Managing dermatologic changes of targeted cancer therapy

Failure to control these dermatologic changes can lead to lower dosages of cancer agents or an interrupted course of Tx. These steps can help you to head off trouble.

Advances in cancer therapy have improved survival, such that many cancers have been transformed from a terminal illness to a chronic disease, and the population of patients living with cancer or who are disease-free has grown. However, these patients face complex medical problems because of the systemic effects of their treatment and many endure a constellation of treatment-emergent adverse effects that require ongoing care and support.1

Primary care physicians have been called on to take a larger role in the care of these adverse effects as the growing number of treatments has meant more affected patients. In addition, an urgent, unmet need has developed for better coordination between specialists and family physicians for providing this supportive care.2

In this article, we (1) describe the most commonly encountered cancer treatment–related skin toxicities, paying particular attention to the effects of epidermal growth factor receptor (EGFR)–targeting therapies, and (2) review up-to-date management recommendations in an area of practice where established clinical guidance from the scientific literature is limited.

Biggest culprit: Targeted cancer therapies

Skin rash and dermatologic adverse effects are commonplace in patients undergoing cancer treatment; timely management can often prevent long-term skin damage.3 Dermatologic effects have been associated with various therapeutic agents, but are most commonly associated with targeted therapies—specifically, agents targeting EGFR.

Why the attention to EGFR inhibition? EGFR is over-expressed or mutated in a multitude of solid tumors; as such, agents have been developed that target this aberrant signaling pathway. EGFR is highly expressed in the skin and dermal...
tissue, where it plays a number of roles, including protection against ultraviolet radiation damage. Blockade of the EGFR molecule leads to dermal changes, however, presenting as acneiform rash, skin fissure and xerosis, and pruritus. In extreme instances, toxic effects can manifest as paronychia, facial hypertrichosis, and trichomegaly. These skin changes can be deforming as well as painful, and can have physiological and psychological consequences.

In turn, a decrease in quality of life (as reported by patients suffering from skin toxicity) can affect cancer treatment adherence and efficacy, and severe skin changes can result in the need to reduce the dosage of anti-cancer therapies. Skillful evaluation and appropriate management of skin eruptions in patients undergoing cancer therapy is therefore vital to an overall satisfactory outcome.

How common a problem? The incidence of EGFR inhibitor (EGFRI)-related rash is noteworthy: Overall incidence ranges from 45% to 100% of treated patients, with 10% experiencing Grade 3 to 4 changes (covering > 30% of body surface, restricting activities of daily living, severe itching). Monoclonal antibody therapies that target EGFR, such as cetuximab, have a reported 90% risk of skin rash, with 10% also being of Grade 3 to 4. Risk factors for rash include skin phototype, male gender, and younger age. Common cancer therapies with known skin effects are listed in the TABLE.

What should you look for? The most common clinical manifestation of dermatologic toxicity is an acneiform, or papulopustular, rash marked by eruptions characterized as “acne-like” pustules with monotonous lesion morphology (FIGURE 1A). A hallmark of these lesions that can be used to help distinguish them from acne vulgaris is the absence of comedones on eruptions.

The timeline of the rash has been well characterized and is another tool that you can use to guide management:
1. During Week 1 of cancer treatment, the patient often experiences sensory disturbances, with erythema and edema.
2. Throughout Weeks 2 and 3, erythematous skin evolves into papulopustular eruptions.
3. By Week 4, eruptions typically crust over and leave persistently dry skin for weeks.

Of note, the rash is dosage related; we recommend scrupulous vigilance when a patient is receiving a high dosage of a targeted therapy agent.

Controlling a rash
Treatment of EGFRI-associated skin changes stems from recommendations from a number of individual investigators and studies; however, few consensus guidelines exist to guide practice. Understanding of the underlying pathophysiological mechanism of skin changes has evolved, but preventive and treatment modalities remain unchanged—and limited.

Always counsel patients before a rash develops (and, ideally, before chemotherapy begins) that they should report a rash early in its development, to you or their oncologist, so that timely treatment can occur. Early recognition and intervention have proven benefits and can prevent the rash and its symptoms from becoming worse; if the rash remains uncontrolled, dosage reduction of the chemotherapeutic agent is an inevitable reality, and the clinical outcome of the primary disease might therefore not be ideal.

Prophylaxis. Daily application of an alcohol-free emollient cream is highly recommended as a preventive measure. Patients should be counseled to avoid activities and skin products that lead to dry skin, including long and hot showers; perfumes or other alcohol-based products; and soaps marketed for treating acne, which have a profound skin-drying effect.

Cornerstones of treatment include topical moisturizers, steroids, and antihistamines for symptom control. Once an identifiable skin rash has developed, a topical steroid cream is first-line treatment. Successful control has been reported with 1% hydrocortisone lotion applied daily to the affected area.
## TABLE

Cancer therapies\(^a\) that have the potential for skin toxicity\(^b\)

<table>
<thead>
<tr>
<th>Generic name (trade name; manufacturer)</th>
<th>Indication(s)</th>
<th>Target</th>
<th>Incidence of all-grade skin toxicity(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab (Erbitux; Bristol-Myers Squibb)</td>
<td>Colorectal Ca</td>
<td>EGFR</td>
<td>12%–90%</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva; Genentech)</td>
<td>NSCLC</td>
<td>EGFR</td>
<td>4.4%–12%</td>
</tr>
<tr>
<td></td>
<td>Pancreatic Ca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib (Iressa; AstraZeneca)</td>
<td>NSCLC</td>
<td>EGFR</td>
<td>47%</td>
</tr>
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<td></td>
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<td></td>
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<tr>
<td>Imatinib mesylate (Gleevec; Novartis)</td>
<td>CML</td>
<td>BCR-ABL</td>
<td>36%–47%</td>
</tr>
<tr>
<td></td>
<td>GIST</td>
<td>c-Kit</td>
<td></td>
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<tr>
<td></td>
<td>Ph+ ALL</td>
<td>PDGFR(\alpha)</td>
<td></td>
</tr>
<tr>
<td>Lapatinib (Tykerb; Novartis)</td>
<td>Breast Ca</td>
<td>EGFR</td>
<td>6%–53%</td>
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<tr>
<td></td>
<td></td>
<td>HER2</td>
<td></td>
</tr>
<tr>
<td>Osimertinib (Tagrisso; AstraZeneca)</td>
<td>CML</td>
<td>EGFR</td>
<td>14%–41%</td>
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<tr>
<td></td>
<td>Ph+ ALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab (Vectibix; Amgen)</td>
<td>Colorectal Ca</td>
<td>EGFR</td>
<td>90%</td>
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<tr>
<td></td>
<td></td>
<td>ErbB-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER1</td>
<td></td>
</tr>
<tr>
<td>Sorafenib (Nexavar; Bayer)</td>
<td>HCC</td>
<td>BRAF</td>
<td>11%–40%</td>
</tr>
<tr>
<td></td>
<td>RCC</td>
<td>c-Kit</td>
<td></td>
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<tr>
<td></td>
<td>Thyroid Ca</td>
<td>FLT3</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PDGFR(\beta)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAF1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VEGFR(_2),(_3)</td>
<td></td>
</tr>
<tr>
<td>Sunitinib (Sutent; Pfizer)</td>
<td>GIST</td>
<td>c-Kit</td>
<td>14%–30%</td>
</tr>
<tr>
<td></td>
<td>RCC</td>
<td>CSF1R</td>
<td></td>
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<td></td>
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<td>FLT3</td>
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<td></td>
<td></td>
<td>PDGFR(\alpha)</td>
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<td></td>
<td></td>
<td>RET</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>VEGFR(_1),(_3)</td>
<td></td>
</tr>
<tr>
<td>Temsirolimus (Torisel; Pfizer)</td>
<td>RCC</td>
<td>mTOR</td>
<td>12%–97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VEGF</td>
<td></td>
</tr>
<tr>
<td>Vandetanib (Caprelsa; AstraZeneca)</td>
<td>Medullary thyroid Ca</td>
<td>EGFR</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDGFR</td>
<td></td>
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<td>RET</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>VEGFR(_1),(_3)</td>
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</tbody>
</table>

\(^a\)Not an exhaustive list. All agents listed here are FDA approved for these indications.

\(^b\)Obtained from package inserts at www.accessdata.fda.gov/scripts/cder/defaf.

BCR-ABL, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog; BRAF, B-rapidly accelerated fibrosarcoma; Ca, cancer; c-Kit, receptor tyrosine kinase; CML, chronic myelogenous leukemia; CSF1R, colony stimulating factor 1 receptor; EGFR, epidermal growth factor receptor; ErbB-1, erythroblastic leukemia viral oncogene 1; FLT3, fms-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HER1, human epidermal growth factor receptor 1; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; NSCLC, non-small-cell lung cancer; Ph+ ALL, Philadelphia-positive acute lymphoblastic leukemia; PDGFR, platelet-derived growth-factor receptor; RAF1, Raf-1 proto-oncogene; RCC, renal carcinoma; RET, rearranged during transfection [proto-oncogene]; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
**Second- and third-line Tx.** If the rash progresses in size or severity, we recommend switching to 2% hydrocortisone valerate cream, applied twice daily. For a moderate-to-severe rash, an oral tetracycline is a valid option for its anti-inflammatory effects and, possibly, to prevent secondary infection. In the event of progression, refer the patient to an oncologist, who can consider suspending the anti-EGRF drug temporarily until the rash improves. If disease persists, consultation with a dermatologist is appropriate for consideration of systemic prednisolone.

**Alleviating discomfort.** Patients commonly report pruritus and mild-to-moderate pain with the rash; standard analgesic therapy is appropriate. Severe pain might indicate secondary infection; in that case, consider antibiotic therapy for presumed cellulitis. Moreover, because of the risk of thrombosis in the cancer population, underlying deep-vein thrombosis must always remain in the differential diagnosis of an erythematous rash.

A short course of systemic steroids might be beneficial for pain control; however, no data from clinical trials suggest that this is beneficial. Dermatology consultation is recommended before prescribing a systemic steroid.

Regrettably, treatment options for pruritus are limited. Antihistamines, such as diphenhydramine and hydroxyzine, can be considered, but their effectiveness is marginal. If a patient reports a painful rash, we recommend that you collaborate with the dermatologist and oncologist to make adjustments to the cancer treatment plan.

**Retinoids: Caution is advised.** Several case reports and a small investigational study describe a potential role for retinoids such as isotretinoin, a 13-cis retinoic acid, in the treatment of chemotherapy-related skin changes. Isotretinoin is available under several trade names in pill and cream formulations.

Retinoids exert their effect at the level of DNA transcription, and act as a transcription factor in keratinocytes. Their downstream signaling pathway includes EGRF signaling ligands; introduction of exogenous retinoids has been shown to deter development of EGFR-associated skin toxicity. Given the

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**FIGURE 1**

Adverse effects of EGFR-inhibitor therapy

**A**

*Acneiform rash.* Papulopustular eruptions resemble acne vulgaris and characteristically lack comedones, unlike acne vulgaris.

**B**

*Paronychia.* Soft-tissue inflammation affects proximal and lateral nail folds.

**C**

*Stomatitis.* Typically, oral mucositis develops 5–10 days after chemotherapy begins.
When a patient reports a painful rash, collaborate with the dermatologist and oncologist to make adjustments to the cancer treatment plan.

- **Recommend a sunscreen?** Given the endogenous role of EGFR in protecting skin from ultraviolet B damage, some clinicians have recommended that patients use a sunscreen. However, randomized, controlled trials have failed to demonstrate any benefit to their use with regard to incidence or severity of rash or patient-reported discomfort. We do not recommend routine use of sunscreen to prevent chemotherapy-induced skin changes, although sensible use during periods of prolonged sun exposure is encouraged.

### Risk of infection and the role of antibiotics

Skin damage can lead to further complications—namely, leaving the skin vulnerable to bacterial overgrowth and serious infection. The primary acneiform eruption is believed to be inflammatory in nature, with most cases being sterile and lacking bacterial growth. However, rash-associated infections are a common complication and leave the immunocompromised patient at risk of systemic infection. Harandi et al reported a 35% rate of secondary infection. Viral or bacterial growth (the primary pathogen is *Staphylococcus aureus*) within the wound can aggravate the severity of the rash, prohibit effective healing, and exacerbate the disfiguring appearance of the rash.

The use of a prophylactic antibiotic for treating a rash in this setting has been an active area of discussion and research, although no guidelines or recommendations exist that can be routinely employed. A comprehensive systematic review and meta-analysis demonstrated that, in patients undergoing EGFR-based therapy, those who received a prophylactic antibiotic had a lower risk of developing folliculitis than those who did not (odds ratio = 0.53; 95% confidence interval, 0.39-0.72; \( P < .01 \)).

A consensus agreement on the use of prophylactic antibiotics has yet to be reached. An emerging clinical practice entails the use of oral minocycline (100 mg/d) during the first 4 weeks of EGFR-based therapy because studies have shown a benefit from this regimen in reducing eruptions.

### Other adverse dermatologic effects to watch for

- **Paronychia** is common in patients undergoing EGFR therapy but, unlike the acneiform rash that typically occurs within 1 week of treatment, paronychia can occur weeks or months after initiation of therapy. Careful examination of the nail beds is important in patients undergoing EGFR therapy. Paronychia can affect the nail beds of the fingers and toes—most often, the first digits.

No evidence-based trials have been conducted to evaluate treatment options; recommendations provided are drawn from the literature and expert opinion. Patients are encouraged to apply petroleum jelly or an emollient daily both as a preventive measure and for mild cases. Patient counseling on the importance of nail hygiene and avoidance of aggressive manicures and pedicures is encouraged.

In the general population, acute and chronic paronychia entail infection with *S aureus* and *Candida* spp, respectively. To this end, there is a role for antibacterial and antifungal intervention. As is the case of the EGFR-associated acneiform rash, inflammation in paronychia is sterile, with only rare pathogen involvement.

There is no role for topical or systemic antibiotics in the cancer population suffering from paronychia. A viable treatment option for moderate lesions is betamethasone valerate, applied 2 or 3 times daily; if there is no resolution, clobetasol cream, applied 2 or 3 times daily, can be prescribed. The role of tetracyclines as anti-inflammatory agents in paronychia has not been studied to the extent it has been for acneiform rash; however, studies have shown a protective effect in small patient samples. In severe disease, the patient can be instructed to temporarily discontinue the drug and you can provide a referral to a dermatologist.

- **Stomatitis** is also an area of concern in this patient population. Prior
to initiating treatment, a thorough examination of the patient’s oral cavity and oropharynx should be conducted. Loose or improperly fitting dentures should be adjusted because they can prohibit effective healing after ulceration develops.

Stomatitis initially presents as erythematous or aphthous-like lesions, and can develop into acutely painful, large, continuous lesions.29 Timely management of stomatitis is beneficial to patient outcomes because it can lead to severe pain and interference in oral intake; uncontrolled disease requires interruption and dosage-reduction of cancer therapy.14,32

Patients should be encouraged to use soft-bristle toothbrushes and rinse with normal saline, not with commercial mouthwashes that typically contain alcohol. Grade 1 stomatitis (ie, pain and erythema) can be treated with triamcinolone dental paste, which can reduce inflammation caused by the ulcers. If disease progresses to Grade 2 to 3 stomatitis (erythema; ulceration; difficulty swallowing, or inability to swallow food), oral erythromycin (250-350 mg/d) or minocycline (50 mg/d) should be prescribed and the patient referred to a dermatologist.30

**Does rash correlate with cancer treatment efficacy?**

Despite troubling dermatologic effects of cancer therapies, a retrospective analysis of several clinical trials has revealed another side to this coin: namely, the appearance, and the severity, of a rash correlates positively with objective tumor response.14 That correlation allows the oncologist to use a rash as a surrogate marker of treatment efficacy20 (although, notably, there remains a lack of prospective trials that would validate a rash as such a marker). Epidermal growth factor receptor-tyrosine kinase inhibitors are mainly prescribed in patients who harbor an activating EGFR mutation; no studies have stratified patients by EGFR mutation and incidence of rash.31

The upshot? Although there are gaps in our understanding of the relationship between a rash and overall survival, we are nevertheless presented with this paradigm: A patient who is taking an EGFR-tyrosine kinase inhibitor and who develops a rash should be continued on that treatment for as long as can be tolerated, because the rash is presumed to be a sign that the patient is deriving the greatest clinical benefit from therapy.14,20,33

**References**

LETTERS

Erratum

The author list for the June 2019 PURL (“A better approach to the diagnosis of PE.” J Fam Pract. 2019;68:286,287,295) should have read: Andrew H. Slatten- gren, DO; Shailendra Prasad, MBBS, MPH; David C. Bury, DO; Michael M. Dickman, DO; Nick Bennett, DO; Ashley Smith, MD; Robert Oh, MD, MPH, FAAFP; Robert Marshall, MD, MPH, MISHM, FAAFP; North Memorial Family Medicine Residency, Department of Family Medicine and Community Health, University of Minnesota, Minneapolis (Drs. Slattengren and Prasad); Madigan Family Medicine Residency, Gig Harbor, Washington (Drs. Bury, Dickman, Bennett, Smith, Oh, and Marshall).

A solution for reducing referrals (and malpractice suits)

I agree with Dr. Hickner’s editorial “To refer—or not?” (J Fam Pract. 2019;68:8) that family physicians could manage about 30% of the patients they refer to specialists. Still, it’s worth noting that many referrals are motivated by the threat of unmerited malpractice suits. Until the medical liability system becomes less adversarial and unmerited suits are eliminated, all primary care doctors—not just family physicians—will continue to send patients to specialists—even when these physicians are themselves capable of treating such patients.

What might help mitigate malpractice suits? There could be benefit from oversight of health courts, which would be presided over by judges with special training in medical malpractice. Being nonadversarial, health courts would cut down on legal wrangling, settle suits, and get awards to patients quicker. They would also cut down on attorney and court fees, which account for almost half of the total amount spent on litigation. These courts wouldn’t completely eliminate unnecessary referrals to specialists, but they could help make a difference.

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