Management of Dermatologic Toxicities

Presented by Mario E. Lacouture, MD

Abstract
Dermatologic toxicities related to cancer therapies have become even more common with the use of targeted treatments. A proactive approach is necessary to reduce the pain and suffering these patients experience. The oncologist should become comfortable in preventing and managing these complications to keep patients on optimal drugs and doses. At the NCCN 20th Annual Conference, Dr. Mario E. Lacouture advised clinicians on appropriate strategies to manage rash, paronychia, alopecia, and other dermatologic conditions frequently seen in patients with cancer. (J Natl Compr Canc Netw 2015;13:686–689)

Oncology providers should take an early, proactive approach in managing dermatologic toxicities associated with cancer treatment, Mario E. Lacouture, MD, emphasized at the NCCN 20th Annual Conference.

These toxicities—which affect the hair, nails, and mucous membranes—strongly impact patients’ quality of life, sense of privacy, and physical, psychological, and financial well-being. Importantly, serious adverse events often result in treatment modification, which can compromise clinical outcomes, said Dr. Lacouture, Associate Professor of Dermatology at Cornell University and Associate Member of Memorial Sloan Kettering Cancer Center.

Skin Rash
Most FDA-approved targeted agents are associated with a wide spectrum of dermatologic toxicities. Dr. Lacouture made several key points about skin rash produced by different cancer therapies:

- Most patients taking EGFR inhibitors develop an acneiform rash on the face, scalp, and upper body, often within the first 4 weeks. This is associated with pruritus, tenderness, and even spontaneous bleeding. When EGFR inhibitors are combined with cytotoxic chemotherapy, the incidence of severe rash almost doubles.
- dMEK inhibitors produce acneiform rash in more than 50% of patients.
- BRAF inhibitors can produce a maculopapular rash that is “explosive,” occurring early and spreading quickly.
- mTOR inhibitors can produce an acneiform rash that is extremely pruritic, rarely affects the face, and mostly affects the trunk.
- Immunotherapies such as ipilimumab and PD-1 inhibitors produce a nonspecific maculopapular rash in about 20% of patients. This rash is usually pruritic.
• Cytotoxic chemotherapy may also be associated with skin toxicities. Gemcitabine, usually in combination with other agents, can produce a macular rash associated with edema in the extremities. Pemetrexed as a single agent produces rash in 17% of patients. Liposomal doxorubicin can produce intertriginous rash in 20%, with pain in the skin folds.

The mainstay of treatment for most macropapular rashes is medium- or high-potency topical steroids. In grade 3 rash, oral corticosteroids and antihistamines may be warranted. Oral aprepitant can address resistant pruritus. Oral corticosteroids and compression therapy can be useful for gemcitabine-associated peripheral edema. Maculopapular rash that is intertriginous (ie, in body folds) may not itch but can be painful and become infected; it is treated with topical corticosteroids and topical antibiotics.

Prophylactics for EGFR Inhibitor-Associated Rash

“The impact of an acneiform rash associated with EGFR inhibitors cannot be understated,” he said. Ironically, however, severity of rash corresponds to better response to treatment, according to several trials of metastatic colorectal cancer, with longer survival times among patients with grade 3 rash.1 Acne-like rash emerges first, followed by postinflammatory effects such as dry skin, fissures in palms and soles, and paronychia (nail changes).

Unfortunately, surveys have shown a high rate of discontinuation or reduction of EGFR inhibitors due to rash, Dr. Lacouture noted, “which underscores the notion that this rash should be prevented or treated very early.”

Dr. Lacouture cited a large body of data supporting prophylactic antibiotics to prevent this rash. Minocycline 100 mg per day was shown to reduce lesions by more than 50% and rash severity within the first 4 weeks of treatment with cetuximab.2 Similarly, 150 mg of minocycline twice per day on day 1 of treatment with erlotinib reduced rash by 40% compared with the reactive use of topical clindamycin plus hydrocortisone with and without minocycline.3 And prophylactic use of doxycycline 100 mg twice per day plus a low-potency topical steroid reduced grade 2 or higher skin toxicity by 70%, versus reactive treatment, and also reduced pruritus, secondary infections, and paronychia as well as non-dermatologic toxicities grade 3 or greater (diarrhea, neutropenia, etc).4

“Importantly, prophylaxis does not negate the beneficial anti-tumor effects of EGFR inhibitors,” he added.

Secondary infections often accompany this rash. He suggested having “a low threshold” for culturing any lesions with discharge, because almost 40% of patients taking EGFR inhibitors with skin toxicities develop secondary bacterial, viral, or fungal infections.

More than 6 months of EGFR inhibition is also likely to produce dry skin. Moisturizing is best accomplished with creams that contain ammonium lactate, salicylic acid, or urea, which provide good moisture retention along with easy application.

Severe pruritus associated with biologic agents often responds to the NK-1 receptor inhibitor aprepitant, as shown in a pilot study of patients with resistance to first-line oral antihistamines and corticosteroids. Of these patients, 91% had more than 50% reduction in intensity of pruritus, and itching recurred in only 13%.5

Paronychia

Some 15% to 25% of patients on EGFR and mTOR inhibitors can develop paronychia as a result of nail plate thinning, ingrowth of particles, and secondary infection. Treatment depends on severity. Nail avulsion sounds extreme, but patients are often relieved by it and return for additional procedures as needed, he said.

A different type of nail change is induced by taxanes, especially docetaxel, with which 30% of patients may demonstrate grade 3 toxicity. This involves elevation of the nail plate, inflammation, and sometimes subungual bleeding and pain. These adverse events can be prevented by cold therapy with ice packs for 15 minutes before infusion, during infusion, and 15 minutes after infusion.

Brittle nails are also a consequence of EGFR inhibition. Brittle nails are also often seen in patients with breast cancer receiving everolimus or trastuzumab/pertuzumab. For repairing splitting, ridges, and fragility, Dr. Lacouture recommended a hydrosoluble nail lacquer or the prescription product polyureaurethane 16%, which produce a rigid barrier to the nail plate. The dietary supplement biotin (2.5

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Hand-Foot Syndrome

Hand-foot syndrome (HFS) can be seen with a variety of cancer drugs, and its manifestations can differ by drug class. With taxanes, lesions are erythematous and maculopapular; with anthracyclines and anti-metabolites, erythema, fissuring, and edema may be seen. With multikinase inhibitors, blisters may form with erythematous halo, followed by hyperkeratosis, which can be painful (seen in 60% of patients treated with regorafenib). Due to peripheral vasoconstriction, patients can develop skin fragility and blisters in other areas subject to trauma, such as the elbow.

The only randomized study of HFS prevention, conducted in patients receiving capecitabine, showed that prophylactic celecoxib 200 mg/day reduced HFS grade 2 or greater by more than 50%.\(^6\) Oral corticosteroids can be beneficial when HFS is due to liposomal doxorubicin.

Anecdotally, several agents may ameliorate HFS induced by multikinase inhibitors: clobetasol foam, salicylic acid 6% cream, and lidocaine creams and patches. Topical urea 10% was only mildly effective in a recent randomized study of 871 patients treated with sorafenib.\(^7\) “There’s lots of room for improvement in treating HFS,” Dr. Lacouture acknowledged.

Alopecia

Alopecia has long been a side effect of treatment that greatly concerns patients. In addition to alopecia related to cytotoxics, hair thinning can also occur with inhibitors of BRAF, MEK, EGFR, and hedgehog signaling pathway. Dr. Lacouture made the following recommendations to prevent or manage hair loss:

- Correcting thyroid, iron, and vitamin abnormalities, in addition to minoxidil 5% twice daily, are mainstays of therapy for alopecia.
- For eyelash alopecia, bimatoprost has been shown to increase the length of eyelashes in patients undergoing chemotherapy almost threefold and to more than double eyelash thickness.\(^10\)
- The use of scalp cooling, ie, a “cold cap,” during chemotherapy has been shown to prevent hair loss. In a study involving 1400 patients, 50% of patients who used scalp-cooling did not wear a head covering during their last chemotherapy session.\(^11\) In another study of 57 patients, protection from severe hair loss was seen in 36% to 92%, depending on chemotherapy regimen.\(^12\)
- Topical minoxidil reduces the duration of complete hair loss by approximately 2 months.\(^13\)

Dr. Lacouture concluded by emphasizing that dermatologic toxicities matter even more to patients now as they are “surviving longer, and therefore have more opportunity to worry about their appearance.
and quality of life issues. In the majority of patients, dermatologic events can be well managed.\textsuperscript{14,15}

References


