

FEATURE ARTICLE

What Kind of Rash Is It? Deciphering the Dermatologic Toxicities of Biologic and Targeted Therapies

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An overwhelming number of new agents, including targeted agents with unique mechanisms of action, are available in oncology practice today. Along with the benefit of new treatments for patients comes the unfamiliarity of associated toxicities and learning the best methods to minimize side effects. One such toxicity has been the spectrum of dermatologic reactions from some of the newer small-molecule inhibitors and monoclonal antibodies. Scientific evidence describing the unique rashes and methodologies to treat various cutaneous toxicities with specific agents is extremely limited. This article reviews the currently available literature related to dermatologic toxicities observed with many newer targeted therapies. Current recommendations for management are based on practices implemented during clinical trials and postmarketing practices. Additional research is needed to further elucidate the most efficacious methods for treating side effects observed with newer targeted therapies.

The field of targeted and biologic therapies has exploded in recent years, with new agents coming into the market at a rapid pace. Oncology nurses are confronted with keeping abreast of new drugs, as well as their side effects and management. Dermatologic side-effect management associated with the agents is of particular concern for oncology nurses. New agents, such as erlotinib and cetuximab, have proven to be especially challenging because of their target—the epidermal growth factor receptor—and associated dermatologic toxicities.

Skin toxicities are not new phenomena with noncytotoxic therapies. Interleukin-2 (IL-2) may cause an erythematous rash, pruritus, dry and peeling skin, and severe itching. Skin biopsies indicate that those reactions to IL-2 result from perivascular infiltration of T cells and increased expression of adhesion molecules on endothelial cells (Schwartzentruber, 2000). Symptoms are managed with a variety of topical lotions, mild soap, and oral agents (e.g., diphenhydramine, hydroxyzine) until all symptoms have cleared (Mavroukakis, Muehlbauer, White, & Schwartzentruber, 2001; Schwartzentruber). Patients treated with alpha interferon have experienced localized reactions at the injection site or more diffuse skin reactions that may be caused by immunologic and inflammatory mechanisms. Knowledge of predisposing factors such as allergies, infections, injection site technique, temperature of injectate, and concomitant medications or herbal supplements guides nurses in educating patients and managing skin-induced reactions (Azagury, Pauwels, Kornfeld, Bataille, & Perie, 1996; Cnudde, Gharakhanian, Luboinski, Dry, & Rozenbaum, 1991; Cuaron & Thompson, 2001; Gallelli, Guadagnino, Caroleo, Marigliano, & De Sarro, 2004; Stafford-Fox & Guindon, 2000).

At a Glance

- ◆ Several molecularly targeted cancer agents cause significant skin toxicities that are challenging for oncology nurses to manage.
- ◆ Recommendations for management have been derived from clinical practice during clinical trials and postmarketing practices.
- ◆ Patient education and early detection and intervention are important in managing dermatologic toxicities.

IL-2 and interferon alpha now are considered “older” cancer therapies. In the 1990s, nurses were challenged with managing skin-related side effects from those therapies. Interventions were developed by understanding the pathology of the skin

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Digital Object Identifier: 10.1188/07.CJON.659-666

reactions as well as trial and error with symptom management. Once again, oncology nurses are employing their vast knowledge to manage side effects with new anticancer agents. However, methods used to treat skin-related toxicities in the past may or may not be appropriate in treating the side effects of newer agents. The purpose of this article is to describe the various skin toxicities that can occur with many newer agents and provide an overview of current management strategies.

Signaling Pathways and Targeted Approaches to Treatment

Molecular targeted therapies include agents or approaches that target cell membrane receptors, signaling pathways and proteins, enzymatic activity, and regulatory cell growth controls that are aberrant or more abundant in malignant cells than healthy cells (Gale, 2005). The human epidermal growth factor receptor (HER1/EGFR) is a common and well-studied target in oncology because of its key role in the tumorigenic process of epithelial cancers (Rhee, Oishi, Garey, & Kim, 2005).

HER1/EGFR is part of a family of receptors (HER1, HER2, HER3, and HER4) that shares a common molecular structure with an extracellular domain, a transmembrane region, and an intracellular component that has tyrosine kinase activity (Roskoski, 2004; Rowinsky, 2004). The activation of HER1/EGFR via the two prominent ligands, EGF and transforming growth factor- α , leads to many processes that regulate cell growth, metastasis, angiogenesis, and protection from apoptosis (Huang & Harari, 1999). HER1/EGFR is overexpressed in 30%–100% of cancers, including head and neck, colorectal, esophageal, breast, cervical, and renal (Roskoski; Rowinsky), which can lead to a high number of HER1/EGFR ligands creating an autocrine loop to promote independent tumor growth (Perez-Soler & Saltz, 2005).

Cutaneous reactions are common in agents that target EGF signaling and pathways. Monoclonal antibodies and small-molecule tyrosine kinase inhibitors are the two main types of agents that inhibit EGFR. Monoclonal antibodies target HER1/EGFR: cetuximab, panitumumab, and matuzumab. Cetuximab has been approved by the U.S. Food and Drug Administration (FDA) for use in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy and as a single agent in patients who are intolerant to irinotecan-based therapy. Panitumumab, a fully human monoclonal antibody, has been approved by the FDA for treatment of patients with EGFR-expressing metastatic colorectal cancer with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens. Zalutumumab is an investigational agent that targets HER1/EGFR and currently is in phase II clinical trials.

Small molecules can be single- or multikinase inhibitors. Multikinase inhibitors block the tyrosine kinase activity of two or more receptors from the same family of receptors, such as HER1 and HER2. The mechanism of action is similar to a single tyrosine kinase inhibitor of the HER1/EGFR pathway with similar side effects (e.g., rash). Other multikinase inhibitors block divergent pathways such as HER1/EGFR and vascular EGF-2, resulting in side-effect profiles from both pathways. Examples

of single- and multitargeted tyrosine kinase inhibitors include erlotinib, sunitinib, and sorafenib.

Potential Etiology of Dermatologic Toxicities

The exact mechanism by which the rash occurs is unknown; however, HER1 receptor is the major receptor in primary human keratinocytes and homodimerization of the receptor is predominant in human skin. EGFR tyrosine kinase is involved in regulating diverse epidermal processes, including keratinocyte proliferation, differentiation, migration, and survival, as well as differentiation and development of the hair follicle epithelium (Busam et al., 2001). Abnormal expression of HER1 has been implicated in hyperproliferative disorders such as psoriasis and epithelial tumor formation (King, Gates, Stoscheck, Underwood, & Nanney, 1990). HER1/EGFR targeted therapies can block human keratinocytes specifically and completely, providing a molecular mechanism for the skin rash (Laux, Jain, Singh, & Agus, 2006).

Skin biopsies from patients treated with agents that target EGFR or EGFR pathways have provided information for better understanding the pathogenesis for some dermatologic toxicities. Most dermatologic side effects do not appear to be related to immune dysfunction, an infectious or allergic process. Skin samples reveal infiltration of inflammatory cells, particularly in the follicles (Herbst, LoRusso, Purdom, & Ward, 2003). Findings in some skin samples demonstrated enlarged follicles obstructed by excess keratinocytes. Thinning of the stratum corneum layer of the skin and alterations in the normal basket-weave configuration were seen in skin biopsies of patients taking gefitinib (Albanell et al., 2002).

Busam et al. (2001) examined skin biopsies from patients on cetuximab and concluded that the rash is characterized by a lymphocytic perifolliculitis or superficial folliculitis without an infectious process. Other published reports support the finding that folliculitis occurs in the absence of an infectious process with the use of EGFR targeted agents (Harding & Burtneiss, 2005; Lenz, 2006). Vasodilation, dermal edema, and follicular degradation also have been reported in the literature (Lacouture, 2006). Although an infectious process can occur, it generally is a secondary infection that does not present initially. The sebaceous glands do not appear to be affected. More studies are needed to elucidate the histology of dermatologic toxicities, key structures involved, and incidence of secondary infection.

Rashes

Dermatologic toxicities from targeted therapies are similar but have unique differences, depending on the type of agent and its target. The unique cutaneous effects of newer agents often are characterized by the degree, location, symptomology, and type of skin lesion. The incidence and severity of the lesions vary among trials. The challenge in classifying dermatologic lesions is the inconsistency in these descriptions and identifications. Common terms used to describe the various toxicities associated with some of the newer agents are acneiform rash, acneiform follicular rash, acne-like rash, maculopapular skin

rash, pustular rash associated with dry skin, and exfoliative dermatitis. A glossary of pertinent terms is found in Figure 1. The rash seen in patients treated with many of the new targeted agents (particularly EGFR inhibitors) is not considered acne vulgaris. Typical characteristics of acne are pustules, papules, microcomedones (blackheads), and comedones (whiteheads), with inflammatory and noninflammatory processes (Perez-Soler et al., 2005). Comedones typically are not seen in the initial presentation and rarely are documented in histologic skin samples taken from patients on targeted agents.

The severity of a rash commonly is related to the agent type and dose. Rashes generally present on the face, head, scalp, and upper torso but can extend to the extremities (Perez-Soler et al., 2005). The rash generally occurs within the first two weeks of initiating therapy. Waxing and waning of the dermatologic toxicities are common and generally are mild to moderate. The incidence of dermatologic effects from EGFR monoclonal antibodies is slightly higher (43%–85%) (Robert et al., 2005) than those seen with small-molecule EGFR tyrosine kinase inhibitors (25%–33%) (Perez-Soler et al.). Most rashes associated with monoclonal antibodies are reported as grade 1–2; grade 3–4 severe rashes are less common (2%–18%) (Robert et al.). Rash occurs in 70%–80% of patients treated with cetuximab (Harding & Burtneiss, 2005). Rashes reportedly occur in 35%–50% of patients taking imatinib for chronic myelogenous leukemia (Cohen, Johnson, & Pazdur, 2005). Rashes occurring with cetuximab also have been described as self-limiting and manageable (Reynolds, 2004). Rare cutaneous reactions such as Stevens-Johnson syndrome and lichenoid reaction have been reported with imatinib (Robert et al.).

The National Cancer Institute (2006) Common Terminology Criteria for Adverse Events frequently is used to grade adverse events in clinical trials (see Table 1). The literature published about rashes associated with targeted agents emphasizes the need for a more specific tool that defines the unique dermatologic characteristics of newer agents. Authors indicate the need for including the description of the dermatologic toxicity by number of papules, severity of discomfort, and extent of erythema in any grading scale (Perez-Soler et al., 2005).

Acral erythema: capillary congestion of the hands or feet causing redness

Desquamation: shedding of the outer layers of skin

Fissures: a linear loss of the dermis and epidermis, with sharply defined, almost vertical walls

Folliculitis: inflammation of the shaft in the skin through which hair grows

Hyperkeratosis: thickening of the outer layer of skin containing keratin

Macule: a circumscribed change in the color of the skin which is flat (neither raised nor indented)

Papule: a solid rounded growth that is elevated from the skin

Paronychia: infection of the skin surrounding a fingernail or toenail

Pustule: a raised lesion that contains pus

Trichomegaly: abnormal length of eyelashes

Figure 1. Terms Related to Cutaneous Toxicity

Xerosis

Xerosis (i.e., dry skin) is reported to occur in approximately 13%–35% of the patients taking gefitinib or erlotinib (Perez-Soler et al., 2005). Commonly, xerosis and rash can occur together (see Figure 2). When they occur concurrently, the dry skin tends to be more extensive (Herbst et al., 2003).

Cutaneous Reactions in Combination Tyrosine Kinase Inhibitors

Multiple targeted tyrosine kinase inhibitors, imatinib, sorafenib, and sunitinib, reportedly have dermatologic toxicities. Cutaneous reactions have been described as acne-form-like rashes accompanied with xerosis and erythema. Maculopapular rash, pustules, exfoliative dermatitis, pruritis, and pain have been documented with the use of those agents. An erythemic face rash and/or scalp rash, which is similar to seborrheic dermatitis, has been reported to occur one to two weeks after sorafenib therapy (Robert et al., 2005). The scalp rash usually is associated with scalp dysaesthesia but can occur alone.

Acral Erythema

Acral erythema in patients treated with sunitinib and sorafenib has a unique presentation. It occurs on the palms of the hands and soles of the feet and has been described as painful, edematous, and erythematous. Paraesthesias may be experienced prior to acral erythema and be exacerbated by warm environments. Formation of hyperkeratosis and desquamation is not uncommon. The hyperkeratotic lesions are different from those appearing with hand-foot syndrome (palmar-plantar erythrodysesthesia) associated with some chemotherapy agents. Histologic changes suggest epidermal alterations in the granular layer of the epidermis. Erythema is believed to be dependent and occurs two to four weeks after the initiation of therapy (Robert et al., 2005).

Subungual Splinter Hemorrhages

Subungual splinter hemorrhage, a mass of blood under the nail bed, is believed to be thrombotic in origin. Subungual hemorrhages have been noted in the fingernails and toenails in patients taking sunitinib and sorfenib (Robert et al., 2005).

Hair and Skin Alterations

Hair depigmentation changes can occur with sunitinib and imatinib. Sunitinib may affect stem cell factors or c-KIT signaling involved in regulating hair pigmentation. Darkening of the skin, areas of hypopigmentation, and increased or decreased photosensitivity have been reported with imatinib. The etiology is unknown, but molecular responses to ultraviolet light have been proposed (Robert et al., 2005). Alteration in androgen signaling with hormones and EGFR also is a suspected mechanism for hair alterations, including alopecia.

Treatment of Cutaneous Toxicities

The literature is sparse in relation to evidence-based reports for treating cutaneous toxicities associated with the administra-

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Dermatology and Skin Reactions

ADVERSE EVENT	GRADE				
	1	2	3	4	5
Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat (<i>also consider induration or fibrosis (skin and subcutaneous tissue)</i>)	Detectable	Marked	—	—	—
Bruising (in absence of grade 3 or 4 thrombocytopenia)	Localized or in a dependent area	Generalized	—	—	—
Burn (<i>refers to all burns, including radiation and chemical</i>)	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Cheilitis	Asymptomatic	Symptomatic, not interfering with activities of daily living (ADL)	Symptomatic, interfering with ADL	—	—
Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss or alopecia (scalp or body)	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration or fibrosis (skin and subcutaneous tissue) (<i>also consider fibrosis, cosmesis</i>)	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction, or fixation	—	—
Injection site reaction or extravasation changes (<i>also consider allergic reaction or hypersensitivity, including drug fever, or ulceration</i>)	Pain, itching, erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
Nail changes	Discoloration, ridging (koilonychias), pitting	Partial or complete loss of nail(s), pain in nail bed	Interfering with ADL	—	—
Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening, disabling	Death
Pruritus or itching (<i>also consider rash or desquamation</i>)	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
Rash or desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Rash: acne or acneiform	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death

(Continued on next page)

Note. Based on information from National Cancer Institute, 2006.

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Dermatology and Skin Reactions (*Continued*)

ADVERSE EVENT	GRADE				
	1	2	3	4	5
Rash: dermatitis associated with chemoradiation or radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy, moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash, painful stomatitis); IV fluids, tube feedings, or total parenteral nutrition indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

Note. Based on information from National Cancer Institute, 2006.

tion of many novel agents. Randomized clinical trials to evaluate interventions for cutaneous toxicities have been initiated only recently.

The literature has reported recommendations related to dermatologic toxicities. Table 2 outlines a number of products being used in various settings to treat cutaneous toxicities. The cutaneous toxicity management strategies for xerosis, rash, papulopustular eruption, paronychia inflammation, hair changes, subungual splinter hemorrhages, and acral erythema will be discussed.

Xerosis

All of the classes of agents described herein have the potential to cause xerosis. Management should be directed at prophylactic and concurrent approaches. Emollient creams can be used from initiation of therapy to promote skin hydration and protection. A number of creams have been recommended in the literature, including Eucerin® (Beiersdorf Inc.), Cetaphil® (Galderma Laboratories), Aquaphor® (Beiersdorf Inc.), Bag Balm® (Dairy Association Co.), and Neutrogena Norwegian Formula® (Neutrogena Corporation) (Dick & Crawford, 2005; Perez-Soler et al., 2005; Robert et al., 2005). Agents that contain urea (e.g., Kerasal™ [Alterna LLC]) and those with 10% salicylic acid also have been suggested. Water-based facial cleansers such as Cetaphil, Neutrogena, Dove® (Unilever), and Ivory Skin Cleansing Liqui-Gel® (Procter and Gamble) also may be recommended. The products are available in different formulations, including lotions and creams. The longest duration of action typically is seen with more dense formulations.

Xerosis can lead to the development of cracks and fissures in the skin. Patients who develop painful fissures may be encouraged to try liquid cyanacrylate (Band-Aid® Liquid Bandage [Johnson & Johnson]) or flurandrenolone tape to

promote healing and increase comfort (Bauer, 2005; Shah et al., 2005).

Patients should be instructed to avoid lotions and creams that contain alcohol, perfumes, or dyes because they can increase dryness and lead to further skin irritation (Bauer, 2005; Dick & Crawford, 2005). Any cutaneous changes may increase sun sensitivity; therefore, patients should be advised to use sunscreen with a sun protection factor of 15 or more and avoid sun exposure when possible (Robert et al., 2005).

Macular

Treatment of rash should be based on the degree to which it interferes with patient function and quality of life. A macular rash that is nonpruritic and causes the patient no additional symptoms may not require treatment. If quality of life is affected because of



Figure 2. Simultaneous Xerosis and Rash

Note. Photo courtesy of Peg Esper. Used with permission.

Table 2. Agents Used to Treat Cutaneous Skin Toxicities

AGENT	MANUFACTURER	POTENTIAL USES	COMMENTS
Antibiotics, systemic	Various	Infected papulopustular eruptions	Minocycline, doxycycline, and tetracycline have been recommended.
Antibiotics, topical	Various	Infected papulopustular eruptions	Benzaclin (1% clindamycin with 5% benzoyl peroxide) or topical erythromycin
Antihistamines	Various	Pruritic rash	Diphenhydramine, hydroxyzine; can cause somnolence and dry mouth
Aquaphor®	Beiersdorf Inc.	Xerosis, acral erythema	—
Bactroban® Mupirocin Intranasal	GlaxoSmithKline	Infected papulopustular eruptions	Apply to each nostril daily.
Bag Balm®	Dairy Association Co.	Xerosis, acral erythema	—
Band-Aid® Liquid Bandage (cyanoacrylate)	Johnson & Johnson	Fissures in skin	Cultures may be indicated.
Blue Lizard®	Crown Laboratories	Ultraviolet A and B sunblock	Water resistant
Cetaphil®	Galderma Laboratories	Xerosis, acral erythema; facial cleanser	Water-based cleanser; use product specifically for desired effect (moisturizer versus skin cleanser)
Cordran Tape® (flurandrenolide)	Watson Pharmaceuticals	Fissures in skin	This topical steroid's potency is determined by dosage.
Corticosteroids	Various	Severe papulopustular eruptions	Use has been debated in the literature. Topical steroids may be used to decrease inflammation, but data are limited.
Dermablend®	Dermablend Corrective Cosmetics	Camouflaging makeup	No evidence suggests that use will aggravate rash.
Eucerin®	Beiersdorf Inc.	Xerosis, acral erythema	Use product specifically for desired effect (moisturizer versus skin cleanser).
Kerasal®	Alterna LLC	Xerosis, acral erythema	Salicylic acid 5% (beta hydroxy acid) and urea 10% (carbamide)
Neutrogena Norwegian Formula®	Neutrogena Corporation	Xerosis; facial cleanser	Use product specifically for desired effect (moisturizer versus skin cleanser).
Silver nitrate	Various	Severe granulomatous changes with paronychia	For reduction of exuberant granulations, apply ointment to affected area and cover with pad for five days.
10% salicylic acid	Various	Papulopustular eruptions	Observe for excessive drying.

the negative aesthetic effects of the rash, a camouflage makeup such as Dermablend® (Dermablend Corrective Cosmetics) can provide good results and has not been found to aggravate the rash in any way (Perez-Soler et al., 2005; Robert et al., 2005).

A rash that becomes pruritic can sometimes be managed with the use of an emollient cream. However, patients also may require oral antihistamines such as diphenhydramine or hydroxyzine (Dick & Crawford, 2005; Robert et al., 2005). Pruritic rashes sometimes respond to bath preparations such as Aveeno® Colloidal Oatmeal Bath (Johnson & Johnson), but patients should be cautioned regarding their use because bath preparations may increase drying of the skin. Cooler water temperatures provide greater relief.

Papulopustular Eruptions

Papulopustular eruptions are raised lesions that occur primarily on the face, neck, and upper torso (Harari, 2004), making them more distressing for patients. Skin lesions often occur in patients receiving EGFR inhibitors. A great deal of debate and uncertainty exist in the literature regarding treatment of papulopustular eruptions. More information has become available about the pathology of the lesions, emphasizing that they are not histologically consistent with acne vulgaris and, as such, should neither be described nor treated as an acneiform rash (Dick & Crawford, 2005; Herbst et al., 2003; Perez-Soler et al., 2005; Robert et al., 2005). Although the lesions typically are not

an infectious process, they have a propensity to cause secondary infections. Patients should be encouraged to regularly use water-based cleansers.

No data exist for prophylactic use of topical or systemic antibiotics. Infection is suspected if lesions begin to develop honey-crusted scabs or purulent drainage. Culturing lesions is appropriate; in addition, most infections have been associated with *Staphylococcus aureus* bacteria (Perez-Soler et al., 2005). If infection is suspected, topical antibiotics such as 1% clindamycin or benzoyl peroxide (Herbst et al., 2003; Warner & Plosker, 2002), erythromycin (Robert et al., 2005), or systemic antibiotics such as minocycline, doxycycline, and tetracycline have been recommended (Dick & Crawford, 2005; Perez-Soler et al., 2005; Shah et al., 2005). Intranasal mupirocin in each nostril daily has been suggested, but the use of retinoids was discouraged in most reports in the literature because the lesions are not related to true acne lesions and the drying induced by retinoids as well as single-agent benzoyl peroxide can make the lesions worse (Perez-Soler et al.).

The use of topical steroids is discussed with significant ambivalence in the literature. Concern exists over the possible interference with therapeutic effect of treatment as well as minimal data to suggest any real efficacy with topical steroids other than to decrease inflammation. However, systemic steroid use may be required in patients experiencing severe reactions (Dick & Crawford, 2005; Perez-Soler et al., 2005).

Immunomodulatory agents such as pimecrolimus and tacrolimus are discussed infrequently in the literature as possible treatments for papulopustular eruptions. They have FDA black box warnings for increased risk of skin cancer. As a result, they should be used only as part of a clinical trial.

Appropriate assessment for the physical and psychological sequelae of rash in patients is critical. Patients may require analgesics for painful pustules. Camouflage makeup can be beneficial at times, but the more severe grades of rash that occur on the face can be extremely distressing to patients from a psychological standpoint. Some may decide to discontinue treatment as a result. The psychological impact on patients should be evaluated and appropriate measures instituted based on identified need. Patients may require counseling, support, and, in some cases, interruption of medication to allow symptoms to subside. Patients must be warned of the potential for and possible severity of symptoms prior to starting therapy.

Paronychial Inflammation

Paronychial inflammation is typically not infectious in nature, but it is susceptible to secondary infection. Prevention appears to be the primary goal of treatment. Patients may be advised to obtain pedicures prior to starting treatment and should be instructed to avoid tight-fitting shoes as well as injury to the feet. If patients experience severe granulomatous changes, some researchers have suggested weekly applications of silver nitrate and/or antiseptic soaks as a potential treatment strategy (Dick & Crawford, 2005; Robert et al., 2005).

Hair Changes

A variety of unique hair changes may occur that appear to be agent dependent. Scalp hair growth may decrease, but facial

hair and eyelash growth may increase, requiring varying levels of emotional support to patients. Patients need to be educated regarding the potential for hair to become dry and brittle or curly and that frontal alopecia can occur with EGFR inhibitors. Some patients may wish to purchase a wig prior to treatment. Depilation treatment may be desired, particularly in women who experience increased facial hair growth. Careful trimming of lashes with trichomegaly should be discussed.

Imatinib and sunitinib can cause hair and skin pigment changes. Patients may experience loss of hair pigment while on treatment with sunitinib that typically reverses once therapy has been discontinued. Although no actual treatment exists for the changes, patients need to be aware of their potential. Conversely, repigmentation of hair has been reported with the use of imatinib (Robert et al., 2005). The use of hair dyes has not been reported in the literature.

Subungal Splinter Hemorrhages

Subungal splinter hemorrhages occur most frequently with the use of sunitinib and sorafenib. Treatment is based on whether patients experience pain. If the lesions are painful, analgesics should be provided (Robert et al., 2005).

Acral Erythema

The development of acral erythema and its associated hyperkeratosis or desquamation is more unique to patients receiving sunitinib and sorafenib. It should be differentiated from the palmar-plantar dysesthesias seen with a number of chemotherapeutic agents. The onset may be preceded with the development of paresthesias. Use of gel inserts in shoes may provide some relief from discomfort. Patients should be advised to wear loose-fitting shoes or slippers. Emollient and urea-based creams may provide comfort and softening of the lesions. The symptoms can become so severe that patients' ability to ambulate is affected. Analgesics are prescribed, and the appropriateness of an interruption in therapy must be discussed among healthcare providers (Robert et al., 2005).

Dermatology Referral

A dermatologist consult should be considered for patients with unique dermatologic presentations or those who are not responding to treatment. Patients on cancer therapy are at risk for many other dermatologic issues and may require more intensive evaluation and intervention.

Conclusion

Evidence-based research is needed regarding best practices for dermatologic side effects. Common clinical practices that develop in clinical trials provide a basis for further research. New molecularly targeted agents are being studied in clinical trials and will continue to be an important part of the anticancer armamentarium. Combination therapies with overlapping dermatologic toxicities further cloud symptom management. Adequate patient education regarding side effects and management is imperative. Research is needed to provide evidence for interventions to manage the dermatologic side effects being

observed with recently approved therapies. Oncology nurses play a key role in the research and patient education related to dermatologic toxicities and must understand the basis of the side effects as well as the level of evidence for management strategies.

The authors gratefully acknowledge Denise Lapka, RN, MSN, AOCN®, CCNS, for her extensive editing and contributions.

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References

- Albanell, J., Rojo, F., Averbuch, S., Feyereislova, A., Mascaro, J.M., Herbst, R., et al. (2002). Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: Histopathologic and molecular consequences of receptor inhibition. *Journal of Clinical Oncology*, 20, 110-124.
- Azagury, M., Pauwels, C., Kornfeld, S., Bataille, N., & Perie, G. (1996). Severe cutaneous reactions following interferon injections. *European Journal of Cancer*, 32, 1821.
- Bauer, C. (2005, Fall). Skin toxicities of EGFR inhibitors. *Oncology Nursing Society Metro Detroit Chapter Capsule*, 20, 1-4.
- Busam, K.J., Capodici, P., Motzer, R., Kiehn, T., Phelan, D., & Halpern, A.C. (2001). Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *British Journal of Dermatology*, 144, 1169-1176.
- Cnudde, F., Gharakhanian, S., Luboinski, J., Dry, J., & Rozenbaum, W. (1991). Cutaneous local necrosis following interferon injections. *International Journal of Dermatology*, 30, 147.
- Cohen, M.H., Johnson, J.R., & Pazdur, R. (2005). U.S. Food and Drug Administration drug approval summary: Conversion of imatinib mesylate (STI571; Gleevec) tablets from accelerated approval to full approval. *Clinical Cancer Research*, 11, 12-19.
- Cuaron, L., & Thompson, J. (2001). The interferons. In P.T. Rieger (Ed.), *Biotherapy: A comprehensive overview* (2nd ed., pp. 125-191). Sudbury, MA: Jones and Bartlett.
- Dick, S.E., & Crawford, G.H. (2005). Managing cutaneous side effects of epidermal growth factor receptor (HER1/EGFR) inhibitors. *Community Oncology*, 2, 492-496.
- Gale, D.M. (2005). Nursing implications of biotherapy and molecular targeted therapy. In J.K. Itano & K.N. Taoka (Eds.), *Core curriculum for oncology nursing* (4th ed., pp. 763-785). St. Louis, MO: Elsevier Saunders.
- Gallelli, L., Guadagnino, V., Caroleo, B., Marigliano, N., & De Sarro, D. (2004). Cutaneous ulceration induced by interferon alfa. *Annals of Pharmacotherapy*, 38, 173-174.
- Harari, P.M. (2004). Epidermal growth factor receptor inhibition strategies in oncology. *Endocrine-Related Cancer*, 11, 689-708.
- Harding, J., & Burtneess, B. (2005). Cetuximab: An epidermal growth factor receptor chemeric human-murine monoclonal antibody. *Drugs of Today*, 41(2), 107-127.
- Herbst, R.S., LoRusso, P.M., Purdom, M., & Ward, D. (2003). Dermatologic side effects associated with gefitinib therapy: Clinical experience and management. *Clinical Lung Cancer*, 4, 366-369.
- Huang, S.M., & Harari, P.M. (1999). Epidermal growth factor receptor inhibition in cancer therapy: Biology, rationale and preliminary clinical results. *Investigational New Drugs*, 17, 259-269.
- King, L.E., Jr., Gates, R.E., Stoscheck, C.M., Underwood, R.A., & Nanney, L.B. (1990). Epidermal growth factor/transforming growth factor alpha receptors and psoriasis. *Journal of Investigative Dermatology*, 95(Suppl. 5), 10S-12S.
- Lacouture, M.E. (2006). Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nature Reviews: Cancer*, 6, 803-812.
- Laux, I., Jain, A., Singh, S., & Agus, D.B. (2006). Epidermal growth factor receptor dimerization status determines skin toxicity to HER-kinase targeted therapies. *British Journal of Cancer*, 94, 85-92.
- Lenz, H.J. (2006). Anti-EGFR mechanism of action: Antitumor effect and underlying cause of adverse events. *Oncology*, 20(5, Suppl. 2), 5-13.
- Mavroukakis, S.A., Muehlbauer, P.M., White, R.L., & Schwartzentruber, D.J. (2001). Clinical pathways for managing patients receiving interleukin 2. *Clinical Journal of Oncology Nursing*, 5, 207-217.
- National Cancer Institute. (2006). *Common terminology criteria for adverse events*. Retrieved September 5, 2007, from <http://ctep.cancer.gov/forms/CTCAEv3.pdf>
- Perez-Soler, R., Delord, J.P., Halpern, A., Kelly, K., Krueger, J., Sureda, B.M., et al. (2005). HER1/EGFR inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist*, 10, 345-356.
- Perez-Soler, R., & Saltz, L. (2005). Cutaneous adverse effects with HER1/EGFR-targeted agents: Is there a silver lining? *Journal of Clinical Oncology*, 23, 5235-5246.
- Reynolds, N. (2004). Cetuximab: In the treatment of metastatic colorectal cancer. *Drugs*, 64, 109.
- Rhee, J., Oishi, K., Garey, J., & Kim, E. (2005). Management of rash and other toxicities in patients treated with epidermal growth factor receptor-targeted agents. *Clinical Colorectal Cancer*, 5(Suppl. 2), S101-S106.
- Robert, C., Soria, J.C., Spatz, A., Le Cesne, A., Malka, D., Pautier, P., et al. (2005). Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncology*, 6, 491-500.
- Roskoski, R., Jr. (2004). The ErbB/HER receptor protein-tyrosine kinases and cancer. *Biochemical and Biophysical Research Communications*, 319, 1-11.
- Rowinsky, E.K. (2004). The erbB family: Targets for therapeutic development against cancer and therapeutic strategies using monoclonal antibodies and tyrosine kinase inhibitors. *Annual Review of Medicine*, 55, 433-457.
- Schwartzentruber, D.J. (2000). Interleukin-2: Clinical applications: Principles of administration and management of side effects. In S.A. Rosenberg (Ed.), *Principles and practice of the biologic therapy of cancer* (3rd ed., pp. 32-50). Philadelphia: Lippincott Williams and Wilkins.
- Shah, N.T., Kris, M.G., Pao, W., Tyson, L.B., Pizzo, B.M., Heinemann, M.H., et al. (2005). Practical management of patients with non-small cell lung cancer treated with gefitinib. *Journal of Clinical Oncology*, 23, 165-174.
- Stafford-Fox, V., & Guindon, K.M. (2000). Cutaneous reactions associated with alpha interferon therapy. *Clinical Journal of Oncology Nursing*, 4, 164-168.
- Warner, G.T., & Plosker, G.L. (2002). Clindamycin/benzoyl peroxide gel: A review of its use in the management of acne. *American Journal of Clinical Dermatology*, 3, 349-360.

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