Dermatologic Infections in Cancer Patients Treated With Epidermal Growth Factor Receptor Inhibitor Therapy

R. E. Eilers Jr, M. Gandhi, J. D. Patel, M. F. Mulcahy, M. Agulnik, T. Hensing, Mario E. Lacouture

Manuscript received January 21, 2009; revised October 6, 2009; accepted November 3, 2009.

Correspondence to: Mario E. Lacouture, MD, Department of Dermatology, Northwestern University Feinberg School of Medicine, 676 North St Claire Street, Ste 1600, Chicago, IL 60611-2941 (e-mail: m-lacouture@hotmail.com).

Background Patients treated with epidermal growth factor receptor inhibitors (EGFRIs) frequently experience dermatologic toxic effects. Whereas the impact of these effects on quality of life and EGFRRI dosing has been described, their impact on physical health has not been ascertained. We examined the prevalence of infections that complicate dermatologic toxic effects of EGFRIs.

Methods We used retrospective chart review methods to analyze 221 patients who were treated in the Skin and Eye Reactions to Inhibitors of EGFR and Kinases clinic, a referral clinic for dermatologic toxic effects of cancer therapies. We reviewed results of bacterial cultures, histopathologic assessment of biopsy samples, and immunohistochemical staining of skin specimens for viral pathogens that were recorded in the patients’ medical records. Associations between patient demographic and treatment characteristics and the development of infections were examined using the Fisher exact test. All statistical tests were two-sided.

Results Eighty-four (38%) of the 221 patients showed evidence of infection at sites of dermatologic toxic effect. Fifty (22.6%) of the 221 patients had cultures positive for Staphylococcus aureus, and 12 (5.4%) of the 221 patients cultured positive for methicillin-resistant S aureus. Less frequent infections included herpes simplex (3.2%), herpes zoster (1.8%), and dermatophytes (10.4%). The seborrheic region was the most prevalent site of infection, and patients with leukopenia had higher risk for infection than patients who did not have leukopenia (P = .005). Demographic factors and associated treatments were not associated with the occurrence of a dermatologic infection (P ≥ .05).

Conclusions Patients with dermatologic toxic effects following treatment with EGFRIs have a high prevalence of cutaneous infections. Most notably, bacterial infections developed at sites previously affected by dermatologic toxic effects, with leukopenic patients being at greater risk.


The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that regulates various cellular processes, including cell proliferation, differentiation, and survival (1). Its dysregulation in various malignancies, including lung, gastrointestinal, and head and neck cancers, has been associated with poor prognosis and increased resistance to chemotherapy and radiotherapy (2). Monoclonal antibodies that act as EGFR inhibitors (EGFRIs), such as cetuximab and panitumumab, and small-molecule EGFRIs, such as erlotinib, gefitinib, and lapatinib, provide a rational approach to cancer therapy because they specifically inhibit EGFR signaling by preventing ligand binding in the extracellular domain or by blocking intracellular phosphorylation, respectively (3). In addition to its prominent role in cancer, EGFR is constitutively expressed in epithelial tissues, such as skin and hair follicles, where it is critical for normal tissue function and reparative capability (1). As a consequence of this constitutive expression, dermatologic toxic effects are frequently observed in patients undergoing therapy with EGFRIs. Observed dermatologic toxic effects include papulopustular eruptions of the face and trunk (60%–80% incidence), nail changes (12%–16%), xerosis (7%–35%), pruritus (10%–16%), and alopecia (5%–6%) (4–6). A retrospective survey of 110 US oncologists who were administering EGFRIs found that 70% reported the need for dose modification and 32% reported the need to discontinue EGFRIs in patients who developed these toxic effects (7). In addition, EGFRI-induced dermatologic toxic effects have the potential to impact a patient’s psychosocial health, particularly the emotional component of health-related quality of life, as well as the physical and functional components (8).

Previous anecdotal reports underscore the frequency of cutaneous infections that complicate the course of therapy in EGFRI-treated patients. For example, Kardaun and Van Duinen (9) report the case of a patient on erlotinib monotherapy at 150 mg daily for non–small cell lung cancer who was hospitalized for diarrhea, otitis externa, ectropion, and purulent conjunctivitis resulting from polymicrobial infection with Staphylococcus aureus, Pseudomonas aeruginosa, and...
Prior knowledge
Patients treated with epidermal growth factor receptor inhibitors (EGFRIs) frequently experience dermatologic toxic effects, which can impact their quality of life and EGFRi dosing. However, the impact of these effects on physical health, particularly the prevalence of infections that complicate dermatologic toxic effects of EGFRIs, has not been ascertained.

Study design
Retrospective chart review was used to collect data on 221 patients who were treated in a referral clinic for dermatologic toxic effects of cancer therapies. Associations between patient demographic and treatment characteristics and the development of infections were examined.

Contribution
Among patients with dermatologic toxic effects following treatment with EGFRIs, 38% had a dermatologic infection of any type and 29% developed bacterial infections at sites previously affected by dermatologic toxic effects. Leukopenic patients had a greater risk of infection than nonleukopenic patients.

Implications
The recognition of these complicating cutaneous infections is critical for clinical management and quality of life in EGFRI-treated patients.

Limitations
Not all of the patients who were undergoing EGFRi therapy were cultured for dermatologic infection. Therefore, the study results likely underestimate the true incidence of dermatologic infection in cancer patients treated with EGFRIs.

From the Editors

Candida albicans. Another case report (10) described a patient with non–small cell lung cancer who required hospitalization with S aureus bacteremia secondary to severe erlotinib skin toxicity. In addition, cultures from erlotinib-induced skin rashes have revealed Serratia marcescens infections that required multiple-agent antimicrobial therapy (11). Lord et al. (12) reported the development of S aureus infections in 10 of the 14 patients undergoing radiation concurrent with chemotherapy. These case reports underscore the notion that infections in EGFRI-treated patients do develop but are being reported anecdotally, all of which motivated the development of this study. We hypothesized that the dermatologic toxic effects of these drugs impair the cutaneous barrier, resulting in an increased incidence of complicating infections in patients with EGFRi therapy–induced dermatologic toxicities compared with untreated patients.

Methods
We conducted a retrospective chart review for patients who were treated in the Skin and Eye Reactions to Inhibitors of EGFR and Kinases (SERIES) clinic at Northwestern University (Chicago, IL), a referral clinic for dermatologic toxic effects of cancer therapy (13). We considered all patients who visited the clinic from August 11, 2005, through June 27, 2008. Demographic information that was provided during initial patient visits was obtained from medical records. We included in this study patients who were treated with lapatinib, cetuximab, panitumumab, or erlotinib from August 11, 2005, through June 27, 2008. Patients who were seen in the clinic for cutaneous toxic effects secondary to non–EGFR-targeted therapies were excluded from the study. This study was approved by the Institutional Review Board of Northwestern University. Patients provided written informed consent before undergoing the skin biopsy.

We reviewed the recorded results of bacterial, viral, and fungal cultures and stains, as well as the histochemical findings for skin biopsy samples. We collected the following data on the microbe culture results: the anatomic location of the culture specimen, the pathogen, and antibiotic resistance of the pathogen. Information pertaining to viral infections (herpes simplex or herpes zoster) was also obtained from progress notes in the patient’s medical chart and from results of biopsy specimens or cultures obtained during patient visits. Results from medical records of skin biopsy samples were analyzed; these samples had undergone staining with hematoxylin–eosin for routine dermatopathologic analysis and with periodic acid–Schiff (14) or immunohistochemistry (15) when infection with fungi or herpes viruses, respectively, was suspected. Other data obtained from the chart review included: patient age at the initial SERIES clinic visit, sex, cancer type, EFGRI used, current and ongoing treatment with radiation and/or chemotherapy, previous treatment with chemotheraphy, leukopenia (defined as leukocyte levels below 3500/μL at any time during the study period), topical corticosteroid use, and antibiotic or corticosteroid use for prophylaxis of skin rash.

We examined associations between median age at initial SERIES clinic visit, sex (male, female), cancer type (aerodigestive tract, breast, central nervous system, colorectal, head and neck, lung, pancreatic, prostate, or unknown primary), EGFRI used (erlotinib, cetuximab, lapatinib, or panitumumab), current and ongoing treatment with radiation and/or chemotherapy, previous treatment with chemotheraphy, leukopenia (yes, no), topical corticosteroid use (yes, no), and antibiotic or corticosteroid use for prophylaxis of skin rash (yes, no) and the presence or type of a bacterial, dermatophytic, or viral dermatologic infection by using the Fisher exact test. Multivariate analysis using stepwise logistic regression with entry into the model of variables that showed a statistically significantly association (P < .05) with dermatologic infection was performed to identify variables that were independently related to the presence of infection. All statistical tests were two-sided. Statistical analyses were conducted using SAS OnlineDoc 9.2 software (2007 version; SAS Institute, Inc, Cary, NC) (16).

Results
The clinical and demographic characteristics of 221 EGFRi-treated patients with and without dermatologic infections are reported in Table 1. Of the 221 patients investigated here, 189 (86%) received topical corticosteroid treatment (73 infected patients [86.9%] and 116 patients without infection [84.7%]) (Table 1). Nineteen uninfected patients (13.9%) and seven infected patients (8.3%) were treated with prophylactic topical corticosteroids (Table 1). There was no association between prophylactic topical corticosteroid use or topical corticosteroid use and occurrence of infection.

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Table 1. Characteristics of 221 patients treated with EGFRIs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>84 Patients with dermatologic infection</th>
<th>137 Patients without dermatologic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td>39 (17.6)</td>
<td>57 (25.8)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (20.4)</td>
<td>80 (36.2)</td>
</tr>
<tr>
<td>Median age at initial visit, y (range)</td>
<td>61 (27–90)</td>
<td>59 (17–88)</td>
</tr>
<tr>
<td>SERIES clinic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer type or site, No. (%)</td>
<td>41 (18.6)</td>
<td>69 (3.1)</td>
</tr>
<tr>
<td>Aerodigestive tract</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Breast</td>
<td>6 (2.7)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0 (0)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>32 (14.5)</td>
<td>36 (16.3)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>5 (2.3)</td>
<td>15 (6.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>30 (13.6)</td>
<td>60 (27.1)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>7 (3.2)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>EGFR therapy, No. (%)</td>
<td>35 (15.9)</td>
<td>72 (32.6)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>37 (16.7)</td>
<td>48 (21.7)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>6 (2.7)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>6 (2.7)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Treatment, No. (%)†</td>
<td>11 (5.0)</td>
<td>21 (9.5)</td>
</tr>
<tr>
<td>Single EGFR therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>65 (29.4)</td>
<td>110 (49.8)</td>
</tr>
<tr>
<td>Chemotherapy concurrent with EGFRi</td>
<td>41 (18.6)</td>
<td>69 (3.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>20 (9.0)</td>
<td>20 (9.0)</td>
</tr>
<tr>
<td>Radiation</td>
<td>26 (11.8)</td>
<td>50 (22.6)</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>73 (33.0)</td>
<td>116 (5.2)</td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>10 (4.5)</td>
<td>23 (10.4)</td>
</tr>
<tr>
<td>Prophylactic topical corticosteroids</td>
<td>7 (3.2)</td>
<td>19 (8.6)</td>
</tr>
</tbody>
</table>

* EGFR = epidermal growth factor receptor inhibitor; SERIES = Skin and Eye Reactions to Inhibitors of EGFR and Kinases.
† Patients with no documented previous medical history are not included.

Of the 221 patients included in this study, 33 were referred to the SERIES clinic before initiation of EGFRi therapy and were treated prophylactically with topical corticosteroids (12%), oral tetracycline antibiotics (15%), or both (14%). Only a minority of patients (<5%) were referred to the SERIES clinic from outside institutions for management of established severe dermatologic toxic effects. Ten patients with dermatologic infections (4.5%) and 23 uninfected patients (10.4%) had received prior prophylactic antibiotics. These results suggest that prophylactic antibiotic treatment of rash with oral semisynthetic tetracycline antibiotics (ie, doxycycline and minocycline) may minimize the risk of cutaneous infections in these patients.

Of the 221 EGFRi-treated patients seen in the SERIES clinic from August 11, 2005, through June 27, 2008, 84 (38%) had a dermatologic infection (Table 2); 52 patients (23.5%) were infected with one or more types of bacteria, 13 patients (5.9%) had infections with a single type of dermatophyte, six patients (2.7%) had infections with a single type of virus, and 13 patients (5.9%) had polymicrobial infections. The frequency of bacteria, dermatophytes, and viruses in these infections is presented in Table 2. The number of infectious microbes listed in Table 2 outnumber the number of infected patients because the infections in a single patient were often polymicrobial. Among the 221 EGFRi-treated patients, eight patients (3.6%) had bacterial and fungal infections; one patient (0.45%) had viral and fungal infections; three patients (1.4%) had bacterial and viral infections; and one patient (0.45%) had bacterial, viral, and fungal infections. The combination of the 52 patients with solely bacterial infections and the 12 patients with polymicrobial infections including bacteria accounts for the total of 64 bacterial infections (Table 3).

Among the 221 EGFRi-treated patients, bacterial infection was the most common infection subtype affecting 64 patients (29%) (Table 3). Bacteria were the sole cause of infection in 52 patients (23.5%), and 12 patients (5.4%) had polymicrobial infections with bacteria and/or viruses and/or dermatophytes. *Staphylococcus aureus* was the most common bacterial pathogen, infecting 50 (22.6%) of the 221 patients who received EGFRi therapy. Twelve (5.4%) of the 221 EGFRi-treated patients were infected with methicillin-resistant *S aureus*, and eight of these 12 methicillin-resistant *Staphylococcus aureus* infections were caused by tetracycline-resistant strains (Table 3). It is important to note that Table 2 shows the frequencies with which bacterial, dermatophytic, and viral microbes were present in infections. Therefore, these values will be greater...
than the total number of infected patients, as many infections were polymicrobial. The majority of bacterial infections were localized to the seborrheic region (Figure 1). The number of bacterial infections listed in Figure 1 is less than that reported in Table 2 because more than one bacterial species was often present in a single bacterial infection. The number of dermatophytic and viral infections listed in Figure 1 is the same as that reported in Table 2 because these dermatophytic or viral infections contained a single infectious microbe. Less frequent cutaneous infections observed in EGFRI-treated patients included those caused by fungal and viral pathogens. Fungal infections occurred in 23 patients (10.4%), whereas viral infections developed in 11 patients (5%). The most common fungal infection was candida onychomycosis, occurring in 13 patients (5.9%), and the most common viral infections were with herpes simplex and herpes zoster, occurring in seven (3.2%) patients.

Twenty-two (10.0%) of the 221 EGFRI-treated patients had S. aureus colonization in the nasopharyngeal region in addition to a bacterial, dermatophytic, or viral dermatologic infection. Five patients (2.2%) without a dermatologic infection had S. aureus, of which two (0.9%) had methicillin-resistant S. aureus colonization.

Leukopenia was statistically significantly associated with presence of a dermatologic infection ($P < .001$). A total of 20 (50%) of the 40 leukopenic patients vs 25 (24.3%) of the 103 nonleukopenic patients had a dermatologic infection ($P = .005$). Seventy-eight patients did not have data available to evaluate their leukopenic status. There was no association between the development of a dermatologic infection and age, sex, cancer type, EGFRI therapeutic agent, prior radiation or chemotherapy, concurrent chemotherapy with EGFRI therapy, topical corticosteroid use, prophylactic antibiotic use, and prophylactic topical corticosteroid use ($P \geq .05$).

In a multivariate analysis, leukopenia was the only factor that was statistically significantly associated with dermatologic infection ($P < .001$). In addition, there was no statistically significant association between any other clinical or demographic variable and the type of dermatologic infection by pathogen ($P \geq .05$).

**Discussion**

We found that 84 (38%) of the 221 patients with EGFRI-induced dermatologic toxicities were positive for skin and nail infections. The most common cutaneous infections were bacterial, occurring in 64 (29%) of the 221 patients. Fifty (22.6%) of the 221 patients had a dermatologic infection yielding S. aureus, and 12 (5.4%) showing methicillin-resistant S. aureus at sites of toxicity (i.e., wound sites, pustules). Viral and fungal infections occurred less frequently than bacterial infections among the analyzed patients. The compromised barrier function of skin or alterations in the cutaneous immune system in patients with dermatologic toxic effects of EGFRI may have contributed to the high prevalence of infections described in this study. Bacterial infections occurred most often in seborrheic areas, which include the scalp, face, neck, and chest, all of which are frequently affected by the prototypal papulopustular rash that affects 71%–90% of patients treated with EGFRI (7). Biopsy specimens of EGFRI-induced rash that predominantly surrounds hair follicles typically reveal an upper dermal inflammatory infiltrate consisting of CD45RO-positive T cells and neutrophils, which may be associated with follicular rupture and epithelial acantholysis (17). In addition, thinning of the epidermis and a thickened more compact stratum corneum with loss of the characteristic basket weave architecture is seen in biopsy specimens of skin from EGFRI-treated patients. To our knowledge, only two cases of leukocytoclastic vasculitis with complement and fibrinogen deposits have been reported in association with erlotinib therapy (18).

**Table 3. Classification of 64 patients with polymicrobial bacterial infection***

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Bacterial infection in EGFRI-treated patient population, No. (%) (n=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>Methicillin-sensitive and tetracycline-sensitive</td>
<td>50 (22.6)</td>
</tr>
<tr>
<td>Methicillin-sensitive and tetracycline-resistant</td>
<td>31 (14.0)</td>
</tr>
<tr>
<td>Methicillin-resistant and tetracycline-sensitive</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Methicillin-resistant and tetracycline-resistant</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Methicillin-resistant and tetracycline-resistant</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Other bacteria†</td>
<td>14 (6.3)</td>
</tr>
</tbody>
</table>

* EGFRI = epidermal growth factor receptor inhibitor.
† Enterobacter aerogenes, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter baumannii complex, Klebsiella oxytoca.

**Figure 1.** Anatomical classification of bacterial, fungal, and viral infections at sites of dermatologic toxic effects in 84 infected patients seen at the Skin and Eye Reactions to Inhibitors of EGFR and Kinases clinic. The number of infections seen here is greater than the total number of infected patients because a single patient could have infections in more than one anatomical region.
The compromised integrity of the skin in patients with psoriasis and atopic dermatitis is believed to result in secondary infections (19). Similarly, structural alterations in the skin of EGFR-treated patients may facilitate the entry of symbiotic bacteria into the lower epidermis and dermis, leading to greater pathogenicity and the ensuing clinical infections seen in the patients in our study.

In this study, we found a high prevalence of dermatologic infections among 221 patients with EGFR-induced dermatologic toxic effects. Of these 221 EGFR-treated patients, 38% had a dermatologic infection of any type and 29% had bacterial infections. Patients were found to culture positive for bacteria, particularly *S aureus* (including methicillin-resistant *S aureus*), at anatomic sites typically affected by EGFR-induced dermatologic toxic effects. Effective management of dermatologic toxic effects and complicating infections is therefore a potential strategy to minimize the need for dose modifications of EGFR therapy because of these untoward events. The clinical significance of dermatologic toxic effects in patients treated with EGFRIs has been attributed to their negative impact on patients’ psychosocial health, which in turn may lead to reductions in quality of life and chemotherapy dose intensity, all of which may affect clinical outcome (7).

We are aware of three systematic investigations that have examined interventions to minimize this initial flare-up phase. First, a prospective evaluation of rash in the placebo arm of a randomized trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption in metastatic colorectal cancer patients (20) demonstrated that the number of dermatologic lesions increased progressively 2–4 weeks after initiation of EGFR therapy, followed by a plateau and a steady decline in weeks 6–8. Therefore, interventions aimed at minimizing this “flare-up” phase are critical to lessen the need for EGFR dose modification and maintain patient quality of life. Second, a placebo-controlled trial involving patients treated for 4 weeks with prophylactic tetracycline vs placebo found a statistically significant reduction in grade 2 or worse rash (17% in the tetracycline group vs 55% in the placebo group, *P* = .009) and less patient-reported skin burning or stinging and irritation in the tetracycline group using Skindex-16, a dermatologic quality-of-life instrument (21). Finally, a randomized trial involving 95 patients who received either 6 weeks of preemptive skin treatment or reactive treatment with moisturizer, sunscreen, 1% hydrocortisone cream, and 100 mg doxycycline twice daily revealed a greater than 50% reduction in grade 2 or worse skin toxicities in the preemptive treatment group compared with the reactive treatment group (22).

In addition to increased rates of infection secondary to diminished dermatologic barrier function in patients undergoing EGFR therapy, it is plausible that the underlying malignancies in these patients may predispose them to development of dermatologic infections. The presence of an underlying malignancy is an independent risk factor for skin and soft tissue infection secondary to *Staphylococcus* (23). Twenty-three percent of all bacteremic episodes seen in cancer patients are caused by *S aureus*, and skin and soft tissue infections are the source of infection in 60% of those cases (23,24). Patients with solid tumors are more likely to develop skin and soft tissue infections compared with those with hematologic malignancies because of the extensive surgical procedures they undergo for diagnosis and treatment of their condition. *Staphylococcus aureus* is the most common pathogen isolated from skin and soft tissue infections in cancer patients, followed by *Escherichia coli*, coagulase-negative *Staphylococci*, *Enterococci*, and anaerobes (25).

It is important to distinguish between patients with bacterial colonization and those with *S aureus* infection. Patients with bacterial colonization have *S aureus* present on tissue surfaces that are in contact with the external environment, whereas the bacterium invades the tissue of patients who are infected. The prevalence of colonization with *S aureus* and methicillin-resistant *S aureus* in the US population is approximately 18%–38% and 0.8%–6%, respectively (19), but the prevalence among EGFR-treated patients remains unclear. Major risk factors for *Staphylococcal aureus* and methicillin-resistant *Staphylococcal aureus* colonization in adult oncology patients include more than five hospital admissions in the previous year, chemotherapy, chronic skin disease, and surgery followed by hospital stays averaging 14 days (26). Although the implications of methicillin-resistant and methicillin-sensitive *Staphylococcal aureus* colonization for the development of infections in this population are unknown, it likely precedes skin infections, as has been seen in the non-oncologic patient population (27). Therefore, eliminating colonization in patients treated with EGFRIs and preventing person-to-person contact between EGFR-treated patients and individuals who harbor these bacteria would be a first step toward minimizing the development of these infections in patients (28).

An important aspect of *S aureus* colonization of skin is its ability to alter the course of existing cutaneous disease (28). Previous studies have demonstrated that *S aureus* enterotoxins A–E and the toxic shock syndrome toxin-1 (a *S aureus* exotoxin) trigger the exacerbation of other inflammatory or neoplastic skin conditions, such as atopic dermatitis, psoriasis, and cutaneous T-cell lymphomas (29–32). Although the effect of EGFR-targeted therapies on immunological competence has, to our knowledge, not been investigated, toxicity data from a pivotal phase III study (33) suggest that use of panitumumab as a single agent did not statistically significantly alter the numbers of immune cells. These findings support the notion that anti-EGFR therapies do not suppress the immune system. It is possible that a mechanism of bacterial exotoxins in inflammatory or neoplastic skin disorders similar to that described above leads to aggravation of EGFR-induced toxic effects. Although EGFRIs per se may not cause immunosuppression, it is possible that the immunosuppression associated with antineoplastic therapy or the underlying disease may have also contributed to the increased prevalence of dermatologic infection in EGFR-treated patients. We found that patients who were leukopenic had a statistically significantly greater risk of developing dermatologic infections at sites of EGFR-induced dermatologic toxicities compared with nonleukopenic patients (50% of leukopenic patients had infection vs 24.2% of nonleukopenic patients, *P* = .005).

The use of tetracycline antibiotics as a prophylactic therapy for the prevention of moderate-to-severe EGFR-induced rash has been instituted as the standard of care at the SERIES clinic following published reports on its effectiveness in placebo-controlled trials (20,21). On the basis of results of the Skin Toxicity Evaluation Protocol with Panitumumab (STEP) trial (22), in which prophylactic antibiotic therapy reduced grade 2 or worse skin toxic...
effects by more than 50%, the SERIES clinic now initiates prophylactic therapy with moisturizers, sunscreen, 1% hydrocortisone cream, and doxycycline (100 mg twice daily) for patients who are starting EGFRi therapy. Previously, antibiotic treatment was initiated when a patient developed skin toxic effects (1,5). Currently, the majority of cancer patients treated at Northwestern University are referred to the SERIES clinic for prophylactic antibiotic therapy when they begin EGFRis. The patients seen in the SERIES clinic comprise all patients treated with EGFRis by medical oncologists at Northwestern University. Therefore, these patients are similar to those who are treated by medical oncologists at other institutions. It is noteworthy that eight of the 12 methicillin-resistant Staphylococcal aureus infections in this study were caused by tetracycline-resistant strains; this finding is consistent with recent reports of high rates of infection with tetracycline-resistant methicillin-resistant Staphylococcal aureus among ambulatory patients (34). Studies comparing the dose of EGFRis to rash severity suggest that in patients with no or mild rash on standard-dose cetuximab, increasing the dose of cetuximab up to 500 mg/m² per week results in an increased response rate (35). In this clinical trial setting, where rash is used as a criterion for increasing EGFRi dose, the use of antibiotics before the trial endpoints are achieved is not recommended because they would decrease the severity of those higher than grade 1 (21,22), which would limit the number of subjects who would be eligible for dose escalation, potentially affecting the response rate.

There is some concern that the use of topical corticosteroids for EGFRi-induced rash may increase the risk of infections because of a previous study that showed that decreases in immune competence and epidermal thickness are associated with prolonged topical steroid use (36). Our finding of a lack of an association between the use of topical corticosteroids or prophylactic antibiotics and the occurrence of infection is consistent with those of a prospective study, which found that patients who used doxycycline and the topical steroid hydrocortisone 1% did not have a greater risk of skin infection compared with those who did not (37).

A limitation of this study involves the population under investigation. Although all patients analyzed in this study were undergoing EGFRi therapy during the study period, not all patients undergoing EGFRi therapy were cultured for dermatologic infection. Therefore, it is likely that the study results underestimate the true incidence of dermatologic infection in cancer patients treated with EGFRis. Future studies may involve obtaining cultures of all EGFRi-treated cancer patients to obtain data that are more representative of the entire population of patients undergoing EGFRi therapy.

In summary, dermatologic toxic effects in patients undergoing EGFRi treatment are frequently complicated by bacterial, viral, and dermatophyte infections, which may occur singly or in combination. These events were more frequent in leukopenic patients than in nonleukopenic patients, underscoring the role of the immune system for the maintenance of dermatologic immune surveillance. Therefore, in addition to treating the characteristic dermatologic toxic effects, attention should be paid to preventing or treating complicating infections, with the goal of maintaining quality of life and dermatologic health, both of which are essential for the optimization of EGFRi therapies in cancer patients.

References


**Funding**

M.E.L. is supported by a Zell Scholarship from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, and a Career Development Award from the Dermatology Foundation.

**Notes**

The study sponsors did not have any role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

J. D. Patel receives research funding from Genentech, Inc. M. Agulnik is a member of the speaker’s bureau for Bristol-Meyer Squibb. M. E. Lacouture is a consultant for and has received honoraria from Amgen, Imclone, Bristol-Myers Squibb, OSI Pharmaceuticals, Inc, Bayer Healthcare, and Onyx Pharmaceuticals. M. E. Lacouture has received research funding from Amgen, OSI Pharmaceuticals, Inc, Bayer Healthcare, Onyx Pharmaceuticals, and Hana Biosciences.

**Affiliations of authors:** Department of Dermatology (REE, MG, MEL), Division of Hematology/Oncology, Department of Medicine (JDP, MFM, MA), and Robert H. Lurie Comprehensive Cancer Center (MEL), Northwestern University Feinberg School of Medicine, Chicago, IL; Division of Hematology/Oncology, Department of Medicine, North Shore University Health System, Evanston, IL (TH).