

# Clinical Approaches to Minimize Rash Associated With EGFR Inhibitors

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**Purpose/Objectives:** To present a systematic approach for managing the skin rash associated with epidermal growth factor receptor (EGFR)-targeted therapies.

**Data Sources:** Clinical research literature, published abstracts, and clinical experience. The approach presented in this article is based on a combination of clinical experience and consultations with dermatologists, oncologists, and pharmacists familiar with EGFR inhibitor-associated rash.

**Data Synthesis:** A proactive approach that includes patient education and the use of a grade-based treatment algorithm. The goal of the approach is to minimize the effects of the rash on patients' quality of life and the course of cancer treatment.

**Conclusions:** Using the approach described in this article to treat the rash associated with the use of EGFR inhibitors, nurses can lessen patient discomfort and help ensure that patients will continue cancer treatment for as long as necessary.

**Implications for Nursing:** The approach described in this article should help nurses to recognize, grade, and treat the skin rash associated with EGFR inhibitors.

## Key Points . . .

- ▶ The clinical use of epidermal growth factor receptor (EGFR) inhibitors will continue to grow as more indications are approved, additional agents enter clinical trials, and new combinations of agents are studied.
- ▶ One of the most common adverse events associated with EGFR inhibitors is a skin rash that, although usually mild to moderate in severity, can negatively affect patients' quality of life and interfere with cancer treatment.
- ▶ The grading of rash can be subjective. Clinicians and patients should collaborate to determine how to treat rashes.
- ▶ Although no evidence-based treatment guidelines have been established for the treatment of the skin rash, this adverse event is manageable using the approach outlined in this article.

Clinical oncology recently has shifted from the use of traditional cytotoxic chemotherapeutic agents that target rapidly dividing cells to the use of therapies that target proteins implicated in the development and progression of cancer. Those proteins include Bcr-Abl fusion protein found in patients with chronic myelogenous leukemia, the vascular endothelial growth factor involved in the development of several solid tumors, and the epidermal growth factor receptor (EGFR) implicated in the development and progression of many different cancers. In contrast to chemotherapeutic agents, which can cause anemia, neutropenia, severe nausea and vomiting, neuropathy, and total alopecia, targeted therapies generally are well tolerated and have less severe systemic adverse events (Herbst & Bunn, 2003; Silvestri & Rivera, 2005).

Targeted agents are not, however, without adverse events. Agents targeted against EGFR have a distinct toxicity profile that includes diarrhea and various cutaneous toxicities, the most common of which is a rash that often is accompanied by dryness and pruritus. Although usually mild to moderate in severity, skin rash can have a significant negative effect on patients' quality of life. In addition to dryness and itching, which can be very uncomfortable, people often are self-conscious about the rash, which is frequently in highly visible areas such as the face, neck, and chest.

This article will focus on effective management of EGFR inhibitor-related adverse events, specifically rash, with an em-

phasis on maintaining patients' quality of life during treatment and limiting the effect of rash on the course of cancer treatment so that patients remain on it for as long as necessary.

## EGFR as a Target for Cancer Therapy

EGFR, also known as human epidermal receptor (HER) 1, is a member of the HER family of receptor tyrosine kinases, which also includes HER2, HER3, and HER4 receptors (Yarden, 2001). After binding their respective ligands (extracellular proteins that specifically bind to them), the receptors pair with each other as homodimers (e.g., EGFR-EGFR) or heterodimers (e.g., EGFR-HER2) and initiate a cascade of signals that direct a cell's growth, proliferation, response to other signals, and ability to move within tissue (Yarden & Sliwkowski, 2001). Consequently, the HER family receptor tyrosine kinases play important roles in the regulation of growth and differentiation in normal and neoplastic

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Digital Object Identifier: 10.1188/08.ONF.103-111

cells (Hynes & Lane, 2005; Rowinsky, 2004; Yarden & Sliwkowski) and have been implicated in the development and progression of many different cancers, including solid tumors of the head and neck, lung, prostate, breast, pancreas, ovary, colon, rectum, and brain (glioblastoma) (Gross, Shazer, & Agus, 2004; Grunwald & Hidalgo, 2003).

Preclinical studies have demonstrated that in malignant cells, EGFR often signals aberrantly (Mendelsohn & Baselga, 2006). For example, EGFR may be more active than usual, which could lead to an increase in signals that instruct cells to divide or could interfere with other signals that would normally instruct cells to die. A variety of mechanisms may contribute to this, including receptor overexpression (when more receptors are on the surface of the cell than usual), the presence of activating mutations (which allow the receptor to transmit signals without binding a ligand), and increased ligand expression (which leads to increased receptor signaling) (Grunwald & Hidalgo, 2003). Those changes promote tumorigenesis and enhance metastatic potential by increasing the rate at which cells divide and their ability to survive, enhancing cell migration, and decreasing cellular adhesion (which is one factor that allows cells to break away from the primary tumor and form a metastasis) (Kalyankrishna & Grandis, 2006; Mendelsohn & Baselga).

Evidence for a direct role of EGFR in tumorigenesis came from studies in which EGFR mutations were found to be more abundant in lung cancer tumors than in normal lung tissue, and in which high EGFR expression was correlated with advanced tumor stage, resistance to therapy (chemotherapy and radiation), and poor patient prognosis (Hirsch et al., 2003; Meert et al., 2002; Nicholson, Gee, & Harper, 2001). These findings provided the rationale to develop EGFR-targeted agents to treat cancer (Chan, Gullick, & Hill, 2006; Grunwald & Hidalgo, 2003; Mendelsohn & Baselga, 2006).

## EGFR Inhibitors

Since the 1990s, several EGFR-targeted inhibitors have been developed for treating cancer (see Table 1). Those inhibitors fall into two main classes (Baselga & Arteaga, 2005; Hynes & Lane, 2005; Mendelsohn & Baselga, 2006). The first class consists of orally available, small-molecule tyrosine kinase inhibitors (TKIs) that include reversible TKIs, irreversible TKIs, and combination TKIs that also affect other kinases. By interfering with the ability of adenosine triphosphate to bind to EGFR, TKIs inhibit autophosphorylation of the receptor and prevent the subsequent downstream intracellular signaling that is required for oncogenic transformation and tumor progression (Yarden & Sliwkowski, 2001). The second class of EGFR-targeted inhibitors is monoclonal antibodies directed against the extracellular domain of EGFR. Those agents block ligand binding and interfere with receptor activation (Mendelsohn & Baselga).

The therapeutic effectiveness of EGFR-targeted agents has been demonstrated in several cancers, including non-small cell lung cancer (NSCLC) (Agelaki & Georgoulis, 2005; Shepherd et al., 2005), head and neck cancer (Kalyankrishna & Grandis, 2006), pancreatic cancer (Moore et al., 2007), and metastatic colorectal cancer (Berlin et al., 2006; Foon et al., 2004; Malik et al., 2005). Evidence for clinical efficacy of those agents currently is being amassed for renal cell and ovarian cancer (Mendelsohn & Baselga, 2006).

**Table 1. EGFR Inhibitors Approved by the U.S. Food and Drug Administration or Currently in Development**

Small-Molecule Tyrosine Kinase Inhibitors	Target(s)
<b>Reversible</b>	
Erlotinib	EGFR
Gefitinib	EGFR
Lapatinib	EGFR, HER2
<b>Irreversible</b>	
Canertinib (CI-1033)	EGFR, HER2, HER3, HER4
EKB-569	EGFR, HER2, HER4
HKI272	EGFR, HER2
<b>Combination</b>	
ZD6474	EGFR, VEGFR2
AEE788	EGFR, HER2, VEGFR2
Monoclonal Antibodies	Target(s)
Cetuximab	EGFR
Panitumumab	EGFR
Matuzumab (EMD72000)	EGFR
MDX214	EGFR
h-R3	EGFR

EGFR—epidermal growth factor receptor; HER—human epidermal receptor; VEGFR2—vascular endothelial growth factor receptor 2

*Note.* Based on information from Dancey & Chen, 2006; Mendelsohn & Baselga, 2006.

In the TKI class, the three drugs currently approved are erlotinib (Tarceva<sup>®</sup>, Genentech), gefitinib (Iressa<sup>®</sup>, AstraZeneca), and lapatinib (Tykerb<sup>®</sup>, GlaxoSmithKline). In the monoclonal antibody class, the two currently approved drugs are cetuximab (Erbix<sup>®</sup>, ImClone Systems Inc.) and panitumumab (Vectibix<sup>®</sup>, Amgen). Many other therapeutic strategies that combine EGFR inhibitors with chemotherapeutics or with other targeted agents also are being investigated (Adjei, 2006; Dancy & Chen, 2006; Zhou et al., 2006). Consequently, adverse events resulting from treatment with anti-EGFR drugs likely will be seen with increasing frequency in the clinic.

## EGFR Inhibitor–Associated Rash

The skin rash that has been observed as a side effect of every anti-EGFR agent tested to date (Busam et al., 2001) usually is mild to moderate in severity (Cunningham et al., 2004; Herbst et al., 2005; Perez-Soler & Saltz, 2005; Shepherd et al., 2005). The skin is disproportionately affected by EGFR inhibitors and probably is caused, at least in part, because EGFR, as a receptor for epidermal growth factor, is involved with the normal development and function of skin (Jost, Kari, & Rodeck, 2000). In addition, EGFR-EGFR homodimers, one of the dimer pairs in which EGFR is found, are particularly abundant in normal skin (Laux, Jain, Singh, & Agus, 2006).

The incidence and severity of rash reported in studies of EGFR inhibitors are shown in Table 2. Incidence of rash ranges from 37% with gefitinib to 80%–90% for cetuximab and panitumumab. Severe (grade 3–4) rash is uncommon, especially when oral TKIs are used. Cetuximab has the highest reported rate of grade 3 and 4 rash combined at 18%, with less than 5% grade 4 rash. In 14 studies of cetuximab

reviewed by Perez-Soler and Saltz (2005), one patient of 2,963 reported grade 4 rash. The only case of grade 4 rash the author observed in clinical practice was in a patient who was immunocompromised as a result of prior chemotherapies.

The skin rash associated with EGFR inhibitors is referred to in the literature as acneform eruption, follicular acneform eruption, folliculitis, papulopustular rash, acneform rash, macropapular rash, or maculopustular rash (Albanell et al., 2002; Dick & Crawford, 2005; Herbst, LoRusso, Purdom, & Ward, 2003; Jacot et al., 2004; Robert et al., 2005; Segart & Van Cutsem, 2005). Despite the frequent use of the term “acneform,” which stems from the superficial resemblance of the rash to acne, the rash is not acne (Perez-Soler & Saltz, 2005). Detailed analysis has revealed that the hallmarks of acne—comedones (blackheads and whiteheads) (Segart & Van Cutsem; Shah et al., 2005), sebaceous gland involvement (Van Doorn, Kirtschig, Scheffer, Stoof, & Giaccone, 2002), a distinct histology (Perez-Soler & Saltz), and the presence of distinct bacteria (Van Doorn et al.)—typically are not observed. To help prevent patients from trying common treatments for acne (e.g., benzoyl peroxide) to treat the rash, which exacerbates it, healthcare professionals are advised not to use the words “acne” or “acneform” when discussing the rash.

As the terms “papulopustular,” “macropapular,” and “maculopustular” suggest, the rash may be composed of more than one type of lesion. Most frequently, the rash begins as reddish, macular lesions. It also can begin as a mixed maculopapular rash, with some lesions flat and others raised or present with some pustular lesions. As the rash progresses over the course of treatment, it can take any or all of these forms.

Generally, the rash develops one to two weeks after treatment with an EGFR inhibitor (Albanell et al., 2002; Hidalgo et al., 2001). In the NSCLC erlotinib pivotal trial, the median time of rash onset was eight days (Shepherd et al., 2005). In another study, 93% of patients developed a rash within 30 days of initiating treatment with erlotinib (Johnson et al., 2005). In the author’s clinical experience, patients receiving erlotinib and cetuximab develop the rash most frequently during the

first week of treatment. Reports have demonstrated that after treatment with panitumumab, a rash usually appears within the first one to three weeks (Saif & Cohenuram, 2006).

The face usually is the first area affected by the rash, often starting out faintly and intensifying over time. The rash spreads most frequently to the chest and back, where it generally assumes a V-shaped pattern (see Figure 1). In most patients, the rash is confined to the face, chest, and upper back (Perez-Soler, 2003), but it also has been observed to progress toward the extremities (Hidalgo et al., 2001). The rash rarely has extended below the chest in the author’s clinical experience, and the buttocks, limbs, and scalp are less frequently affected than the face and upper trunk.

The rash may be accompanied by xerosis (dry skin) (Roe et al., 2006; Segart & Van Cutsem, 2005) that can become severe in some patients (Dick & Crawford, 2005). In one study, almost 100% of patients were reported to have xerosis (Herbst et al., 2003). Variability in the reported incidence of xerosis likely reflects differences in the way clinicians score events. The author has found that although many patients have some degree of skin dryness during treatment with EGFR inhibitors, some patients experience more discomfort from skin dryness than others. The rash also may be accompanied by pruritus (Van Doorn et al., 2002), but not all patients experience pruritus and it does not necessarily correlate with rash severity.

The rash may remain stable over time or periodically worsen. In one phase II monotherapy trial of panitumumab, no worsening of the rash was observed (Saif & Cohenuram, 2006). However, in certain patients treated with erlotinib and cetuximab, the author has seen an apparently stable rash suddenly worsen.

The rash usually resolves completely within two to three weeks of discontinuing treatment (Herbst et al., 2003). The only lasting effect is a residual hyperpigmentation that has been observed in some patients (Hidalgo et al., 2001). In the author’s clinical practice, less than 10% of patients experience scarring (i.e., hyperpigmentation) and those who do scar tend to be patients with darker skin. In the author’s experience,

**Table 2. Incidence and Severity of Rash**

Drug	Incidence of Rash (%)		Patients on Drug	Study
	All Grades	Grade 3 or 4		
Cetuximab	86	18	57	Saltz et al., 2004
Cetuximab	87	17	211	Bonner et al., 2006
Erlotinib	76	9	485	Shepherd et al., 2005
Erlotinib	72	–	282	Moore et al., 2007
Gefitinib <sup>a</sup>				
250 mg	60	4	342	Herbst et al., 2004
500 mg	74	12	342	
Gefitinib	37	2	1,126	Thatcher et al., 2005
Lapatinib	44	–	208 <sup>b</sup>	Ravaud et al., 2006
Panitumumab	80	3	148	Malik et al., 2005
Panitumumab <sup>c</sup>	90	–	231	Peeters et al., 2006

<sup>a</sup> In combination with paclitaxel and carboplatin

<sup>b</sup> This is an estimate; 417 patients were randomized, but patients receiving lapatinib were not indicated.

<sup>c</sup> In addition to best supportive care (excluding antineoplastic therapy)

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*Note.* This patient has macular and papulopustular lesions on her face and upper torso that were grade 3 on day 7 of the epidermal growth factor receptor inhibitor. She was already on hydrocortisone cream 2.5% and clindamycin gel from day 5 when the rash started. On day 7, a medrol dose pack and doxycycline were added for seven days. In addition, she had a break from the treatment for a week. These measures downgraded the rash to grade 1, and the patient did not have to discontinue treatment. After she was restarted on the treatment, the dose was reduced and she tolerated the treatment well with grade 1 rash until the disease progressed a few months later.



*Note.* This patient has grade 3 macular and papulopustular lesions on his chest. He was on erlotinib 150 mg daily. After four days, the patient developed grade 3 rash. Hydrocortisone 1% was applied and 100 mg of doxycycline was administered by mouth twice daily for seven days; the rash downgraded to grade 1. No dosage modification of erlotinib was required. Subsequently, the rash was grade 2 or 3 on erlotinib until disease progression. When the rash worsened, topical hydrocortisone cream and oral doxycycline were rechallenged with success.

### **Figure 1. Grade 3 Papulopustular Rash in Patients Treated With Erlotinib for Non-Small Cell Lung Cancer**

although occasionally patients with grade 3 rash have some mild residual scarring, the rash usually resolves without any residual marks.

## **Management of EGFR Inhibitor–Associated Rash**

At present, evidence-based guidelines for the routine management of the skin rash caused by EGFR inhibitors do not exist (ArcMesa Educators, 2006; Herbst et al., 2003; Perez-Soler et al., 2005; Rhee, Oishi, Garey, & Kim, 2005; Segafort et al., 2005). Although the rash currently cannot be eliminated

completely or prevented, the author has found that the rash usually is manageable and has never had a patient discontinue therapy because of rash. Continuing therapy is especially important because the primary goal in treating rash is to prevent it from interfering with cancer treatment and to minimize its effect on patients' quality of life.

The author's approach to rash treatment is based on clinical experience and the recommendations of dermatologists, oncologists, and pharmacists familiar with EGFR inhibitor–associated rash. The approach consists of two key components: patient education and a grade-based treatment algorithm (see Figure 2 and Table 3). Patient education is provided at the start of treatment, usually at the time patients receive their first prescription (for oral agents) or their first infusion (for antibody therapies) of the EGFR inhibitor. Patients receive written information about the drug they will be receiving and have a consultation with nurses and pharmacists to discuss dosing, general treatment guidelines, and the treatment of adverse events. Patients are instructed to call the office for guidance whenever they have symptoms or adverse events. To facilitate treatment, patients are given prescriptions for clindamycin gel, a common topical antibiotic that has anti-inflammatory properties, to treat pustular rash and a prescription for hydrocortisone cream for macular rash. Patients are instructed to begin using medications at the first sign of rash.

At the first sign of rash, the treatment algorithm described in Table 3 is initiated. Using one of the currently available grading systems for skin rashes (see Table 4), the clinician determines the grade of the rash and extent of the symptoms. In general, grade 1 rash is asymptomatic (i.e., no discomfort), consisting of either macular or papular rash but few or no pustules. Grade 2 rash is characterized by pruritus and general discomfort. Grade 3 rash is characterized by general worsening of symptoms and early desquamation or ulceration. Grade 4 rash involves further worsening of grade 3 symptoms, particularly ulceration and exfoliation.

Although the grading systems refer to macular, papular, and vesicular (pustular) forms, rash may present in various combinations, including maculopapular, papulopustular, maculopustular, or maculopapulopustular. Such combinations generally mean a grade 2 or 3 rash. The author has found maculopapular rash to be most common. The treatment algorithm should not be considered a firm set of rules but rather a general guideline. Selection of a grade can be somewhat subjective, especially when it involves assessing levels of discomfort. The author is aware of many cases when objective criteria designated a patient's rash as one grade and subjective criteria designated it another. For example, in a clinic in southeastern Texas, one patient had grade 2 rash by objective measures. However, because pruritus and dry skin were extremely uncomfortable, the rash was upgraded to grade 3. Whenever objective measures do not adequately reflect patients' perceptions, clinicians should make treatment decisions together with patients.

Because patients in the clinic have been educated about the potential for rash, most are compliant and cooperative with a proactive management approach and develop only a grade 1 or 2 rash. For grade 1 rash, topical hydrocortisone (1%) is prescribed. Patients are given verbal and written instruction on how to use the hydrocortisone cream as well as education on the grading system of rash. The amount of cream patients should use is not specified and depends on the area of skin being treated. Patients with a rash that exhibits some pustular

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### Basic Principles of Treatment

- **Be proactive.** When treatment is initiated, give patients written information about their prescription, including general treatment guidelines, adverse events, and treatment procedure. Arrange a consultation for patients with nurses and pharmacists to discuss how dose decisions are made. To facilitate treatment, patients should be given a prescription for clindamycin gel.
- **Use a treatment algorithm as a guideline.** The course of treatment should be determined together with patients, depending on symptoms and grade.

### Treatment Guidelines

- Assess whether patients are taking any medications that could interfere with the metabolism of erlotinib. Patients should avoid grapefruit, grapefruit juice, or supplements containing grapefruit extracts.
- Refer patients to a dermatologist when necessary (i.e., if they are not responsive to standard treatment or are particularly uncomfortable).
- Use dose reduction only when necessary. The goal is to keep patients on a clinically effective dose of their anticancer therapy for as long as possible.

### Patient Guidelines

- Patients receiving erlotinib should be instructed to take the medication on an empty stomach (at least one hour before or two hours after a meal).
- Starting at treatment initiation, have patients use an alcohol-free emollient (e.g., Eucerin® [Beiersdorf], Cetaphil® [Galderma Laboratories], Aquaphor® [Beiersdorf]), preferably all over the body twice daily, to prevent and alleviate dry skin.
- Caution patients not to use any products on the skin, including perfume, lotions, and shampoos that are not dye-, alcohol-, and perfume-free. Baby shampoos and body washes, which are very mild, are good choices.
- Makeup can be used to conceal the rash, but properly cleansing skin and removing makeup daily using mild, hypoallergenic liquid cleansers are important.
- Avoid the sun as much as possible. When in the sun, wear protective clothing and use sunscreen (preferably titanium dioxide- or zinc oxide-based formulations).
- Over-the-counter acne medications that contain benzoyl peroxide are not recommended because they are drying and may exacerbate the rash.

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## Figure 2. Clinical Approach to Rash Management

characteristics can use hydrocortisone cream and clindamycin gel (Herbst et al., 2003). Patients routinely receive prescriptions for clindamycin gel at the beginning of treatment so that they can begin using it at the first sign of pustules. If the rash becomes more pustular and widespread (i.e., it spreads beyond the face) or if the rash begins to show drainage, it is classified as grade 2 or 3 depending on the severity of the area involved and the amount of pustules and drainage, and the use of oral antibiotics, such as minocycline, doxycycline, or trimethoprim and sulfamethoxazole is advised. Treatment at that point also involves a short course of systemic steroids, usually methylprednisolone.

Although traditionally used for treating acne, the tetracycline-based antibiotics minocycline and doxycycline also possess anti-inflammatory properties (Sapadin & Fleischmajer, 2006) and have been used successfully to treat EGFR inhibitor-induced rash (Dick & Crawford, 2005). For patients who cannot tolerate tetracycline, trimethoprim and sulfamethoxazole is a good alternative. Likewise, minocycline or doxycycline is a good alternative for patients who are allergic to sulfa drugs. Depending on the patient, systemic antibiotics may be needed only for a short course or for the duration of anti-EGFR therapy (Shah et al., 2005). Long-term use of systemic antibiotics is considered

relatively safe based on studies for treating other dermatologic conditions (Del Rosso, 2000). Oral antibiotics also work well for rash that has become secondarily infected (Perez-Soler & Saltz, 2005; Segart & Van Cutsem, 2005).

If the rash has progressed, but has not become pustular, systemic steroids alone are a good option. For patients who develop a grade 3 or 4 skin rash, topical silver sulfadiazine ointment is recommended because it facilitates healing by forming a protective barrier. Use of topical retinoids remains controversial and is not recommended. Those preparations have been found to exacerbate rash and dry skin in some patients (Hidalgo et al., 2001). Over-the-counter antihistamines (e.g., diphenhydramine) and analgesics (e.g., ibuprofen) can be used by patients at anytime.

Perez-Soler, Zou, Li, Tornos, and Ling (2006) reported that topically applied vitamin K (menadione) increases the EGFR pathway or regeneration of the skin pathway, thereby providing a means to prevent rash and related cutaneous toxicities. Hopefully, clinical trials to evaluate the finding in patients using EGFR inhibitors will soon be under way.

### Dosage Modification

If the rash does not respond to treatment or worsens, patients should be referred to a dermatologist, preferably someone familiar with EGFR inhibitor-associated rash. If, however, the rash still cannot be managed satisfactorily and patients are considering discontinuing treatment, modifying the dosage of the EGFR inhibitor should be considered instead. Because the goal is to keep patients on a clinically effective dose of anticancer therapy until disease progression, the option is a last resort. Furthermore, although the precise nature of the relationship remains unclear, a positive correlation between the severity of a patient's rash and survival has been reported (i.e., patients with more severe rash tend to have significantly longer survival and progression-free survival) (Agero et al., 2006; Perez-Soler & Saltz, 2005). That finding has suggested to some that reducing the severity of the rash could lead to decreased treatment efficacy. In the author's opinion, so long as patients are responding to treatment, if dosage modification helps ensure patients' quality of life, it is an acceptable approach.

Dosage modification can be accomplished by reducing the dose or altering the dosing schedule. For small-molecule TKIs, dose modification usually is accomplished by reducing the daily dose. In the Shepherd et al. (2005) erlotinib trial, dose reductions to help control rash were required by 29 of 485 patients (6%). Erlotinib was withheld until the rash improved to at least grade 1, at which point the drug was restarted at a reduced dose that was maintained for the remainder of the trial. Erlotinib prescribing information suggests reducing the dose by 50 mg decrements (erlotinib is supplied as 50 mg tablets) (Genentech, 2007). However, if a 25 mg reduction is desired, breaking up tablets does not affect bioavailability or pharmacokinetics (Frohna et al., 2006). Gefitinib prescribing information recommends that, when necessary, the drug be withheld (for up to 14 days) before restarting the full recommended dose (AstraZeneca, 2005). For cetuximab, a one- to two-week treatment delay is recommended (ImClone, 2006). If rash reoccurs when cetuximab is reinitiated, the dose should be reduced in 50 mg/m<sup>2</sup> decrements (Imclone). For patients who do not show improvement with the rash after dosage modification, treatment discontinuation should be considered. Panitumumab prescribing guidelines recommend withholding the drug in patients with grade 3 or 4 rash or who

**Table 3. Oncology Treatment Algorithm for Epidermal Growth Factor Receptor Inhibitor–Associated Rash**

Grade <sup>a</sup>	Macular <sup>b</sup> Rash	Pustular <sup>c</sup> Rash	Dry Skin	Pruritus	Ulcerative Lesions
1 (Mild)	Topical hydrocortisone cream or lotion (1%)	Clindamycin topical gel for isolated scattered lesions; clindamycin lotion for multiple scattered areas	–	–	–
2 (Moderate)	If limited to face and neck, fluticasone propionate topical steroid twice daily; if trunk involved, oral methylprednisolone from dose pack	Oral antibiotics: minocycline or doxycycline hydrochloride (200 mg twice daily day 1, then 100 mg twice daily) or trimethoprim and sulfamethoxazole (twice daily)	Perfume-, alcohol-, and dye-free lotion (applied twice daily)	Topical antihistamine, oral diphenhydramine (25–50 mg daily every six hours or as needed), or hydroxyzine hydrochloride (25–50 mg by mouth daily every six hours or as needed)	–
3 or 4 <sup>d</sup> (Severe)	Oral methylprednisolone from dose pack	Oral antibiotics: minocycline or doxycycline hydrochloride (200 mg twice daily day 1, then 100 mg twice daily) or trimethoprim and sulfamethoxazole (twice daily)	Perfume-, alcohol-, dye-free lotion (applied twice daily)	Oral diphenhydramine (25–50 mg daily every six hours or as needed) or hydroxyzine hydrochloride (25–50 mg by mouth daily every six hours or as needed)	Silver sulfadiazine ointment twice or three times daily

<sup>a</sup> Based on Common Terminology Criteria for Adverse Events version 3.0 guidelines

<sup>b</sup> Rash remains flat to the touch.

<sup>c</sup> Rash characterized by raised lesions containing pus that may or may not be sterile.

<sup>d</sup> Consultation with a dermatologist should be considered.

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can no longer tolerate the rash and request discontinuing treatment for any period of time) (Amgen, 2007). If the rash does not improve to grade 2 or less after dosage reduction, panitumumab should be discontinued.

Those dosage modifications are only recommendations. In the author’s experience, additional approaches have been successful. For example, treatment for a patient with a maculopustular rash accompanied by extreme dryness and pruritus included hydroxyzine and diphenhydramine to ameliorate pruritus and an over-the-counter skin moisturizer that was perfume-, dye-, and alcohol-free to combat dryness. After approximately eight months of therapy, the rash worsened considerably, at which point the dose was reduced, first to 100 mg (down from 150 mg) for two weeks. The patient wanted to go back to the full dose of the drug at 150 mg by mouth instead of 100 mg, so she was returned to a full dose but permitted to skip the Sunday dose. This regimen worked well and the patient continued it for two months, during which time her skin rash improved and her cancer remained stable. She then returned to the standard dose and, although diphenhydramine was required occasionally, the rash did not worsen.

### Additional Considerations

The incidence of skin rash in patients with cancer correlates positively with steady-state plasma levels of the EGFR inhibitor (Siegel-Lakhai, Beijnen, & Schellens, 2005; Strother et al., 2006). This is consistent with the finding that the occurrence of rash is dose-dependent (Herbst et al., 2004; Perez-Soler & Saltz, 2005). Therefore, to minimize the potential for rash, factors that affect steady-state plasma levels should be considered. Two principal variables control the plasma concentration of orally administered drugs—their bioavailability and the rate at which they are metabolized and cleared from the body (Singh &

Malhotra, 2004). For erlotinib, bioavailability is affected by the presence of food in the stomach. The mean oral bioavailability of erlotinib is approximately 60% when it is taken on an empty stomach (Frohna et al., 2006) as compared with almost 100% when it is taken with food (Genentech, 2007). The increased bioavailability increases the side effects of rash; therefore, to reduce variability in its bioavailability and minimize any effect on rash on other adverse events, erlotinib is recommended to be taken on an empty stomach (at least one hour before or two hours after a meal) (Genentech).

The rate at which drugs are metabolized can be influenced by concomitant medications that may inhibit or slow the metabolism of EGFR inhibitors. For example, erlotinib and gefitinib are metabolized primarily by cytochrome CYP3A4 (Hidalgo & Bloedow, 2003; Siegel-Lakhai et al., 2005). When administered at the same time as other drugs that are substrates or inhibitors of CYP3A4, erlotinib and gefitinib rates of metabolism and clearance will be decreased, leading to an increase in their plasma levels. In one study, coadministration of erlotinib and the antifungal medication ketoconazole, a known CYP3A4 inhibitor, led to a 67% increase in the blood plasma level of erlotinib (Smith, 2005). Such a significant increase in plasma concentration, especially for a drug being administered at its maximum tolerated dose (Genentech, 2007; Hidalgo et al., 2001), could increase the incidence or severity of rash (Siegel-Lakhai et al.). Table 5 lists some other common CYP3A4 inhibitors. Compounds found in grapefruit juice also are known to inhibit intestinal CYP3A4 (Paine, Criss, & Watkins, 2004), and patients receiving gefitinib or erlotinib should be cautioned not to drink grapefruit juice or take supplements containing grapefruit extracts.

Another important consideration is sun exposure. Some evidence suggests that use of sunscreen may prevent the

**Table 4. Current Grading Systems for Rash**

Grade	National Cancer Institute (2003)	Eastern Cooperative Oncology Group (n.d.)	Busam et al. (2001)
1	Macular or papular eruption or erythema without associated symptoms	Scattered macular or papular eruption or erythema that is asymptomatic	Asymptomatic macular or papular erythematous eruption in an acneform distribution
2	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering less than 50% of body surface area (BSA)	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Same as grade 1 plus symptoms such as pruritus
3	Severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering greater than or equal to 50% BSA	Generalized symptomatic macular, papular, or vesicular eruption	Extension of the eruption beyond acneform distribution of the head, chest, and back, or the development of confluent or painful lesions or minor ulceration
4	Generalized exfoliative, ulcerative, or bullous dermatitis	Exfoliative or ulcerating dermatitis	Exfoliative or ulcerating dermatitis

*Note.* From "Case Studies in Oncology Nursing," by K.J. Oishi, 2005, *Physicians' Education Resource*, 1(3), p. 5. Copyright 2005 by Physicians' Education Resource. Adapted with permission.

occurrence of rash or prevent it from worsening (Herbst et al., 2003; Perez-Soler et al., 2005). Therefore, patients being treated with EGFR inhibitors should be instructed to avoid the sun as much as possible, wear protective clothing, and use sunscreen on all exposed skin when in the sun. Sunscreens should have a protective factor of at least 30, preferably be titanium dioxide- or zinc oxide-based formulations, and be reapplied every two hours.

## Nursing Implications

Oncology nurses are an important component of the treatment team and need to understand how to assess and manage toxicities so that patients can avoid unnecessary dosage modification or treatment discontinuation. Nursing education prior to the start of the drug is essential so that patients recognize and minimize any potential side effects or complications. Continuing nursing education and follow-ups also are necessary throughout the course of treatment.

Important tips include educating patients that the skin rash may be a positive sign associated with tumor response. This reinforcement may support patients staying on therapy for as long as they continue to respond to therapy and the side effects are tolerable. Early intervention to prevent the rash from worsening is critical. Patients should be instructed to call as soon as possible if the rash worsens or if the prescribed measures are not effective. Nurses also should stress the importance of pa-

tients staying well hydrated and using water-based instead of alcohol-based skin products that might exacerbate the dryness that often is associated with the rash. In addition, nurses need to instruct patients that although the rash usually is limited to the face, neck, and torso, it can occur on any skin surface, including the ears, nose, scalp, armpits, genital regions, and lower extremities.

Psychological effects of the rash on patients have not been addressed or studied. Oncology nurses generally are the first healthcare professionals in contact with patients and often uncover the many psychological issues that patients are experiencing. Nurses can assist patients by providing them with specific coping mechanisms and other evidence-based nursing measures. For example, nurses should employ empathetic listening as patients voice their psychological concerns, provide appropriate referrals to psychosocial counselors or providers, stress the potential response from the therapy, provide a list of cosmetic products that are less irritating to the skin, and emphasize the importance of washing affected areas with mild cleansing products. Currently, no studies have examined nursing interventions in the management of EGFR inhibitor-induced rash nor have any assessed the effectiveness of the specific guidelines discussed in this article. Studies need to be done to test those and other interventions.

## Conclusions

EGFR inhibitors have become a mainstay of therapy for several cancers, including NSCLC, pancreatic, head and neck, and metastatic colorectal. With five EGFR inhibitors currently approved and several others in development, skin rashes are likely to be seen with increasing frequency in clinical practice.

Nurses need to understand how to assess and manage the rash associated with EGFR-targeted therapies so that patients can avoid unnecessary dosage modification or treatment discontinuation. The interventions described in this article will assist nurses with the assessment and treatment of patients receiving EGFR inhibitors by providing them with better tools.

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**Table 5. Commonly Used Drugs That Can Increase Serum Plasma Concentrations of Gefitinib or Erlotinib**

Drug Class	Examples
Antiepileptic drugs	Carbamazepine, phenobarbital
Azole antifungals	Fluconazole, itraconazole, ketoconazole, voriconazole
Calcium channel blockers	Diltiazem, nifedipine, nimodipine, verapamil
Immunosuppressants	Cyclosporin, pimecrolimus, tacrolimus
Other	Warfarin

*Note.* Based on information from Indiana University Department of Medicine, 2007.

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