

Vitamin B Derivative (Nicotinamide) Appears to Reduce Skin Cancer Risk

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ABSTRACT

Nicotinamide, an amide form of vitamin B3, has shown the potential to treat a variety of dermatological conditions, including acne, rosacea, and atopic dermatitis. Recent studies have demonstrated the role of nicotinamide, in both topical and oral forms, as a chemopreventive agent against skin cancer. Its anti-carcinogenic role may be due to its ability to enhance DNA repair and prevent ultraviolet (UV)-induced immunosuppression, which is known to contribute to the progression of pre-malignant lesions. Furthermore, nicotinamide is a precursor of essential coenzymes for many important reactions in the body, including the production of nicotinamide adenine dinucleotide (NAD). NAD is a key coenzyme in the synthesis of adenosine triphosphate (ATP), which transports chemical energy within cells. Therefore, nicotinamide plays a significant role in supporting energy-dependent cellular processes, including DNA repair.

Key words: vitamin B, nicotinamide, skin cancer, chemoprevention

Introduction

Nicotinamide is an amide form of vitamin B3. The other main form of vitamin B3 is niacin (Figure 1).

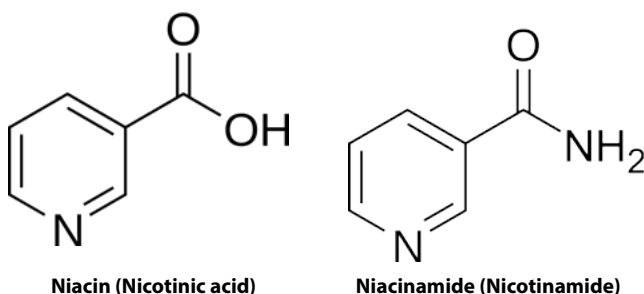


Figure 1. Chemical structures of the two main forms of vitamin B3.¹

Vitamin B3 is an essential water-soluble vitamin. It is not stored in the body, and is maintained by dietary intake of both vitamin B3 and tryptophan. Tryptophan is an essential amino acid found in most forms of protein.¹ Vitamin B3 is found in foods such as legumes, nuts, grain products, mushrooms, chicken, pork, beef and fish.² The recommended daily intake of niacin for men and women is 16 mg and 14 mg, respectively; this dose increases

to 18 mg during pregnancy and 17 mg for lactating women.³ Diets deficient in vitamin B3 can result in a condition known as pellagra, which is characterized by diarrhea, dermatitis, dementia and death (the 4 D's).⁴

Both vitamin B3 derivatives, niacin and nicotinamide, are precursors for the production of nicotinamide adenine dinucleotide (NAD), which is a key coenzyme in the synthesis of adenosine triphosphate (ATP).⁵ Since ATP is responsible for transporting chemical energy within cells, nicotinamide and niacin play a significant role in boosting cellular energy and supporting many energy-dependent cellular processes, such as DNA repair.¹ Nicotinamide has been shown to prevent the depletion of cellular NAD levels, which occurs as a result of ultraviolet (UV) exposure.⁶ Decreased NAD levels are associated with increased susceptibility to cell genotoxicity, indicating that there is an inverse relationship between cellular NAD concentration and susceptibility to DNA damage.⁵ A study conducted by Gensler et al. (1999) demonstrated that in mice there is an inverse relationship between niacin supplementation and UV-induced skin cancer susceptibility due to niacin's role in increasing cellular NAD levels.⁷ The findings of the study showed that dietary supplementation with 0.1%, 0.5% or 1.0% niacin reduced the incidence of skin cancer from 68% to 60%, 48% and 28%, respectively. These results demonstrate a dose-dependent reduction in skin cancer risk with the use of niacin supplementation.

Cellular Mechanisms

Nicotinamide and PARP-1

One mechanism by which cellular NAD levels influence responses to DNA damage involves the consumption of NAD for the synthesis of adenosine diphosphate (ADP)-ribose polymers and cyclic ADP-ribose, both of which are critical for apoptosis and necrosis.⁵ In addition, NAD is the single known substrate and inhibitor of the nuclear enzyme poly-ADP-ribose polymerase-1 (PARP-1).⁵ PARP-1, shown to be activated by UV radiation, plays a significant role in DNA repair and genomic stability.⁵ It does so by regulating transcription factors that are associated with the expression of inflammatory cytokines, chemokines, adhesion molecules and inflammatory mediators.⁸ Both PARP-1 and NAD influence cellular responses to genotoxicity and, as a result, may prevent mutagenesis and cancer formation.

Nicotinamide and Sirtuins

Sirtuins, NAD-dependent enzymes, play a key role in cellular responses to environmental stressors.⁹ Their effect on various transcription factors, including the tumor suppressor protein p53, contributes to their role in modulating cell metabolism and regulating cell survival.⁹ Sirtuin gene expression is triggered by UV irradiation. Actinic keratosis (AK) and squamous cell carcinoma (SCC) lesions show an upregulation of sirtuin gene expression, indicating that sirtuin may be associated with early stages of skin cancer formation.⁹ Nicotinamide inhibits sirtuin activity, which likely contributes to its protective effect against UV mutagenesis.⁹

Nicotinamide and DNA Repair

Nicotinamide plays an important role in DNA repair due to its function as an NAD precursor and as a substrate for PARP-1.¹⁰

PARP-1 is involved in several DNA damage responses, including DNA repair, maintenance of genomic stability, transcriptional regulation, signaling pathways involved in apoptosis, and telomere functions.¹⁰ As can be seen in Figure 2, nicotinamide and niacin are key components of NAD synthesis. This, in turn, is essential for ATP production and the activation of PARP-1. DNA strand breaks result in the activation of PARP-1, cleaving NAD into nicotinamide and ADP-ribose.⁵

The activation of PARP-1 by DNA strand breaks can activate 3 different cellular pathways, depending on the severity of DNA damage. When DNA damage is mild, PARP-1 activation enhances DNA repair by interacting with p53, signaling cell cycle arrest and facilitating DNA repair enzymes.⁵ Irreparable DNA damage causes PARP-1 activation to lead to apoptotic cell death by preventing ATP depletion and DNA repair through caspase-mediated PARP-1 cleavage. Finally, severe DNA damage leads to the overactivation of PARP-1. This causes NAD depletion and a cellular energy crisis as cells consume ATP in an attempt to replenish depleted NAD stores. The result is necrotic cell death.

UV radiation (from both UVA and UVB exposure) is the primary cause of skin cancer. UVB exposure damages DNA, which results in the formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts (6-4PPs).¹¹ CPDs lead to signature C to T and CC to TT transition mutations. UVA exposure also induces CPDs, but causes singlet oxygen photosensitization-induced DNA photolesions including 8-oxo-7,8-dihydro-2'-deoxyguanosine (8oxoG).¹¹ In 2013, Surjana et al. conducted a study to observe nicotinamide's effect on DNA repair following UV irradiation. The results showed that nicotinamide increases DNA excision repair activity in immortalized human keratinocytes (HaCaT cells) and enhances the repair of CPDs

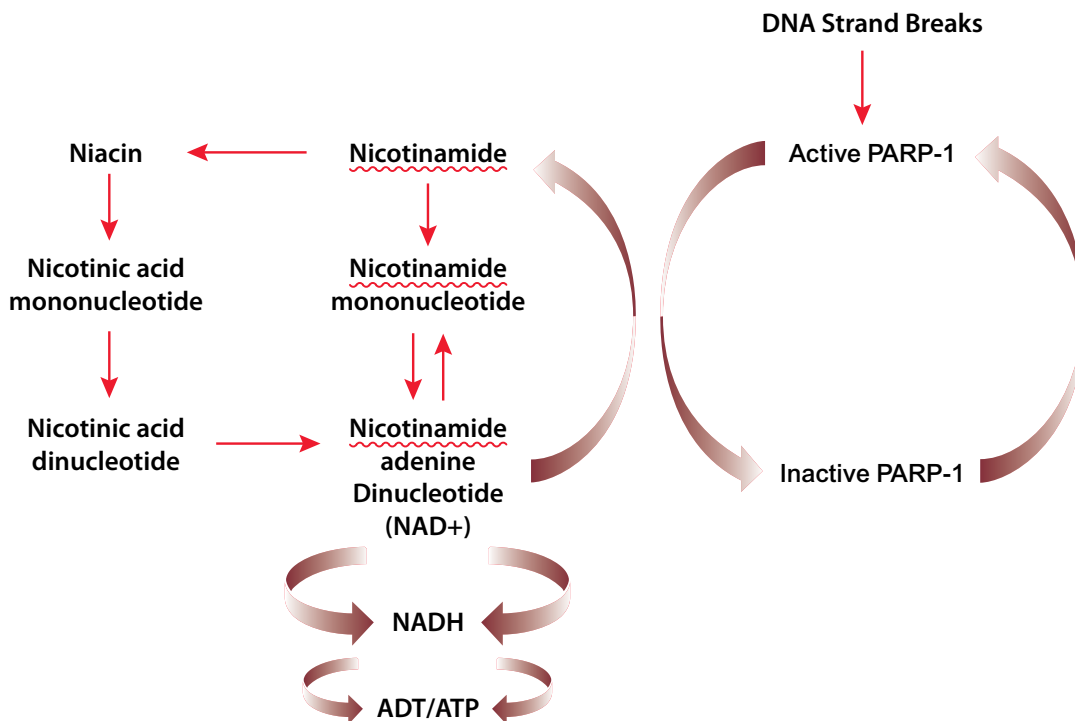


Figure 2. Simplified pathways for nicotinamide, niacin, NAD+ and PARP-1 metabolism.⁵

and 8oxoG following the exposure of human keratinocytes and *ex vivo* human skin to solar-stimulated UV.¹¹ This may contribute to nicotinamide's apparent chemoprotective effects against skin cancer. Further evidence to support nicotinamide's chemoprotective effects is that, under conditions of NAD depletion, human HaCaT keratinocytes showed increased DNA damage, even if genotoxic stressors were not present.¹² The addition of nicotinamide to the NAD-depleted cell cultures reversed this effect.

Nicotinamide and Immunosuppression

UV radiation, even in small doses, can cause immunosuppression, which contributes to the development of skin cancer by impairing the immunosurveillance of DNA damage.¹³ Sivapirabu et al. (2009) conducted a randomized, double-blinded study involving 70 healthy participants to show that topical nicotinamide (5%) prevents UV-induced immunosuppression.¹⁴ Skin immunity was determined by the Mantoux reaction, which measures the erythematous component of the delayed-type hypersensitivity response. The results showed a reduction of immunosuppression by approximately 50% after both single and multiple UV exposures. Similar results were found when the study was repeated using a much lower dose of topical nicotinamide (0.2%). Another study conducted by Damian et al. (2008) showed that applying 5% topical nicotinamide 3 days before solar-simulated UV exposure significantly suppressed Mantoux reactions.¹⁵ Based on this evidence, topical nicotinamide is effective at preventing UV-induced immunosuppression, whether it is applied prior to or after UV exposure.

Oral nicotinamide has also been shown to be effective in protecting against UV-induced immunosuppression. A randomized, placebo-controlled study using 30 healthy Mantoux-positive participants showed that 500 mg of oral nicotinamide taken 3 times daily for 7 days significantly reduced UV-induced immunosuppression.¹³ The study was repeated with 31 participants using a once daily dose of 500 mg oral nicotinamide. The results showed that the lower dose was equally as effective in reducing UV-induced immunosuppression.¹³

Clinical Evidence

Numerous studies have demonstrated the ability of nicotinamide to decrease the incidence of new nonmelanoma skin cancers (NMSCs) and AKs in susceptible individuals. Kim et al. (2015) combined the results of 2 randomized, double-blinded phase 2 trials that examined the effect of oral nicotinamide on AK counts in individuals with photo-damaged skin.¹⁶ Seventy-four patients were enrolled in the 2 trials (37 in the placebo group and 37 in the nicotinamide group). Approximately 81% of participants in the placebo group and 79% of participants in the nicotinamide group had previous skin cancers; 11 patients developed a total of 20 new skin cancers at 4 months in the placebo group, while 2 patients developed a total of 4 new skin cancers at 4 months in the nicotinamide group. The results demonstrated a significant reduction in the odds of developing at least 1 skin cancer with the use of nicotinamide in comparison to placebo ($p=0.019$).

A recent phase 3 randomized, double-blind, controlled trial conducted by Chen et al. (2015) recruited 386 patients who had been diagnosed with at least 2 NMSCs, specifically basal cell carcinomas (BCCs) plus SCCs, in the previous 5 years.¹⁷ The

participants were randomized in a 1:1 ratio to receive either 500 mg nicotinamide twice daily or placebo for 12 months. Dermatologists evaluated participants at 3-month intervals for the 12-month trial period, as well as for 6 months after the intervention period. The primary endpoint of the trial was the number of new NMSCs during the 12-month intervention period. Secondary endpoints included the number of new BCCs, SCCs, and AKs during the 12-month period, the number of NMSCs in the 6-month post intervention period and the safety of nicotinamide. The results of the trial showed a 23% reduction in the rate of NMSCs in the nicotinamide group compared to the placebo group at 12 months ($p=0.02$). Similar results were found for the rate of BCCs and SCCs (20% and 30% lower in the nicotinamide group than in the placebo group, respectively). The number of AKs was also found to be lower in the nicotinamide group than in the placebo group at 3 months, 6 months, 9 months, and 12 months. The trial reinforced the safety profile of nicotinamide by showing no between-group differences with regards to the number or types of adverse events during the intervention period.

Other Skin Conditions

Nicotinamide has also shown to be beneficial in treating various dermatological skin conditions, including acne and rosacea. In addition, used together with corticosteroids, it is commonly prescribed for inflammatory autoimmune conditions like bullous pemphigoid and pemphigus.¹⁸

Acne Vulgaris

Acne vulgaris is one of the most common skin conditions for which patients seek dermatologic care.¹⁹ Factors contributing to acne vulgaris include sebum production, bacterial growth, and associated inflammation.¹⁹ Nicotinamide has anti-inflammatory, sebo-suppressive, and healing properties, which have shown benefit for acne vulgaris when used topically. A study of 50 Japanese participants treated with 2% topical nicotinamide showed significantly lowered sebum excretion rates after 2 and 4 weeks of application.¹⁹ An earlier double-blind trial by Shalita et al. (1995) involved 76 participants with moderate inflammatory acne.²⁰ The results demonstrated that 4% topical nicotinamide gel and 1% clindamycin gel were statistically similar in decreasing acne symptoms over an 8-week period. From the participants treated, 82% showed improvement in acne symptoms.

Rosacea

Rosacea is a chronic facial dermatosis, characterized by the presence of erythema, papules, pustules, telangiectasias and sebaceous gland hyperplasia.²¹ Wozniacka et al. (2005) treated 34 patients with rosacea using a gel containing 0.25% N-methylnicotinamide (a metabolite of nicotinamide) for 4 weeks.²¹ The results indicated a good to moderate improvement in rosacea in 76% of participants. After 2 weeks of use, the majority of patients experienced a 50-75% reduction in the appearance of erythema and papules.²¹

Aging Skin

Nicotinamide also improves the appearance of aging skin.²² A double-blind randomized controlled trial with 50 Caucasian female participants observed the effect of topical nicotinamide on the appearance of photo-aged skin.²² Participants used 5% nicotinamide cream on their faces for 12 weeks. The results

showed a significant improvement in skin appearance, including reductions of fine lines and wrinkles, hyperpigmented spots, red blotchiness and skin sallowness, as well as improved elasticity.

Inflammatory Autoimmune Conditions

Nicotinamide has shown to be an effective treatment for a variety of autoimmune conditions, particularly autoimmune blistering disorders. Nicotinamide, in combination with tetracycline, inhibits neutrophil and eosinophil chemotaxis, resulting in inhibition of the humoral immune response.²³ Thus, the combination of these two drugs has been shown to be an effective treatment in patients with bullous pemphigoid.²³ Nicotinamide has also been demonstrated to be a beneficial adjunctive therapy for patients with pemphigus vulgaris. A study conducted by Iraj and Banan (2010) showed that nicotinamide gel, applied topically, is an effective alternative to corticosteroids for treating pemphigus vulgaris lesions.²⁴

Conclusion

Nicotinamide is a widely available, inexpensive and well-tolerated agent. It has been reported in a small number of studies to be of benefit in a range of skin conditions, including acne, rosacea, immunobullous disease and photoaging. Recent studies show that it may also be an effective chemopreventive agent against skin cancer, possibly due to its ability to both augment cellular DNA-repair mechanisms and counteract UV-induced immunosuppression. Due to its favorable safety profile and demonstrated effectiveness, nicotinamide supplementation should be considered as an adjunctive chemopreventative treatment for patients at high risk of developing NMSC or AKs.

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Epidermal Growth Factor Receptor Inhibitors: Cutaneous Side Effects and Their Management

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ABSTRACT

Epidermal growth factor receptor (EGFR) inhibitors are part of an emerging class of anticancer medicines known as “targeted therapy,” which target pathways more specific to neoplastic proliferation than traditional chemotherapeutic agents. Adverse effects of such treatments are thought to be less severe, but can still be significant. Because EGFR is preferentially expressed in epithelial tissues, including the skin and hair follicle, cutaneous side effects of these agents are quite common. Not only can these toxicities severely affect patients’ quality of life, but in some specific instances, they can be associated with increased response to therapy. It is of paramount importance that clinicians familiarize themselves with and understand the basic management of the range of cutaneous adverse effects caused by these drugs.

Key words: epidermal growth factor receptor, EGFR, epidermal growth factor receptor inhibitor, EGFR inhibitor, erlotinib, cetuximab, targeted therapy, antineoplastic therapy, medication toxicity, cutaneous side effects, cutaneous adverse events, acneiform eruption, paronychia

Introduction

The epidermal growth factor receptor (EGFR) is expressed in epithelial tissues as well as hair follicles. It contributes to epidermal proliferation, differentiation, and hair growth. Upregulating mutations of EGFR have been found in many solid tumors.¹ The discovery of EGFR’s role as an oncogene has led to the development of many new inhibitors for the treatment of various neoplasms of the head, neck, colon, and lung. These drugs have been shown to increase the rate of response to treatment, delaying disease progression and improving quality of life. Standard chemotherapeutic agents nonspecifically affect cells that proliferate rapidly; in contrast, EGFR inhibitors (EGFRIs) target pathways more specific to survival of neoplastic cells, thus belonging to a new class of chemotherapeutic agents – so-called “targeted therapy.” These targeted therapies are usually associated with fewer systemic side effects than standard chemotherapy.²

There are several different types of EGFRIs, including small molecule tyrosine kinase inhibitors, monoclonal antibodies, and multikinase inhibitors. Small molecule tyrosine kinase inhibitors, such as gefitinib and erlotinib, selectively bind the adenosine triphosphate (ATP)-binding site of the EGFR tyrosine kinase receptor, inhibiting the receptor’s intracellular domain via preventing phosphorylation.^{3,4} Both gefitinib and erlotinib are approved for the treatment of non-small cell lung cancer, and erlotinib in combination with gemcitabine is approved for the treatment of advanced pancreatic cancer.

In contrast, monoclonal antibodies that target EGFR, such as cetuximab and panitumumab, bind to its extracellular domain and competitively inhibit endogenous ligand binding to the receptor.^{3,4} These antibodies are approved for the treatment of advanced EGFR-expressing colorectal cancer, and cetuximab is also approved for treatment of squamous cell carcinoma of the head and neck. There are also combination therapies that affect multiple receptors such as lapatinib (approved for human epidermal growth factor receptor 2-positive [HER2+] breast

cancer) and afatinib (approved for non-small cell lung cancer), which inhibit both the EGFR and HER2 receptors, and vandetanib (approved for advanced medullary thyroid cancer), which inhibits EGFR, vascular endothelial growth factor (VEGFR), and rearranged during transfection (RET) activities.

Although these drugs have been proven to be very effective for normally untreatable advanced neoplasms, EGFRIs cause cutaneous side effects in 50% or more of patients undergoing treatment.¹ The most common of these adverse reactions include acneiform eruptions, paronychia, xerosis, mucositis, and alopecia, and less common side effects include trichomegaly, hirsutism, and hyperpigmentation. The occurrence of some EGFR-associated cutaneous toxicities is actually associated with clinical response to the medication. However, cutaneous side effects can result in decreased quality of life and may cause interruption or discontinuation of therapy despite effectiveness.³ Therefore, it is important to understand the cutaneous side effects of EGFRIs and their management in order to improve quality of life, increase compliance and avoid unnecessary interruption or cessation of treatment.

Cutaneous Toxicities

Mechanism

EGFR is expressed in undifferentiated keratinocytes in the basal layer of the epidermis and the outer layers of the hair follicle, and plays a key role in normal differentiation and proliferation in these tissues. EGFR is activated by ligands such as EGF and transforming growth factor- α (TGF- α), and its effects are mediated via downstream pathways including the MAPK (mitogen-activated protein kinase) and PI3K (phosphatidylinositol 3-kinase)-Akt pathways. Downstream effects include growth stimulation, protection from apoptosis, inhibition of differentiation, loss of intercellular attachments, and increased migration. EGFR expression is lost as keratinocytes leave the basal layer and terminally differentiate towards corneocytes.³⁻⁶

Inhibition of EGFR signaling leads to apoptosis of normal keratinocytes, but not of melanocytes or fibroblasts. EGFR inhibition also induces terminal differentiation, and has been shown to inhibit formation of the cornified cell envelope and cause premature hair keratinization and maturation of the inner root sheath. Migration of cells is also decreased and attachment is promoted, interfering with normal movement of cells towards the layers of the epidermis and follicle as they mature. These effects are reflected in findings of decreased epidermal thickness and decreased stratum corneum found in skin specimens of patients treated with EGFRIs. Downregulation of EGFR-signaling also seems to result in increased recruitment of inflammatory cells, contributing to the inflammatory nature of several EGFR-related cutaneous toxicities.³⁻⁶

The culmination of all of these effects of EGFR blockade results in overall disruption of the integrity of the skin and follicle with associated inflammation. The high incidence of mucocutaneous side effects reflects the importance of EGFR and its function in the epidermis, hair follicle and periungual tissue.

Acneiform Eruptions

Acneiform eruptions are the most common skin reaction found in those undergoing EGFRi therapy, with 43-85% of patients affected. It is the most common side effect of cetuximab and panitumumab, reported in up to 90% of patients. It is also the earliest side effect, presenting only 7-10 days after initiation of drug therapy. The pathological mechanism underlying EGFRi-associated acneiform eruptions differs than that of traditional acne, lying mainly in the follicular instability caused by disruption of EGFR-related normal growth, induction of apoptosis and early differentiation, as opposed to follicular occlusion.²

The acneiform eruption manifests as a papulopustular eruption that affects mainly the head, neck, and upper trunk, normally sparing sites undergoing radiation therapy. It can, however, affect areas spared by traditional acne, such as the lower legs and dorsal arms.² Acneiform eruptions due to EGFRi therapy are characterized by a lack of comedones and often display crusting and confluence. Pruritus is more frequent than in traditional acne.² This eruption is associated with treatment efficacy, showing an increased survival rate when present.^{3,4} The effects are dose dependent and improvement in the eruption can be seen within 1-2 weeks of discontinuation of therapy.

Treatment focuses more on reducing inflammation than relieving follicular occlusion, and current treatment guidelines are based on the severity of the eruption. A grading scale from 1-4 is used to determine severity (Table 1). For grade 1 eruptions, sun protection, emollients, topical clindamycin, and topical hydrocortisone 1-2.5% are recommended. For grade 2 eruptions, oral tetracyclines such as doxycycline or minocycline 100 mg twice daily should be added. Progression to grade 3 calls for EGFRi dose reduction, oral corticosteroids, and delay in the interval of treatment.^{5,7,8} Patients will rarely present with grade 4 lesions, but should immediately discontinue EGFRi therapy and be seen by a burn care specialist. It is important to note that, in contrast to traditional acne, retinoids are not effective. Retinoids do not improve the follicular instability caused by EGFRIs and can even exacerbate it. They can also aggravate the concomitant xerosis that is seen with EGFRi therapy. Prophylactic treatment

is controversial, as the eruption aids in determining treatment efficacy; however, oncologists will often recommend emollients and may prescribe hydrocortisone or topical clindamycin in anticipation of at least a mild eruption.

Severity of cutaneous toxicity	Description of symptoms
Grade 1	Asymptomatic macular or papular eruption or erythema
Grade 2	Symptomatic macular or papular eruption or erythema affecting <50% of body surface area (BSA); localized desquamation or other lesions affecting <50% of BSA
Grade 3	Symptomatic macular, papular, or vesicular eruption affecting ≥50% of BSA; desquamation affecting ≥50% of BSA; severe, generalized erythroderma
Grade 4	Generalized exfoliative, ulcerative, or bullous dermatitis

Table 1. Classification system of acneiform eruptions caused by EGFRIs

Adapted from Hu JC, et al. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. *J Am Acad Dermatol.* 2007 Feb;56(2):317-26.⁷

Paronychia

Nail changes are a common cutaneous side effect in those undergoing EGFRi therapy and are seen in up to 17% of patients.^{9,10} Patients present with painful inflammation and suppuration of the periungual skin 4-6 weeks after initiation of therapy. EGFRi-induced paronychia is characterized by abnormal periungual desquamation that results in friable pyogenic granuloma-like changes of the lateral nail folds, as well as pain of the distal finger tufts.^{11,12} Disruption and fragility of the epidermis caused by EGFRIs may lead to increased susceptibility of skin to penetration by nail fragments, which may be more brittle with EGFR inhibition, a mechanism similar to that seen in retinoid-induced periungual inflammation.²

Paronychia rarely leads to the cessation of therapy; however it does have a significant impact on the patient's quality of life.¹ Although the lesions are sterile, secondary infection with *Staphylococcus aureus* or *Candida albicans* has been documented.^{1,3,13} Treatment is dependent on the severity of the reaction. Local care consists of using petrolatum emollients, as well as antiseptic soaks and cushioning of the soles. For reactions that are mild-to-moderate, disinfectants, topical antibiotic ointments, and mid to high potency topical corticosteroids under occlusion are recommended. Although rare, certain cases may be severe enough to require surgical debridement, electrodesiccation, or cessation of therapy.^{3,14}

Alopecia

Both non-scarring and scarring alopecia has been documented as a side effect of long-term EGFRi therapy. EGFR seems to play a role in maintaining the immune privilege of the hair follicle, and the resultant inflammation leads to hair loss, with eventual follicular destruction.² Patients usually present with fine,

brittle hair with frontal balding about 2-3 months after drug initiation. At this non-scarring stage, alopecia typically resolves after discontinuation of therapy, although hair quality may be affected.¹³ With time, scarring alopecia can occur and lead to permanent hair loss. Management usually consists of topical steroids to reduce inflammation and prevent scarring.^{13,15}

Xerosis

Xerosis is a common side effect of EGFR therapy due to the deteriorated stratum corneum, which results in increased transepidermal water loss. This can lead to inflammation and xerotic dermatitis. Patients present 1-2 months after initiation of therapy. Pruritus is also a frequently occurring symptom. Xerosis can accompany or follow the acneiform eruption associated with therapy. Treatment for EGFR-induced xerosis follows a strategy similar to atopic dermatitis, which includes avoidance of hot baths and extreme temperatures, and using moisturizing soaps that are free of fragrances and thick moisturizing creams or emollients. Preventative measures, consisting of education on dry skin care and bathing techniques, are recommended.¹³ If the xerosis is severe, topical steroids may be required.¹³

Other Cutaneous Toxicities

There have been other rare side effects reported with the use of EGFRs, including trichomegaly and facial hirsutism. Patients may present 1-2 months after initiation of therapy, and the abnormal hair growth lasts for the duration of therapy with the EGFR. Patients with trichomegaly may experience discomfort and corneal abrasions due to abnormal eyelash growth. Management consists of eye lash clipping every 2-4 weeks and referral to an ophthalmologist for complications. Patients with hirsutism can be managed with laser hair removal as well as topical eflornithine.^{16,17} Oral complications are uncommonly reported in patients receiving EGFR therapy. The most common oral side effect observed is mucositis. Patients present with broad areas of erythema and aphthous-like stomatitis.¹³ Localized measures for symptom relief such as ice chips and thorough oral care are normally sufficient; pain management with analgesics may be necessary.

Although eventually fading over several months, hyperpigmentation has also been reported in a few cases, which is believed to be due to post inflammatory changes secondary to EGFR-induced acneiform eruptions and dermatitis. Management guidelines for this hyperpigmentation focuses on treating the acneiform eruption and eczema. It is also recommended for these patients to limit sun exposure in order to prevent exacerbation of existing hyperpigmentation. There has been no efficacy shown in the use of bleaching creams.⁷

Conclusion

The use of EGFRs for chemotherapy is on the rise due to their observed efficacy and decreased rate of nonspecific and hematopoietic side effects. However, due to EGFR's important role in the skin and hair follicle, EGFRs are associated with frequent mucocutaneous toxicities. It is important to understand these adverse effects and their management in order to avoid unnecessary interruption of therapy and decreased quality of life. The most common dermatologic toxicities include acneiform

eruptions, paronychia, alopecia, and xerosis. Many of these side effects can be managed, which can increase compliance and help reduce the physical and emotional burden that patients face.

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Update on Drugs

Name/Company	Approval Dates/Comments
Isopropyl myristate solution <i>Resultz</i> ® Piedmont Pharmaceuticals	In May 2017, the US FDA granted 510(k) clearance to Resultz® Lice & Egg Elimination Kit, an odorless noninsecticidal product containing isopropyl myristate 50% and ST-cyclomethicone 50%, that kills and removes head lice with a 5-minute application time. This treatment works by dissolving the insect's waxy exoskeleton, resulting in dehydration and death.
Delafloxacin oral and IV formulations <i>Baxdela</i> ™ Ligand / Melinta	The FDA approved delafloxacin in June 2017 for the treatment of adults with acute bacterial skin and skin structure infections caused by susceptible bacteria. Delafloxacin is a fluoroquinolone that exhibits activity against both gram-positive and gram-negative pathogens, including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA).
Plasma-derived concentrate of C1 esterase inhibitor SC (human) <i>Haegarda</i> ® CSL Behring	In June 2017, the FDA approved Haegarda®, the first and only self-administered, twice-weekly, subcutaneous (SC) therapy indicated for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescent and adult patients. The safety and efficacy of Haegarda® were established in the Phase III COMPACT trial, which showed that at the approved dose of 60 IU/kg, this therapy reduced the median number of HAE attacks by 95% vs. placebo.
Oral dimethyl fumarate <i>Skilarence</i> ® Almirall S.A.	The European Commission (EC) approved this new oral formulation of dimethyl fumarate (DMF) in June 2017 for treating moderate-to-severe chronic plaque psoriasis. Skilarence® is the first DME, a type of fumaric acid ester (FAE) with anti-inflammatory and immunomodulating properties, approved by the EC for psoriasis. Treatment is indicated for first-line induction and long-term maintenance.
Abatacept for IV or SC injection <i>Orencia</i> ® Bristol-Myers Squibb	In July 2017, both the FDA and EC approved abatacept, a selective T-cell co-stimulation modulator, for the treatment of adults with active psoriatic arthritis. The co-stimulation blockade of abatacept inhibits T-cell activation and suppresses the resulting inflammatory cascade.
Secukinumab for SC injection <i>Cosentyx</i> ® Novartis AG	In July 2017, secukinumab received approval in the EU for a label update that includes 52-week data from the CLEAR study, which demonstrated long-term superiority of secukinumab vs. ustekinumab (Stelara®, Janssen) in psoriasis. The update also includes the use of secukinumab to treat moderate-to-severe scalp psoriasis. This is the first interleukin-17A inhibitor approved to treat psoriasis, psoriatic arthritis and ankylosing spondylitis.
Guselkumab for SC injection <i>Tremfya</i> ™ Janssen Biotech	The FDA approved guselkumab in July 2017 for treating adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Guselkumab is a human monoclonal antibody that functions by selectively blocking the cytokine interleukin (IL)-23. It is administered as a 100 mg SC injection, first at two starter doses at weeks 0 and 4, then every 8 weeks afterwards.
Ipilimumab for IV injection <i>Yervoy</i> ® Bristol-Myers Squibb	The FDA approved an expanded indication for ipilimumab in July 2017 to include the treatment of unresectable or metastatic melanoma in pediatric patients ≥12 years of age. The approved ipilimumab dose for pediatric melanoma patients is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses.
Belimumab for SC injection <i>Benlysta</i> ® GSK	In July 2017, the FDA approved a new SC formulation of Benlysta® for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy. The approval marks the first SC self-injection treatment option for patients with SLE.