiseptics (ie, benzoyl peroxide, acetic acid) may potentially exacerbate the rash.[56] Several other agents are under clinical evaluation for the treatment of EGFR inhibitor-associated skin rash, including topical urea and vitamin K_1 cream, which have shown promising symptom control upon rash onset.[56,57]

Patients receiving radiotherapy

In patients, particularly those with locally advanced cancers of the head and neck, receiving concurrent radiotherapy (RT) and cetuximab, acneiform rash can present in conjunction with radiation dermatitis.[58] Radiation dermatitis is not related to EGFR inhibition and can be distinguished from cetuximab-associated rash. Onset of radiation dermatitis begins within 3 to 4 weeks of RT initiation, an event typically occurring after the initial onset of acneiform rash. Radiation dermatitis onset and severity is determined by factors intrinsic to RT such as the radiation dose, overall time of exposure, and surface area of skin exposed to radiation, and appears to present independently of cetuximab-associated rash.[58] A large phase 3 trial comparing concurrent cetuximab plus conventional RT to RT alone in patients with SCCHN demonstrated that the addition of cetuximab to RT improved patient overall survival and locoregional control compared with RT alone, without exacerbating the incidence (all grades, 86% vs. 90%; $P = .24$) or severity (grades 3-5, 18% vs. 23%; $P = .27$) of radiation dermatitis,[59] though more recent reports have indicated a higher level of severe toxicity than this original report (grade 3 or 4, 49%-77%).[60-62]

In patients with co-existing RT dermatitis and cetuximab-related rash, each reaction should be graded separately based on location and appearance whenever possible, and management should be based on the grade of dermatitis.[48,58] Skin care recommendations for cetuximab-associated rash co-existing with grade 1 (or no) dermatitis are the same as those for nonirradiated skin, and include the same basic approach including pharmacologic treatments and general care practices, though prophylactic doxycycline may be considered in these patients. When radiation dermatitis reaches grade 2 or higher, the recommendations for management of radiation dermatitis can be prioritized and are discussed elsewhere.[52,58] Patients experiencing grade 3 toxicity, either RT dermatitis or cetuximab-related rash, may require a short cetuximab treatment break to allow the skin to heal (Table 2). Radiation interruptions for dermatitis, however, do not require discontinuation of cetuximab treatment, and delays in cetuximab infusions do not imply interruptions in RT delivery. Cases in which the combined symptoms warrant total discontinuation (or substantial delay) of therapy are infrequent and can often be avoided by collaborative effort of the RT and medical oncology nursing teams.

Nail and periungual toxicity

Clinical onset and presentation

Nail and periungual toxicities usually develop later than acneiform rash with onset in both fingers and toes seen typically 4 to 8 weeks after treatment initiation.[15,52] In these patients, nail plates may grow slowly and become discolored, ridged, brittle, ingrown, or may separate from the nail bed (onycholysis). Periungual toxicities may present as xerosis, erythema, desquamation of the distal digits, and fissures. In severe cases, pyogenic granuloma-like inflammation, periungual abscesses, and acute paronychia may occur.[12,49,52] As seen with papulopustular rash, yeast and bacterial cultures are typically negative upon initial presentation of periungual toxicity, though secondary infection with *Candida albicans* or *Staphylococcus aureus* is common upon persistent toxicity.[12,50,52]

Toxicities involving the nail and periungual tissue affect approximately 12% to 16% of patients receiving cetuximab therapy, and up to 25% of those receiving panitumumab therapy, but rarely becomes severe (grade 3 or 4 incidence $< 1\%$-2%), whereas the rate appears to be lower

in patients receiving the TKI erlotinib (3.6% overall).[15,32,34,35] Most patients who do experience nail and periungual toxicities also developed acneiform rash.[52] Similar to the rash, symptoms tend to wax and wane with continued EGFR inhibition, usually respond to local symptomatic care, and subside slowly upon cessation of EGFR inhibitor therapy,[12] though nail changes can persist long after treatment discontinuation.[52] Symptoms, if present and not adequately managed, can be quite painful and significantly hinder a patient's ability to perform daily life activities.[49]

Management

The severity of nail and periungual toxicities determines the extent of symptom control that is needed on an individual patient basis. The most widely used toxicity grading scale, NCI-CTCAE version 4, has expanded its nail toxicity section from previous versions to include 3 separate adverse events: nail discoloration, loss, and ridging. This improved version 4, however, is still not validated for, and does not adequately characterize, the toxicities specifically associated with EGFR inhibitors.[48] In response to this unmet need for a standardized, comprehensive, and class-specific grading system, the Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group has proposed an enhanced grading scale to more accurately reflect the nail toxicities observed in patients receiving EGFR inhibitor therapy.[49] The MASCC grading scale may provide a frame for consistent reporting and perhaps reduce underreporting and poor grading, ultimately improving management of treatment side effects and decisions for dose modifications.[49]

As with the management of skin rash, prophylactic treatment of nail and periungual toxicities may reduce symptom severity, improving patient QoL and compliance with treatment. Upon initiation of therapy, patients should avoid exposing their fingers and toes to chemical irritants, such as solvents and polishes. Additionally, patients should avoid excess friction or pressure on the nail fold (avoid tight-fitting shoes, protect hands with gloves) and apply frequent petroleum jelly emollition[12] with a product such as vitamin A and D ointment.

If mild-to-moderate nail changes ensue, we recommend daily 5-minute soaks with a solution of vinegar diluted 1 to 10 in water for local care. Petroleum emollition should be applied once digits are thoroughly dried. For inflamed, cracked areas, the patient may benefit from cushioning the area and applying a topical corticosteroid. Our center recommends applying Flurandrenolide Tape, USP (4 mcg/cm^2) to affected areas and replacing it every 12 hours. The plastic tape is impervious to moisture and is convenient for application on the nail and periungual area. If secondary infection develops, tea tree (*Melaleuca alternifolia*) oil may be effective as a natural antiseptic, which has the ability to kill many fungal and bacterial strains, including *C. albicans*,[63] and various types of *S. aureus*,[64] and may be a good alternative or addition to topical antibiotic treatment. Metronidazole 1% topical gel applied once or twice daily to affected areas as well as systemic antibiotics with good coverage of skin flora may also be appropriate in the case of infection. In the rare case of severe toxicity that interferes with a patient's daily activities, cetuximab dose modification or treatment discontinuation may be required.

Concluding remarks

Dermatological toxicities are experienced by the majority of patients treated with anti-EGFR therapy.[32] Although these toxicities are typically considered as mild or moderate in severity,[15,32,33] the onset, frequency, and severity varies on an individual patient basis. Occasionally, with inadequate symptom management, these adverse events can intensify and significantly impact a patient's QoL and ability to perform necessary daily activities. The physical pain and psychological stress imposed by these dermatological toxicities also varies on an individual patient basis, and can depend not only on the severity of symptoms but on social factors such as patient age, with younger patients ($\leq$ 50 years) reporting a higher detrimental physical and emotional impact.[13,38] Effective management is necessary to maintain patient comfort, and importantly, to ensure that therapy administration continues without significant dose modification or interruption to achieve the maximum benefit.

To properly prepare patients who are scheduled for cetuximab therapy for potential dermatological toxicities, our treatment center proactively educates patients of the possible symptoms and emphasizes the importance of taking pre-emptive measures to reduce skin and nail toxicity through maintaining adequate skin hygiene and moisture and avoiding sun exposure. We recommend providing patients with a prescription for a systemic tetracycline (generally for use only upon onset of acneiform rash) to avoid delays in antibiotic treatment. Upon onset of toxicities, a combination of topical and systemic agents can effectively control intensity and symptoms. This multimodal approach has been successful, and patients rarely need to discontinue cetuximab treatment.

Chronic underreporting of EGFR inhibitor-associated adverse events has plagued the field.[45,47] With recent advances towards a standardized, comprehensive, EGFR inhibitor-specific adverse event grading scale,[37,48,49] we can

expect to see better reporting behaviors, and subsequently, improved management strategies. These enhanced tools enable oncology nurses to better assess their patients' condition and provide the appropriate supportive care. Communication and collaboration with the patient, other caregivers and members of the supportive team, as well as with the oncology community as a whole, is crucial for this task. Successful management of cetuximab-associated dermatological toxicities enables maximum patient comfort without compromising compliance to cetuximab treatment.

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