

Title

Clinical Practice Guidelines for the Prevention and Treatment of EGFR Inhibitor-associated Dermatologic Toxicities

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Running Title: EGFR inhibitor dermatologic toxicity treatment recommendations

Abstract

Background: EGFR inhibitors produce various dermatologic side effects in the majority of patients, and guidelines are crucial for the prevention and treatment of these untoward events.

The purpose of this panel was to develop evidence-based recommendations for EGFR associated dermatologic toxicities.

Methods: A multinational, interdisciplinary panel of experts in supportive care in cancer reviewed pertinent studies using established criteria in order to develop first-generation recommendations for EGFR associated dermatologic toxicities.

Results: Prophylactic and reactive recommendations for papulopustular (acneiform) rash, hair changes, radiation dermatitis, pruritus, mucositis, xerosis/ fissures and paronychia are presented, as well as general dermatologic recommendations when possible.

Conclusion: Prevention and management of EGFR related dermatologic toxicities is critical to maintain patients' health related quality of life and dose intensity of antineoplastic regimens. More rigorous investigation of these toxicities is warranted to improve preventive and treatment strategies.

Background

Over expression of the epidermal growth factor receptor (EGFR) is strongly associated with cancer development and progression of a number of malignancies. EGFR Inhibitors (EGFRI) are targeted agents used for treating lung (erlotinib), pancreatic (erlotinib in combination with gemcitabine), breast (lapatinib in combination with capecitabine or anastrozole), head and neck (cetuximab in combination with radiotherapy), and colorectal cancers (cetuximab, panitumumab) [1]. EGFRI may be used as first through third line treatments, alone or in combination with other agents in the aforementioned cancers.

Commonly experienced dermatologic side effects include papulopustular (acneiform) rash, hair changes, radiation dermatitis enhancement, pruritus, mucositis, xerosis/fissures and paronychia. Incidences of these side effects are frequent and range from 36% for mucositis to 80% for the papulopustular (acneiform) rash. Clinical presentation, incidence, impact on quality of life and cost, and effect on EGFRI dosing, and risk factors for these toxicities have been described elsewhere [1]. When severe, dermatologic toxicities may lead to dose modification or discontinuation by 36% and 72% of health care providers, respectively [2]. Although the side effect profile may be primarily dermatologic, toxicities result in significant physical and emotional discomfort, thus it is critical to maximize supportive measures.

Although most patients receiving EGFRI experience these toxicities, few controlled studies have been conducted to determine the best practices for their management. Instead, much of the literature contains prevention and treatment recommendations based on case reports or

studies with small samples sizes and non-randomized patient allocation. In addition, available reports are beset with methodological issues including: failure to adequately describe assessment tools or frequency, lack of validated tools for assessment of dermatologic toxicities and passive data collection. Given that these agents are relatively devoid of systemic and hematopoietic toxicities and have shown benefit in a variety of solid tumors, further large scale studies to define best supportive care are necessary but are unlikely to become available in the foreseeable future. The purpose of this article is to provide comprehensive supportive care prevention and treatment recommendations for EGFR induced dermatologic toxicities based on the pertinent literature currently available. In cases where randomized clinical trials specific to EGFR toxicities were not available, trials investigating phenotypically similar dermatologic conditions were analyzed and reported.

Methods

Participants

The Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group assembled an international, interdisciplinary group of experts in dermatology, medical and supportive oncology, health-related quality-of-life (HQOL) and pharmacovigilance. Topic review committees were formed according to expertise to review the literature and develop guidelines for the following dermatologic toxicities: papulopustular (acneiform) rash, hair changes, radiation dermatitis, pruritus, mucositis, xerosis/ fissures and paronychia.

Recommendation Development

Each review committee consisted of three members with a primary reviewer to present the findings of the committee to the Skin Toxicity Study Group. Literature reviews were performed via databases such as Ovid- MedLine (National Library of Medicine, Bethesda, MD, USA) and EMBASE (Elsevier B.V Amsterdam, The Netherlands). Published literature as of November 2010 was included and each committee reviewed between 17 and 35 papers to formulate the recommended guidelines. Randomized clinical trials were considered the best source and considerations for recommendations included Level of Evidence and Grade of Recommendation (Tables 1 and 2) [3]. In the absence of experimental evidence, pertinent studies and case reports were presented in conjunction with expert opinion derived from clinical practice. Recommendations were developed based on the presented findings and panel consensus. When available, data was extrapolated from other dermatologic conditions with similar clinical or pathologic characteristics (xerosis, alopecia and hirsutism, pruritus, paronychia, radiation dermatitis).

Results and Recommendations

Papulopustular (acneiform) rash

During the first weeks to months of EGFRi therapy, a papulopustular (acneiform) rash is the most clinically significant dermatologic toxicity. The rash usually develops in cosmetically sensitive areas, and it affects the majority of treated patients. Pruritic and tender erythematous papules and pustules develop in skin with a high density of sebaceous glands (scalp, face, upper chest and back). Histological analyses reveal a superficial inflammatory cell infiltrate surrounding hyperkeratotic or ectatic follicular infundibula or a florid neutrophilic suppurative

folliculitis with rupture of epithelial lining. The rash is noteworthy for its impact on psychosocial well-being, related costs, secondary infections, and effects on dose intensity. As measured using Skindex-16, an HQOL tool used in dermatology, greater severity of rash will result in a greater decrement in HQOL, with emotions being the most important aspect of people's lives affected. Pain, burning, and irritation were common symptoms affecting the majority of patients [4]. Moreover, a survey of oncology practitioners demonstrated that 32% of providers discontinued therapy and 76% modified dose due to rash when severe [5].

Several factors have been associated with an increased risk of developing rash: for erlotinib, non-smokers, people with fair skin, and older than 70; for cetuximab, male gender and those younger than 70. Moreover, severe rash is more frequent with monoclonal antibodies (10-17%) than with low-molecular-weight TKIs (5-9%). As with other toxicities, management can be preventive/prophylactic or treatment/reactive.

Randomized controlled trials for EGFRi rash have been conducted in the preventive/prophylactic setting, whereas uncontrolled reports reveal options for reactive treatment. Table 3 displays the recommendations for prevention and treatment of papulopustular (acneiform) rash. Based on the high frequency of rash in EGFRi treated patients and the consistent presentation within the first 2-4 weeks of therapy, preventive/prophylactic management is recommended unless there are contraindications based on patient and/or healthcare provider factors [6-12]. Hydrocortisone 1% combined with moisturizer, sunscreen, and doxycycline 100mg bid for the first 6 weeks is recommended based on randomized data. Another study revealed that prophylactic minocycline 100mg daily as an effective agent in

reducing the number of lesions during the first 8 weeks. Doxycycline appears to have a more favorable safety profile, especially in patients with renal dysfunction, whereas minocycline is less photosensitizing, thus preferable in geographic or seasonal locations with a high UV index.

Reactive use of medium to high potency topical corticosteroids is recommended based on studies showing in vitro release of inflammatory chemokines after EGFRi therapy. Vitamin K3 (menadione) is currently being investigated, but published reports on vitamin K1 are based on studies without control groups [13,14]. Similarly, studies investigating isotretinoin for treatment of EGFRi induced rash have not included control groups, but consistent reports of isotretinoin at doses lower than those used for acne support the recommendation of their use when other measures have failed, the impact on HQOL is significant as reported by the patient, and there is evidence of clinical response to the EGFRi. [1,15-17]. Although the rash peaks in weeks 4-6 after EGFRi initiation and decreases in severity after week 6-8, post-inflammatory skin alterations (erythema and hyperpigmentation) are long-term sequelae that can last for months or years. Therefore, prophylactic strategies are important, and appropriate treatment should be considered throughout treatment and follow-up in order to minimize these late effects.

Hair changes

A variety of hair changes have been described in patients taking EGFR inhibitors and include trichomegaly (elongation and curling of the eyelashes), hypertrichosis often presenting as facial hirsutism, and scalp hair changes ranging from brittleness and slowed growth to alopecia. Non-scarring alopecia occurs after 2-3 months of therapy and may present as frontal or patchy patterns, with a tendency to progress to diffuse alopecia with prolonged EGFRi therapy, which may resolve spontaneously in some patients. Alopecia generally resolves after discontinuation

of therapy, though hair regrowth may be of varying quality. No interventions to reduce or prevent non-scarring alopecia in these patients have been published in the literature, and recommended interventions are supportive (education, cosmetic approaches for patient comfort) and based on studies in androgenetic (male-pattern) and female alopecia.

Minoxidil has been found effective for treating non-scarring alopecia in the general patient population [18-20]. In two studies, males' subjective reporting of increased hair growth was statistically significant for both the 2% and 5% minoxidil groups versus placebo and objective hair counts also were significantly higher in the two treatment groups [18,19]. Similar findings were reported in one study with females randomized to the same two treatment groups versus placebo group for hair count, although no difference was found between the groups for subjective reporting of increased hair changes [20]. Higher incidences of pruritus and hypertrichosis were reported in the minoxidil 5% than in the 2% [18,19], so these should be monitored if minoxidil is prescribed for patients receiving EGFRIs as these also are possible skin toxicities associated with the EGFRi therapy.

Scarring alopecia also has been reported in these patients and is consequent to scalp, facial and chest lesions that can lead to permanent hair loss. Prevention and management strategies, based on expert opinion, aim to reduce inflammation and scarring. Options include topical hydrocortisone 0.2%, steroid shampoos and class 1 steroid lotions [21]. Use of oil baths or mild shampoo followed by antibiotic spray has been recently reported [22]. Preventive strategies for reducing papulopustular (acneiform) rash severity, as described above, also should be employed to minimize scarring alopecia.

Facial hypertrichosis (hirsutism) and trichomegaly appear after the first 1-2 months of therapy, and these symptoms do not wane over time; instead, they tend to persist for the duration of therapy with EGFRIs. Unwanted or excess facial hair may be treated with temporary or permanent hair removal. Trichomegaly is associated with patient discomfort and the abnormal eyelash growth can lead to corneal abrasions and further ocular complications. Trichomegaly can be treated with lash clipping every 2-4 weeks, and referral to an ophthalmologist is indicated for patients with irritation or persistent discomfort. Eflornithine has been well tolerated and efficacious for treatment of hirsutism in open-label trials with the general female population and has been found to significantly improve HQOL in a randomized clinical trial [23,24]. Laser hair removal has been shown to reduce hair growth in a small sample [25], but eflornithine plus laser hair removal has been reported to be more effective than laser hair removal alone in randomized trials with the general population [26,27]. Amelioration of symptoms, patient education and support are recommended for patients with hair changes so that EGFRi therapy may continue.

Radiation Dermatitis

The development of some degree of radiation dermatitis is considered inevitable for the majority of patients receiving radiotherapy due to direct injury to epidermal basal cells and connective tissue changes that usually develop within the first few weeks of radiation initiation. Radiation dermatitis ranges from erythema and dry or wet desquamation to skin necrosis or ulceration of full thickness dermis with spontaneous bleeding from the involved site, and the addition of EGFRIs to radiotherapy results in a higher incidence of high-grade radiation dermatitis [28].

The establishment of a proper technique to minimize the dose delivered to the epidermis and a quality assurance program for radiotherapy planning and delivery is critical not only in therapeutic terms but also from the perspective of avoiding unnecessary skin toxicity. A primary step in management of radiation dermatitis of any severity is to establish that the skin reactions are not a result of any concomitant medication, other than EGFRi. In the case of more severe skin reactions, correct radiation dose and distribution should be verified.

Table 5 displays the recommendations for prevention and treatment of radiation dermatitis. An important step in managing and treating radiation dermatitis is to keep the irradiated area clean and dry, even when ulcerated. Gentle washing and drying of the skin within the radiation portal have been shown to reduce the acute radiotherapy-associated skin reactions in patients receiving radiotherapy for breast cancer and is now routinely recommended for all patients receiving radiotherapy [29,30]. A number of topical agents can be considered, all of which are considered high-potency topical corticosteroids (mometasone, methylprednisolone, beclomethasone, betamethasone creams [31,32]).

The recently reported results of RTOG trials (99-13) in patients with SCCHN failed to show any benefit of the systematic use of interventional or prophylactic trolamine emulsion in reducing skin toxicity [33]. Another study showed no significant benefit of pentoxifylline prophylaxis on the development of acute skin reactions [34]. The potential benefit of oral zinc supplementation in postponing the development of severe mucositis and dermatitis, and in alleviating the degree of mucositis and dermatitis, in patients receiving radiotherapy for cancers of the head and neck [35] warrants additional confirmatory studies.

Where infection is suspected, the treating physician should use best clinical judgment for management, including considering swabbing the affected area for identification of the infectious agent. In patients for whom skin infection is suspected or documented, the blood granulocyte count also should be checked, especially if the patient is receiving concomitant chemotherapy. Indeed, severe desquamation is associated with a risk of septicemia. Blood cultures also should be carried out if additional signs of sepsis and/or fever are present, particularly if the granulocyte count is low.

Where there is coexistence of radiation dermatitis and EGFRi related papulopustular (acneiform) rash within an irradiated field, management depends on the severity of radiation dermatitis. Prophylactic therapy directed against the radiation dermatitis (with high-potency topical corticosteroids) and an oral antibiotic (doxycycline or minocycline) for the EGFRi rash should be considered. For mild radiation dermatitis, it is prudent to follow the published general guidelines on the management of EGFRi related papulopustular (acneiform) rash outside irradiated fields [35-37]. For moderate-severe radiation dermatitis, it is important to investigate for possible secondary *Staphylococcus aureus* infection.

Pruritus

Pruritus occurs in approximately half of all EGFRi treated patients and, although it rarely requires dose modifications or discontinuation of drug therapy, it can have dramatic impact upon the patient's HQOL. It is important to note that the occurrence of pruritus often accompanies papulopustular (acneiform) rash at onset; hence, it is important to emphasize that appropriate

treatment of underlying rash also can alleviate the pruritic symptoms. Because itching also can occur as a consequence of dry skin, it is important to ensure adequate measures are provided to prevent dryness (see xerosis section below). Currently, the mechanism of action behind pruritus induced by EGFRIs is not clearly elucidated. Histamine, which is released by mast cells in persons with urticaria, classically is associated with pruritus. It is unknown whether other neurotransmitters or receptors (including serotonin, opioids and GABA) explain the pruritus that is experienced by patients treated with EGFRIs.

In the literature, no clinical studies are designed to study specific primary endpoints to evaluate the most optimal therapy for EGFRi induced pruritus. Hence, much of the data originated from case series as well as case reports on various agent approaches for pruritus relief. However, a number of clinical management guidelines have provided insights how EGFRi induced pruritus should be managed [38,39]. Table 6 displays the recommendations for treatment of pruritus.

In general, antihistamines have been used to provide symptom relief to patients with mild to moderate pruritus of various etiologies. Data in the setting of EGFRi is limited and conflicting. In one study, two patients were given loratadine for 14 days; however, patients did not find it useful and discontinued treatment [22]. Thus, pharmacologic guidance must be sought from trials conducted in other patient populations.

In another study, a second generation antihistamine (loratadine) was shown to be equally effective as hydroxyzine (a first generation antihistamine) in patients with chronic idiopathic

urticaria and atopic dermatitis. Moreover, loratadine is not associated with sedative side effects that are commonly observed with hydroxyzine. One study has demonstrated that somnolence or sedation was recorded in 5% of loratadine patients and 40% of hydroxyzine patients after one week of drug usage [40]. Another study involving loratadine and hydroxyzine demonstrated similar results. The efficacy is similar between treatment groups, but patients treated with loratadine had significantly less ($p < 0.01$) sedation and dry mouth as compared to patients treated with hydroxyzine [41]. Hence, non-sedating second generation antihistamines are recommended as first approach for systemic therapy for pruritus during daytime. Dosing of antihistamines also should be kept to the minimum to avoid adverse drug reactions, particularly in the elderly, as these medications may cause severe anticholinergic reactions. For patients who suffer from pruritus during nighttime, first generation antihistamines (such as diphenhydramine and hydroxyzine) are preferable given their sedative properties.

Antiepileptic agents, such as pregabalin and gabapentin, are reported to provide pruritic relief in the general patient population. It was suggested that pregabalin is capable of relieving pruritus centrally and peripherally by reducing the release of calcitonin gene-related peptide, which is a mediator of itching in the periphery, as well as modification of central perception of itch by a modulation of μ -opioid receptors centrally [42]. The efficacy of gabapentin to reduce pruritus was reported in randomized trials of gabapentin alone and gabapentin with antihistamines versus chlorpheniramine alone or with antihistamines pruritus associated with burns, and in a trial of gabapentin versus placebo in a renal failure population [43,44]. However, data in the setting of EGFR associated pruritus is based on small case series [42]. In summary, these antiepileptic agents should only be recommended as second line in patients who failed antihistamines and therapies against underlying rash and/or xerosis and continue to experience

clinically significant pruritus. Recently, aprepitant, an NK-1 antagonist was reported to reduce pruritus that is caused by erlotinib [38]. However, caution must be taken as aprepitant may cause drug-drug interactions, and potentially affect the concentrations of erlotinib [45].

A number of over the counter topical agents are available for pruritus reduction. Topical menthol, a naturally occurring cyclic terpene alcohol of plant origin, frequently is used as a topical antipruritic at concentrations of 1-3%. It has been shown that menthol elicits the same cooling sensation as low temperature through the TRPM8 receptor. Skin cooling has been demonstrated to provide therapeutic relief in patients who experience pruritus. Menthol is a benign topical agent with minimal side effects which can be used concurrently with systemic agents to relieve rash and itch [46]. Topical and oral doxepin have been found to relieve pruritus in the general patient population [47-49]. At this time, it is unknown whether other topical agents, such as topical antihistamines, topical lidocaine and topical calamine will provide adequate efficacy to alleviate pruritus induced by EGFRIs. In the literature, topical antihistamines produce mixed efficacy results as reported in a recent review [50]. Furthermore, these agents are known to be sensitizers, which may further induce secondary allergic contact dermatitis after long term usage of these agents [51]. Hence, we recommend against routine usage of these topical agents to manage EGFRi induced pruritus.

Oral Complications

Oral complications reported in EGFRi treated patients are infrequent. The most commonly reported oral complication is mucositis. Oral mucositis may present with broad areas of erythema, aphthous-like stomatitis, or superimposed upon those of radiation and conventional

chemotherapy [52]. Severe mucositis is uncommon with single agent therapy; however, in combination with other cytotoxic chemotherapy or radiation, severe and prolonged mucositis may be seen. The pathobiology of EGFR associated mucositis has yet to be elucidated. Other oral side effects including taste change and salivary changes have not been specifically reported. Sporadic patient self-reporting indicates that other oral complications may be under-reported [53-61]. EGFRs are commonly used in combination with either chemotherapy or radiation therapy (in the head and neck patient population). EGFR associated mucositis may occur independent of or additive to oral complications associated with radiation therapy and conventional cytotoxic chemotherapy.

There are no trials investigating the management of EGFR associated mucositis, thus guidance for prevention and treatment was informed by current approaches to management of cytotoxic chemotherapy and radiation therapy induced mucositis as described in the MASCC guidelines [62,63]. Table 7 displays the recommendations for prevention and treatment of oral complications. The approach recommended includes the foundation of 1) thorough oral care, 2) aggressive pain management, 3) adequate nutritional support, 4) radiation treatment planning that optimizes therapeutic index, and 5) benzydamine rinse (not available in the USA) for radiation mucositis.

Oral health should be assessed prior to treatment and a plan of care developed and implemented for individual patients. Oral health status and oral care should be evaluated periodically during treatment as well as after the completion of therapy. Mucositis associated pain should be aggressively managed with topical analgesics and systemic analgesics as needed.

As mucosal pain has both nociceptive and neuropathic components, opioids and adjuvant medications should be considered [64]. Nutrient and calorie support of patients during and following cancer therapy is strongly supported.

Many preventive and treatment strategies have been investigated for oral mucositis; unfortunately, few have been found to be efficacious (see the MASCC guidelines for specific agents that have failed to demonstrated efficacy). Diagnosis of contributing oral infections such as candida and herpes virus reactivation to mucositis allow for specific intervention. Other approaches to EGFRI dermatologic toxicities are reported in this paper and some may have application for management of oral mucositis. For example, minocycline and doxycycline have been studied for management of oral aphthous lesions [65,66] and study of their potential application in management of mucositis associated with targeted therapies may be indicated. Dermatitis also is managed with steroids, and while use of steroids increase risk of secondary oral infection (e.g., candidiasis), this may be managed with currently available azole antifungals, although further study is needed.

Xerosis and Fissures

Abnormal keratinocyte differentiation due to EGFRI leads to a deteriorated stratum corneum with a decrease in loricrin, which is the main protein holding together the scaffolding of the epidermis [67,68]. This process results in an unwoven epidermal layer that cannot preserve moisture, thus resulting in xerosis. Xerosis often is referred to as dry skin or cutaneous dryness, which can turn into xerotic dermatitis (asteatotic eczema), an inflammation resulting from dry skin. It generally has a later onset, around 30-60 days or more into EGFRI treatment, and often

accompanies or succeeds the papulopustular (acneiform) rash [22,68]. Age, pre-existing eczema, and prior treatment with cytotoxics pose a greater risk of xerosis [36,67,69].

To date, there are no existing randomized clinical trials assessing prevention or treatment of EGFRi induced xerosis. Table 8 displays the recommendations for prevention and treatment of xerosis. Preventive strategies start with bathing techniques. Avoiding bathing in excess and using tepid water as opposed to hot water is recommended. When bathing, patients should be advised to use bath oils or mild moisturizing soaps that are free of fragrances or perfumes. Avoiding extreme temperatures, such as severe cold, dry weather or significant heat, and direct sun exposure, which can cause sunburns, also is recommended [70]. Patients should refrain from using alcohol-containing lotions or skin products that may dehydrate skin [36,38,71].

Treatment of mild or moderate xerosis consists of thick moisturizing creams without fragrances or potential irritants. Moisturizers should be occlusive, emollient creams that are generally packaged in a jar or tub rather than a lotion that can be pumped or poured. Specific creams can include urea, colloidal oatmeal, and petroleum-based creams. For scaly areas of xerosis, ammonium lactate or lactic acid creams can be utilized. Greasy creams may be used on the limbs for better control of xerosis but are cautioned on the face and chest, along with extremely hairy sites, due to risk for folliculitis secondary to occlusion [36,38]. For more severe xerosis causing inflammation with or without eczema, topical steroid creams may be necessary. Topical retinoids and benzoyl peroxide gels are not recommended due to their drying effect [38,70,72].

Skin fissures and deep cracks in the skin can form due to significant xerosis. Fissures and skin cracking are termed rhagades in the European literature [73]. They often occur in the fingertips, in the palms or knuckles and in the soles-like xerosis, are a late side effect of EGFRi therapy, occurring around 30-60 days into therapy [19,36]. They can be very painful and create risk for infection. As with xerosis, there is no randomized clinical trial data supporting prevention or treatment guidelines. All recommendations are based on case studies, observation, and expert opinion, as well as dermatologic studies from the non-cancer population.

Table 9 displays the recommendations for prevention and treatment of fissures. Wearing protective footwear or covering the fingertips to avoid friction can prevent skin fissures and aid healing. Treatment for skin fissures varies, with many recommendations. Thick moisturizers or zinc oxide creams can be applied. Bleach soaks can prevent infection, with a dilution rate of one quarter cup of bleach to 3 gallons of water [34]. Liquid glues, like cyanoacrylate preparations (Superglue® or Liquid Bandaid®) can be used to seal the cracks and keep them from worsening or becoming infected [21,34,68,74]. Sealing the cracks with these products also can help relieve pain and allow for healing [21,74]. Propylene glycol 50% solution and salicylic acid 10% ointment are other recommendations [1,34,67,75]. Steroid tape (Cordran tape®) and hydrocolloid dressings are recommended for painful, erythematous areas [34,68,73]. Limited evidence also supports the use of silver nitrate or potassium permanganate foams and topical antibiotics [38]. Oral antibiotics may be necessary if infection worsens despite topical treatment.

Paronychia

All patients receiving EGFRIs are at risk for developing nail changes, which typically develop after two or more months of chemotherapy exposure [22,76-80]. The most commonly seen nail changes include nail fold inflammation (paronychia) and periungual pyogenic granuloma-like lesions. Resultant onycholysis or onychodystrophy may result as a secondary process from the presence of nail matrix inflammation.

Paronychia is characterized by tender, edematous, often purulent inflammation of the nail folds. Fingernails and toenails may be affected, with the first digits most commonly affected. Precedent trauma is not believed to be causative but rather an aggravating factor. Morbidity is high leading to significant pain, functional limitation, and impairment of activities of daily living. Periungual pyogenic granulomata are characterized by friable vascular tissue overgrowths on lateral nail folds. Easy bleeding is a common complaint. Increased local trauma is believed to be an aggravating factor in inciting lesion development. The mechanism for these vascular overgrowths is unclear, but it is hypothesized to be related to EGFRi interruption of retinoic acid metabolism [81].

There are no approved treatments for EGFRi associated nail changes. Similarly, there have been no randomized controlled studies evaluating therapies for paronychia. Recommendations are based on expert opinion and anecdotal reports and Table 10 displays the recommendations for prevention and treatment of paronychia. Much of our knowledge comes from prior experience with drug-induced paronychia and periungual pyogenic granulomata, most notably from high-dose systemic retinoid therapy and indinavir (HIV protease inhibitor) [82,83].

Paronychia is a sterile process, but it has the potential to become superinfected. Culturing of lesional skin to determine if superinfection is present is universally recommended so that antimicrobials can be directed accordingly [84]. A retrospective study of 152 patients treated with cetuximab revealed 27 instances of paronychia (incidence of 17.7%). A total of 42 culture swabs were performed in which all grew some organisms. The rate of coagulase negative gram positive bacteria (nosocomial colonization) was 31%, which was higher than the rate of *Staph aureus* infection (23%) [85].

Management strategies are aimed at minimizing periungual trauma, decreasing periungual inflammation, preventing superinfection, and eliminating excessive granulation tissue. Wearing comfortable shoes, trimming nails but avoiding aggressive manicuring and wearing gloves while cleaning (e.g., household, dishes) are recommended to minimize periungual trauma. Biotin has been found effective for the treatment of brittle nails in the general population [86]. Topical corticosteroids and anti-inflammatory dose tetracyclines to decrease periungual inflammation and antimicrobial soaks (e.g., dilute bleach in water; dilute white vinegar in water) to prevent superinfection are recommended [87-97]. Additionally, electrocautery, silver nitrate and nail avulsion also are recommended to eliminate excessive granulation tissue [98,99].

Correlation of Rash and Therapeutic Response

One of the observations made by early clinical investigators was the correlation between the development of rash and response to EGFRi therapy [100]. Clearly this was an important observation because if rash proved to be a clinical marker for response, it would offer patients a

motivating factor to work through the rash associated with the first two months of therapy in order to establish drug efficacy.

There are several methodological issues that must be noted when interpreting the data addressing this question. First, for most of the reported studies, the primary outcome parameter was either response to therapy or overall survival. Reporting of toxicities was a secondary aim, thus, data collection has been largely passive by spontaneous report. Passive data collection is believed to lead to underreporting [101]. In addition, most clinical researchers are not well versed in the assessment of dermatologic toxicity. Finally, most clinical trials use toxicity assessment scoring systems that are rather blunt outcome measures.

Although mixed, the bulk of data would tend to support the correlation between rash and outcomes in patients treated with EGFRi therapy. Positive correlations between rash and outcome have been reported in studies using cetuximab [102,103], erlotinib [104,105], gefitinib [106-107] and panitumumab [108]. Data supports not only an increase in response but an increase in survival for those patients experiencing a rash [102-107]. Although less robust, there also is data to support that increasing severity of rash is correlated with increasing response and survival [109]. These correlations appear across tumor types including head and neck [104,107], lung [105,106], and colorectal cancer [102,103]. Conversely, there have been a small number of studies that fail to correlate rash response with outcome. In a 1037 patient trial comparing paclitaxel and carboplatin to paclitaxel, carboplatin and gefitinib, no correlation between rash and survival was seen. It should be noted that this was a negative trial and that gefitinib failed to improve outcome, thus obviating the potential predictive benefit of rash [110].

Summary and Discussion

Specific recommendations for preventative and reactive interventions for EGFR associated dermatologic toxicities are proposed herein. Patients should be educated about these potential dermatological events before receiving EGFRIs and, where possible, be encouraged to use preventive measures. Regardless of strategy, patient education prior to EGFR therapy is critical in order to ensure anticipatory coping, in which expectancy and preparation for dermatologic changes allows patients not only to cope but also to overcome the significant decrement to HQOL posed by the toxicity (See Patient Education Brochure, Appendix A).

In addition to specific recommendations, we propose that multidisciplinary teams including radiation oncologists, nurses, medical oncologists, dermatologists, pharmacists, oral health care provider and wound care specialists should assess occurrence and management of EGFR associated dermatologic toxicities. Universal recommendations for certain toxicities are not possible; therefore, it is vital that the treatment team seek input from wound care specialists, oral health care providers and dermatologists for specific and severe toxicities. Furthermore, oncologists need to know how to address commonly seen issues and to establish a referral pattern with a dermatologist or oral health care provider with an oncology area of focus.

Recommendations were based on randomized clinical trials with control groups when possible; but, as mentioned previously, the lack of quality studies investigating EGFR associated dermatologic toxicities necessitates that many recommendations be based on expert

opinion and consensus. For most of the EGFRi associated dermatologic toxicities, it is unlikely that large randomized clinical trials will be conducted to investigate management options. That being said, important information may be garnered from treatment trials utilizing EGFRi either alone or in combination. We would therefore recommend that dermatologic toxicities be documented in a consistent and thorough manner in all future studies of EGFRi.

One of the problems hindering the effective reporting and management of EGFRi associated dermatologic toxicities is the use of varied, inconsistent toxicity criteria. To this end, the Skin Toxicity Group proposed the use of the MASCC EGFRi Skin Toxicity Tool (MESTT) [111] in clinical trials and in clinical practice [see 112 for website to download the MESTT]. Although clinical trials often use the Common Terminology Criteria for Adverse Events (NCICTCAE) version 4.03 [113], this tool was not designed for reporting EGFRi associated dermatological events. The MESTT is a more precise tool that can address the current state of under reporting and inadequate assessment of these dermatologic adverse events. In fact, a recent study has demonstrated that while the grades of MESTT and CTCAE are well correlated, the CTCAE tends to underreport the severity of some of the dermatologic side events which can lead to the under adjustment/discontinuation of treatment [114]. However, even with the use of standardized criteria, grading of reactions remains somewhat subjective and this may impede the comparison of toxicity findings between clinical studies. An additional way to minimize discrepancy is to document dermatologic toxicity photographically, thus enabling subsequent independent confirmation of grading where necessary. It is recommended that digital photographic documentation be adopted as a standard practice in clinical trials.

In summary, the mechanism of dermatologic toxicities attributed to targeted therapies requires assessment of mechanistically directed interventions for prevention and management. A greater understanding of the biological mechanisms responsible for the toxicity of the individual agents would lead to the development of rational and more effective management strategies for the dermatologic reactions of patients receiving radiotherapy and EGFRIs.

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Table 1 [3]

Levels of Evidence

Level I evidence is reserved for meta-analyses of randomized controlled trials or randomized trials with high power.

Level II evidence includes randomized trials with lower power.

Level III evidence includes nonrandomized trials, such as cohort or case-controlled series.

Level IV evidence includes descriptive and case studies.

Level V evidence includes case reports and clinical examples.

Table 2 [3]

Recommendation Grades

Grade A is reserved for Level I evidence or consistent findings from multiples studies of Level II, III, or IV evidence.

Grade B is for Level II, III, or IV evidence with generally consistent findings.

Grade C is similar to grade B but with inconsistencies.

Grade D implies little or no evidence.

Table 3

Papulopustular (Acneiform) Rash Recommendations

Preventive (Weeks 1-6,8 of EGFR initiation)	Recommend	Not Recommended	Level of Evidence	Recommend- ation Grades	Comments
Topical	Hydrocortisone 1% cream with moisturizer and sunscreen twice daily	-Pimecrolimus 1% cream -Tazarotene 0.05% cream -Sunscreen as single agent	II*	C	
Systemic	-Minocycline 100mg daily -doxycycline 100mg bid	Tetracycline 500mg bid	II*	A	Doxycycline is preferred in patients with renal impairment. Minocycline is less photosensitizing.
Treatment	Recommend	Not Recommended	Level of Evidence	Recommend- ation Grades	Comments
Topical	-Alclometasone 0.05% cream -Fluocinonide 0.05% cream bid Clindamycin 1%	Vitamin K1 cream	IV*	C	
Systemic	-Doxycycline 100mg bid -Minocycline 100mg daily -Isotretinoin at low doses (20-30mg/day)	Acitretin	IV*	C	photosensitizing agents

* EGFR study/ **Non-EGFR, cancer treatment study/ ***Non-EGFR, non-cancer treatment study

Table 4

Hair Changes Recommendations

Preventive Hair Loss	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	For scarring alopecia, follow rash recommendations	Preventive interventions for non-scarring alopecia	V	D	
Systemic	For scarring alopecia, follow rash recommendations	Preventive interventions for non-scarring alopecia	V	D	
Treatment Hair loss	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Non-scarring: Minoxidil 2%, 5% bid Scarring: -class 1 steroid lotion, shampoo, or foam -antibiotic lotion		I***/II/III/IV*	B/D	consensus of experts
Preventive Increased Hair	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
	Patient education and support		IV	B	consensus of experts
Treatment Increased Hair	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Facial hypertrichosis	- Eflornithine -Lasers	Waxing, chemical depilatories	IV*, II***	B	consensus of experts
Eyelash Trichomegaly	Eyelash trimmings regularly		IV	B	

* EGFR1 study/ **Non-EGFR1, cancer treatment study/ ***Non-EGFR1, non-cancer treatment study

Table 5

Radiation Dermatitis Recommendations

Preventive	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Maintain hygiene, gently clean and dry skin in the radiation field, shortly before radiation treatment	Moisturizers, gels, emulsions & dressings should not be applied shortly before RT	IV**	A	
Topical	High-potency topical steroids	Trolamine LED (photons)	I**	A	
Systemic		Pentoxifylline/ Oral Zinc supplementation	II**/ V**	B/D	Consensus of experts: No systemic treatment in the preventive setting
Treatment	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Maintain hygiene and gently clean and dry skin in the radiation field, even when ulcerated	Hyaluronic acid cream	IV	A	Consensus of experts
Topical	Moisturizers/ Antibacterial moisturizers	Antiinflammatory emulsion (Trolamine)	IV**/ V***	B/ C	Consensus of experts
Topical	-Drying gels - Topical Antiseptics (chlorhexidine)		IV***	B	Consensus of experts
Topical	Hydrophilic dressings		V***	D	
Topical	Topical antibiotics when infection is suspected		IV**	B	Consensus of experts
Systemic	Antibiotics: Doxycycline		II*	B	Consensus of experts
Others	Blood cultures should be carried out if fever and/or signs of sepsis		I***	A	

* EGFR1 study/ **Non-EGFR1, cancer treatment study/ ***Non-EGFR1, non-cancer treatment study

Table 6

Pruritus Recommendations

Preventive	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Gentle skin care instructions		IV*, ***	D	Consensus of experts
Systemic		Oral steroids	IV*, ***	D	Consensus of experts
Treatment	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Menthol 0.5%, pramoxine 1%, doxepin medium-high potency steroids (Triamcinolone acetonide 0.025%; Desonide 0.05%; Fluticasone propionate 0.05%; Alclometasone 0.05%)		III***	B	Treat underlying condition first (rash, xerosis)
Topical		-antihistamines -Lidocaine	II***	C	These agents can become allergens, and can be absorbed systemically
Systemic	Antihistamines**		I**	A	Non-sedating first; some may need adjustment for renal impairment
Systemic		Aprepitant*	V*	D	
Systemic	Gabapentin/ Pregabalin*		V***/*	D	Recommended as second line only if Antihistamines fail.
Systemic	Doxepin		V***	D	

* EGFR1 study/ **Non-EGFR1, cancer treatment study/ ***Non-EGFR1, non-cancer treatment study

Table 7

Oral Complications Recommendations

Preventive	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Benzydamine (Not FDA approved)	Topical antimicrobials (chlorhexidine, lozenges)	II**	B	Studied in radiation therapy alone, Not available in USA,
Topical	Steroids		III*	B	For EGFRi dermatitis; consensus of experts
Topical	Cryotherapy (ice chips)		I**	A	For short half-life bolus chemotherapy
Topical	Low level laser therapy		II**	B	Suggested; More studies needed
Topical		-Azelastine, chamomile, coating agents, traumeel, tretinoin cream	III**	C	Insufficient evidence for guideline
Systemic	Patient controlled analgesia for oral mucositis pain	Antimicrobials (antiviral, antifungal, antibacterial)	II**	B	Consensus of experts
Systemic		KGFI (Kepivance)	I**	A	Recommended for autologous-HCT only
Systemic		Pentoxifylline	II**	B	Not recommended in HCT
Miscellaneous	Radiation blocks, IMRT		IV**	D	Consensus of opinion with Radiation therapy
Treatment	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical		-Coating agents -topical antimicrobials (chlorhexidine)	II**	B	Insufficient evidence for guidelines; Consensus of experts
Topical		-Steroids -Traumeel -tretinoin -nonsteroidals -prostaglandin	III**	D	Insufficient evidence for guidelines; Consensus of experts
Topical		Hematopoietic growth factors (GCSF, GMCSF)	III**	B	Not recommended
Systemic	-Antibiotics (radiation & EGFRi dermatitis) -Doxycycline	pentoxifylline	II*/ II**	B	Consensus of experts

* EGFRi study/ **Non-EGFRi, cancer treatment study/ ***Non-EGFRi, non-cancer treatment study

Table 8

Xerosis Recommendations

Preventive	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	-Bathing techniques using bath oils or mild moisturizing soaps and bathing in tepid water -Regular moisturizing creams		III	B	
Other	Avoid extreme temperatures and direct sunlight		III*	B	
Treatment	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical (mild/moderate)	-Emollient creams that are packaged in a jar/tub that lack fragrances or potential irritants -Occlusive emollients containing urea, colloidal oatmeal and petroleum-based creams - For scaly areas, use exfoliants: ammonium lactate 12% or lactic acid cream 12% -Urea creams (10-40%) -Salicylic acid 6% -Zinc oxide (13-40%)	-Alcohol-containing lotions -Retinoids or benzoyl peroxide	III	B	More greasy creams for use on the limbs, but caution use of greasy creams on the face and chest. Exfoliants may sting or burn when applied to eroded or erythematous skin-apply only on intact skin.
Topical (severe)	Topical medium-high potency steroid creams (Triamcinolone acetonide 0.025%; Desonide 0.05%; Fluticasone propionate 0.05%; Alclometasone 0.05%)		III	B	

* EGFR1 study/ **Non-EGFR1, cancer treatment study/ ***Non-EGFR1, non-cancer treatment study

Table 9

Fissure Recommendations

Preventive	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	Wear protective footwear and avoid friction with fingertips, toes, and heels		III	B	
Treatment	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	-Thick moisturizers or zinc oxide (13-40%) creams -Liquid glues or cyanoacrylate to seal cracks^ -Topical steroids or steroid tape, hydrocolloid dressings, topical antibiotics^^ -Bleach soaks to prevent infection^^ -Zinc Oxide		III^*/^^**	B	Cream application often impractical

* EGFR1 study/ **Non-EGFR1, cancer treatment study/ ***Non-EGFR1, non-cancer treatment study

Table 10

Paronychia Recommendations

Preventive	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	-Diluted Bleach soaks -Avoid irritants		II***	A	Recommend final concentration of approximately 0.005% (approximately ¼-1/8 cup of 6% bleach for 3-5 gallons water)
Treatment	Recommend	Not Recommended	Level of Evidence	Recommendation Grades	Comments
Topical	-Topical Corticosteroids -Topical Calcineurin inhibitors	-Topical antifungals -Topical antibiotics	II***	A	Recommend usage of ultrapotent topical steroids as first line therapy given cost and availability of these agents.
Systemic	-Systemic tetracyclines -Systemic Antimicrobials – reserved for culture proven infection	-Empiric antibiotics – employed without culturing lesional skin -Systemic antifungals	IV*/ II***	D/ A	
Systemic	Biotin for brittle nails		III***	B	
Other	-Silver Nitrate chemical cauterization weekly^ -Electrodessication -Nail Avulsion		IV***	D	^ Reserved for pyogenic granulomata Consensus of experts

* EGFR1 study/ **Non-EGFR1, cancer treatment study/ ***Non-EGFR1, non-cancer treatment study