An Interdisciplinary Consensus on Managing Skin Reactions Associated With Human Epidermal Growth Factor Receptor Inhibitors

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The use of human epidermal growth factor receptor (HER1/EGFR) inhibitors, such as erlotinib, cetuximab, and panitumumab, often is accompanied by the development of a characteristic spectrum of skin toxicities. Although these toxicities rarely are life threatening, they can cause physical and emotional distress for patients and caregivers. As a result, practitioners often withdraw the drug, potentially depriving patients of a beneficial clinical outcome. These reactions do not necessarily require any alteration in HER1/EGFR-inhibitor treatment and often are best addressed through symptomatic treatment. Although the evidence for using such therapies is limited, an interdisciplinary HER1/EGFR-inhibitor dermatologic toxicity forum was held in October 2006 to discuss the underlying mechanisms of these toxicities and evaluate commonly used therapeutic interventions. The result was a proposal for a simple, three-tiered grading system for skin toxicities related to HER1/EGFR inhibitors to be used in therapeutic decision making and as a framework for building a stepwise approach to intervention.

At a Glance

- The use of human epidermal growth factor receptor (HER1/EGFR) inhibitors often is accompanied by the development of a characteristic class-specific spectrum of skin toxicities.
- Skin toxicities related to HER1/EGFR inhibitors do not necessarily require alteration in HER1/EGFR-inhibitor treatment and often are addressed best through symptomatic management.
- Evidence-based treatment recommendations for skin toxicities related to HER1/EGFR inhibitors are not available because no data from controlled clinical studies have been published.

Clinical Journal of Oncology Nursing • Volume 12, Number 2 • Managing Skin Reactions
emerged since the mid-1990s as a new strategy in the treatment of various malignancies. These targeted agents interact with specific molecules that are pivotal in tumor growth and development. Traditional “cytotoxic” chemotherapies not only kill tumor cells by affecting processes that commonly are overactive or enhanced in cancerous tissue but also may be important in affecting normal cells. Targeted agents can exert their influence by, among other things, inhibiting tumor-cell proliferation, inducing programmed cell death, inhibiting angiogenesis, and enhancing antimtumor immune responses (Hoang & Schiller, 2002). Common targets for these agents include growth factors such as the vascular endothelial growth factor (VEGF); intracellular signaling molecules, including cyclooxygenase-2 and the BCR-ABL tyrosine kinase; and cell-surface receptors (e.g., members of the HER family, which includes HER1/EGFR).

The HER1/EGFR is an attractive target for new biologic targeted agents because it has been implicated in the development of a range of tumor types (Greatens et al., 1998; Ohskai et al., 2000; Salomon, Brandt, Giardiello, & Normanno, 1995). Overexpression of the receptor also has been correlated with disease progression, poor prognosis, and a reduced sensitivity to chemotherapy (Cooke, Reeves, Lannigan, & Stanton, 2001; Nicholson, Gee, & Harper, 2001). Several HER1/EGFR inhibitors are in clinical development, and three (erlotinib, cetuximab, and panitumumab) have demonstrated efficacy in a range of tumor types (Greatens et al., 1998; Ohsaki et al., 2000).

Table 1. Spectrum of Dermatologic Reactions Associated With Human Epidermal Growth Factor Receptor–Targeted Therapies

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>DESCRIPTION</th>
<th>FREQUENCY (%)</th>
<th>TIME COURSE</th>
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<tr>
<td>Rash (follicular-pustular)</td>
<td>Monomorphous erythematous maculopapular, follicular, or pustular lesions, which may be associated with mild pruritus</td>
<td>60–80</td>
<td>Onset: one to three weeks of treatment; maximum: three to five weeks of treatment; resolution: within four weeks of treatment cessation but may wax and wane</td>
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<tr>
<td>Paronychia and fissuring</td>
<td>Painful periungual granulation-type or friable pyogenic granuloma-like changes associated with erythema, swelling and fissuring of lateral nailfolds, and/or distal finger tufts</td>
<td>6–25</td>
<td>Onset: after two to four months of treatment; resolution: persistent, several months after withdrawal</td>
</tr>
<tr>
<td>Hair changes</td>
<td>Curlier, finer, and more brittle hair on scalp and extremities; also extensive growth and curling of eyelashes and eyebrows</td>
<td>5–6</td>
<td>Variable onset: after 7–10 weeks to many months</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Diffuse fine scaling</td>
<td>4–35</td>
<td>Occurs after appearance of rash</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Flushing, urticaria, and anaphylaxis</td>
<td>2–3</td>
<td>Occurs on the first day of initial dosing</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Mild to moderate mucositis, stomatitis, aphthous ulcers</td>
<td>2–36</td>
<td>Onset during treatment, not related to dose or schedule; resolution without specific measures</td>
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Largely because of their specificity of action, biologic targeted agents often are considered to have a more favorable toxicity profile than traditional chemotherapy. This also is true for HER1/EGFR-targeted therapies, which generally are associated with fewer hematologic adverse events than chemotherapy. However, patients treated with HER1/EGFR-targeted therapies often do present with a unique group of skin reactions (Rhee et al., 2005), which occur in more than 50% of patients receiving these treatments (Segaert & Van Cutsem, 2005).

Clinical trials with HER1/EGFR-targeted inhibitors have revealed a spectrum of skin toxicities of varying severity (see Table 1 and Figure 1). The most commonly reported reactions are mild-to-moderate skin rashes that occur most frequently on the face and upper trunk. Other common dermatologic reactions include xerosis (dry skin), pruritus, nail changes...
(usually manifested as paronychia), and hair changes (usually manifested as mild hair loss) (Lacouture, 2006; Segaert & Van Cutsem, 2005). These adverse events are observed during treatment with all HER1/EGFR-targeted agents, MAbs, and TKIs, and their etiology suggests that such skin toxicities are a class effect of HER1/EGFR-targeted therapies. However, differences may exist in the incidence and manifestation of these events with different treatments.

The papulopustular rash generally develops along a characteristic course. Within the first week, patients experience a sensory disturbance on the face with erythema and edema, followed by a papulopustular eruption (in weeks 1–3). In week 4, a crusting of the rash develops. Provided that the rash is treated successfully, patients may continue to experience erythema and dry skin in the areas previously affected by the papulopustular eruption.

Incidence

Directly comparing the incidence of skin toxicities (and, in particular, rash) for different agents is challenging. Descriptive terms often differ in gradation schemes between trials, and in some instances skin toxicities are recorded as a single event (e.g., dermatitis), whereas in others, they may be broken down into separate categories (e.g., rash, acne, dry skin).

Severity

The severity of rash also appears to vary between agents. In general, rash associated with the use of anti-HER1/EGFR MAbs tends to be more severe than that observed with TKIs, presenting as a more purulent and pustular reaction, which may require more aggressive interventions (Sipples, 2006).

The different modes of administration for these agents might be one reason: TKIs (e.g., erlotinib, gefitinib) are administered orally on a daily basis, whereas MAbs (e.g., cetuximab, panitumumab) are given intravenously once a week or every two weeks. The pharmacokinetic properties of these agents are therefore different, with potentially greater differences in peak and trough concentrations for MAbs than for TKIs. This may explain the differing incidence and manifestation of rash observed with these agents, particularly because preclinical data support a correlation between the appearance of rash and concentration for these agents (Bruno, Mass, Jones, Lu, & Winer, 2003).

Some evidence suggests that the appearance of skin rash may be useful as a marker of efficacy for HER1/EGFR-targeted agents. Several studies with erlotinib have demonstrated a relationship between severity of skin reaction and treatment efficacy. Phase II studies in NSCLC, head and neck cancer, and ovarian cancer suggest that survival rates are significantly increased in patients with skin reactions, compared to those without (Clark, Perez-Soler, Siu, Gordon, & Santabarbara, 2003; Perez-Soler et al., 2004). This observation was repeated in the pivotal phase III trial of erlotinib monotherapy for NSCLC, in which the patients who developed a rash (75%) survived significantly longer than those who did not: 8.5 months for patients with grade 1 rash and 19.6 months for patients with grade 2 or 3 rash versus 1.5 months for patients who did not develop any rash (p < 0.0001) (Perez-Soler, 2006). Overall, these observations support the consensus that patients who develop rash should be treated for the reaction while being maintained on anti-HER1/EGFR therapy; those patients may obtain the greatest benefit from the drugs.

Pathobiology of Skin Reactions Associated With Human Epidermal Growth Factor Receptor Inhibitors

Although the pathobiology of HER1/EGFR-targeted inhibitor-associated skin reactions is not understood fully, drug-induced inhibition of the HER1/EGFR is believed to affect keratinocyte proliferation, differentiation, migration, and attachment (Jost, Kari, & Rodeck, 2000; Woodworth et al., 2005). HER1/EGFR is expressed in epidermal keratinocytes, sebaceous and eccrine glands, and the epithelium of the hair follicle (Nanney, Stoscheck, King, Underwood, & Holbrook, 1990). Such expression is particularly high in proliferating and undifferentiated keratinocytes, which commonly are found in the basal and suprabasal layers of the epidermis, and in the outer root sheath of the hair follicle (Fox, 2006). Inhibition of the HER1/EGFR signaling pathway is believed to play a critical role in inflammatory cell recruitment and subsequent cutaneous injury, which can lead to the development of dry skin, papulopustules, and periungual inflammation (Lacouture, 2006). The potential effects of HER1/EGFR inhibition in the skin are illustrated in Figure 2.
Guidelines for the Treatment of Skin Reactions Associated With Human Epidermal Growth Factor Inhibitors

As yet, no data from controlled clinical studies investigating treatment options for HER1/EGFR-targeted inhibitor-associated skin reactions have been published; therefore, no peer-reviewed, evidence-based treatment recommendations are available. To date, proposed treatments are based mostly on qualitative rather than quantitative evidence (Lacouture, Basti, Patel, & Benson, 2006; Rhee et al., 2005). However, patients still require treatment and advice for skin reactions, and in the absence of suitable clinical data, best practice offers the best treatment advice.

The aim of the forum in Chicago was to bring a number of experts together in an attempt to amalgamate their interdisciplinary knowledge (published or otherwise) as well as to distill the common practices employed by their institutions into a consensus approach for the treatment of dermatologic adverse events associated with HER1/EGFR-targeted inhibitor therapy. Discussion at the forum focused primarily on the clinical management of cutaneous toxicities; however, the experts also advocated a proactive approach for patients that could minimize the occurrence and severity of toxicities.

Practical Guidelines for Patients

Two key patient education recommendations were made at the forum: Patients should regularly use a thick, alcohol-free emollient for dry skin (alcohol can dry the skin). A number of recommended emollients are listed in Table 2. Application of high-sun protection factor (≥15) physical sunscreen (i.e., containing zinc oxide or titanium dioxide) each morning and prior to sun exposure is recommended for all patients receiving HER1/EGFR-targeted agents.

Based on the existing literature, a range of other practical guidelines also might be considered to help prevent rash and other cutaneous toxicities, which include the following (Herbst, Fox, Viele, & Messner, 2006; O’Keeffe, Parrilli, & Lacouture, 2006; People Living With Cancer, 2006).

- Patients should take care to remain hydrated.
- Patients should ensure that they apply an adequate amount of sunscreen: more than half a teaspoon of sunscreen to each arm, the face, and neck, and a little more than one teaspoon to the chest and abdomen, back, and each leg. The use of a broad-brimmed hat also is advised if going outside.
- Patients should avoid long, hot showers. Instead, patients should use lukewarm water and mild (preferably scent-free) soap, ensuring that genital, rectal, and skin-fold areas are cleaned thoroughly. A moisturizer should be applied within 15 minutes of showering or bathing (to prevent skin drying).
- Patients should avoid laundry detergent with strong perfumes and use only hypoallergenic makeup.
- The use of saline nasal spray followed by petroleum jelly may reduce risk of nosebleeds.
- Patients should use personal lubricant for intercourse.
- To prevent nail problems, patients should keep finger and toenails clean and trimmed; avoid biting of nails, pushing back cuticles, tearing the skin around the nail bed, or applying artificial nails; and avoid tight-fitting shoes. Patients also are advised to
Table 2. Recommended Agents for Dry Skin, Itching, and Sun Exposure

<table>
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<tr>
<th>CONDITION</th>
<th>RECOMMENDED AGENTS</th>
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<tr>
<td>Dry skin</td>
<td>Emollients • Vanicream® (Pharmaceutical Specialties, Inc.), Eucerin® (Beiersdorf AG), Aquaphor® (Beiersdorf AG), Aveeno® (Johnson &amp; Johnson Consumer Companies, Inc.), and Cutemol® (Summers Laboratories Inc.) as needed</td>
</tr>
<tr>
<td>Exfoliants (for scaly areas)</td>
<td>• Ammonium lactate12% (Am-Lactin®, Upsher-Smith Laboratories, Inc.) for body • Urea 20%-40% cream for palms, soles, and fissures</td>
</tr>
<tr>
<td>Itching</td>
<td>Topical agents • Body: Sarna Ultra® (PharmaDerm) cream and Regenecare® (MPM Medical, Inc.) gel as needed • Scalp: Fluocinonide 0.05% shampoo or clobetasol foam daily</td>
</tr>
<tr>
<td>Sun exposure</td>
<td>Oral agents • Antihistamines (diphenhydramine 25–50 mg twice daily and/or cetirizine 10–20 mg per day) • Pregabalin (Lyrica®, Pfizer) 75–100 mg twice daily • Any broad-spectrum sunscreen containing zinc oxide or titanium dioxide</td>
</tr>
</tbody>
</table>

wear gloves when washing dishes or using chemical cleaning agents. Hands and feet should be moisturized frequently; petroleum jelly is particularly effective and should be applied to the skin around the nails periodically throughout the day. At night, applying a thick coat to hands and feet and covering with white cotton gloves and socks may be helpful.

• If a patient develops trichomegaly (i.e., excessive eyelash growth) or eye complaints, the eyelashes should be trimmed and the patient should have an ophthalmologic consultation. Most importantly, patients should be educated to call a healthcare professional as soon as they develop any symptoms of cutaneous toxicity. Early intervention is critical in the clinical management of these events, so an early (< 14 days from EGFR-inhibitor therapy onset) follow-up is advisable.

**Clinical Management**

The treatment algorithm presented in Figure 3 represents the key output from the forum. The effective treatment of skin rashes associated with HER1/EGFR-targeted inhibitors depends largely on accurate grading of skin reactions to allow for appropriate intervention. The National Cancer Institute (2006) Common Toxicity Criteria (NCI-CTC) is used most commonly to grade adverse events in clinical trials with HER1/EGFR-targeted agents (see Table 3); it is designed, primarily, as a surveillance tool and is of limited use as an aid to selecting intervention. Although certain categories are relevant to events associated with HER1/EGFR inhibitors, including rash and desquamation, they often are not sufficiently specific. For example, within the NCI-CTC, rash severity is based on body surface area coverage; this can be misleading because rash associated with HER1/EGFR inhibitors generally are confined to the face and upper trunk. For the purposes of therapeutic decision making, forum attendees felt that a simple, more specific grading system would be the most appropriate rash associated with HER1/EGFR-targeted inhibitors. Thus, classifying skin reactions as mild, moderate, or severe was believed to be the most effective system for assigning therapeutic intervention.

The following is a stepwise approach to intervention, employing the suggested three-tiered grading system developed by the consensus group.

**Mild Skin Toxicity**

Mild skin toxicity (papulopustular rash) is defined as generally localized, minimally symptomatic, with no sign of superinfection, and no impact on daily activities. Some attendees suggested that, in many instances, no intervention was necessary, whereas others felt that intervention of either topical hydrocortisone (1% or 2.5% cream) or clindamycin (1% gel) would be beneficial. Dose reduction of the HER1/EGFR-targeted agent was not recommended.

**Moderate Skin Toxicity**

Moderate rash is defined as papulopustules with mild pruritus or tenderness, with minimal impact on activities of daily living and no signs of superinfection. The suggested therapeutic intervention is hydrocortisone (2.5% cream), clindamycin (1% gel), or pimecrolimus (Elidel®, Novartis) (1% cream), with the addition of doxycycline (100 mg PO BID) or minocycline (100 mg PO BID) (Micantonio et al., 2005; Molinari, De Quatrebarbes, Andre, & Aractingi, 2005; Sapadin & Fleischmajer, 2006). Dose reduction of the HER1/EGFR-targeted agent was not recommended.

**Severe Skin Toxicity**

Severe skin toxicity is defined as a rash that may be generalized and accompanied by severe pruritus or tenderness; this level of toxicity has a significant impact on activities of daily living and has the potential for superinfection. The dose of the HER1/EGFR inhibitor should be reduced (according to the principal investigator). The skin toxicity should be treated the same as for moderate rash but with the addition of a methylprednisolone dose pack. In the event that severe rash symptoms fail to respond to the above-mentioned interventions, interruption of the HER1/EGFR-targeted therapy is recommended. However, treatment may resume (most likely at a lower dose) once skin reactions have diminished in severity at a recommended follow-up of two weeks.

The use of pimecrolimus or tacrolimus (Protopic®, Astellas Pharma, Inc.) for HER1/EGFR-associated skin reactions is being investigated at a number of institutions; however, it is an immunosuppressant, which should be taken into account when considering treatment options (Novartis, 2006). Although a causal relationship has not been established, rare cases of skin malignancies and lymphoma have been observed in patients treated with calcineurin inhibitors, such as pimecrolimus (Novartis). Such incidences most likely are associated with long-term usage; pimecrolimus is not recommended, however, in immunosuppressed patients (Novartis). As a result, great care should be taken when considering its use in patients with cancer.

**Conclusion**

The skin toxicities associated with HER1/EGFR-targeted inhibitors can cause patients physical and psychological symp-
toms, particularly given that rash characteristically occurs on exposed areas such as the face. Although the concerns of patients (and caregivers) must be addressed sympathetically, in most cases, these adverse events can be managed without the need for dose modification or interruption to the HER1/EGFR-inhibitor regimen. Moreover, in refractory cases, the suspension of HER1/EGFR inhibitor therapy is temporary, allowing for appropriate intervention and diminution of skin-toxicity severity.

The algorithm suggested by the consensus group and presented in this article represents current best practice for the treatment of rash associated with HER1/EGFR inhibitors. Controlled studies remain necessary to fully evaluate the efficacy of the strategies presented in the algorithm, but this approach hopefully will be a useful guide for nurses and other healthcare professionals, ensuring that patients receive the maximum possible clinical benefits from the continued and uninterrupted use of the HER1/EGFR inhibitors.
### Table 3. Classification of Dermatologic Toxicities Associated With Human Epidermal Growth Factor Receptor Inhibitors

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>GRADE</th>
</tr>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Nail changes</td>
<td>Discoloration, ridging, pitting</td>
</tr>
<tr>
<td>Pruritus/itching</td>
<td>Mild or localized</td>
</tr>
<tr>
<td>Rash/ desquamation</td>
<td>Macular or papular eruption or erythema without associated symptoms</td>
</tr>
<tr>
<td>Rash: acne/ acneform</td>
<td>Intervention not indicated</td>
</tr>
<tr>
<td>Dermatology/ skin—other</td>
<td>Mild</td>
</tr>
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ADL—activities of daily living; BSA—body surface area  

The authors gratefully acknowledge the participants of the October 2006 interdisciplinary forum: Jean Pierre DeLord, Jody Gary, Giuseppe Giaccone, Patricia LoRusso, Thomas J. Lynch, Barbara Melosky, Martin Reck, Roman Perez-Soler, Jennifer Temel, and Dennis P. West. The authors also acknowledge third-party medical writing support from Gardiner Caldwell US, funded by Genentech, Inc., OSI Pharmaceuticals, Inc., and F Hoffmann-La Roche Ltd.

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### References


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