Targeted Agents: Management of Dermatologic Toxicities

Presented by Barbara Burtness, MD

Abstract

Epidermal growth factor receptor (EGFR) inhibitors are widely used in the treatment of many cancers, and the cutaneous toxicity profile associated with these agents has become prominent. In fact, dermatologic side effects have also been reported with other targeted agents, including both BRAF and mTOR inhibitors. During her presentation at the NCCN 19th Annual Conference, Dr. Barbara Burtness reviewed the array of skin complications caused by many targeted therapies, focusing on the more common culprits, the role of prophylactic versus reactive management strategies, the need to be attentive to potential infections, the importance of mastering local measures to improve quality of life and cosmetic issues, the therapeutic mainstays (oral and topical antibiotics and topical steroids), and the preference of improving these cutaneous complications over suspending anticancer treatment. (*J Natl Compr Canc Netw* 2014;12:793–796)

"The advent of targeted therapies has been an enormous breakthrough for our patients, but it certainly has not been as free of side effects as we initially hoped it might be," declared Barbara Burtness, MD, Clinical Research Program Leader of the Head and Neck Cancers Program, Smilow Cancer Hospital at Yale-New Haven. Dr. Burtness is a member of the NCCN Guidelines Panel for Head and Neck Cancers and the NCCN Task Force on Management of Dermatologic and Other Toxicities Associated with EGFR Inhibition in Patients with Cancer. Although typically not dramatic, these skin complications can represent a chronic struggle for patients, negatively impacting their overall quality of life.

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Dermatologic Complications of Targeted Therapy

A wide assortment of adverse skin effects are associated with the use of epidermal growth factor receptor (EGFR) inhibitors such as cetuximab and erlotinib. Although papulopustular rash may be the most commonly observed side effect of these targeted agents, non-rash skin toxicities often affect the hair, nails, and eyes as well.[1] Regardless of where they manifest, these dermatologic complications require early detection and management.

Dr. Burtness focused first on skin rash, which affects the face and upper body. It generally occurs within 8 to 10 days of targeted therapy and peaks in 2 weeks. "Although clinically it may look a lot like acne, this rash is not acne," warned Dr. Burtness. The phases of the papulopustular reaction begin with sensory disturbance (erythema or edema) and may progress to papulopustular skin eruption, skin crusting, and telangiectasia.

Although these skin rashes can negatively affect a patient's quality of life, physicians and patients alike should view their development as a positive event, indicative of a greater likelihood of clinical benefit.[2] Evidence has shown that the intensity of the rash seems to correlate with outcome.[2] For example, in almost 90 patients treated with the EGFR inhibitor erlotinib who had no rash, the median survival was 3.3 months, whereas in more than 200 patients with at least a grade 2 rash, the median survival was 11.1 months, according to the findings of 2 large phase III studies.[2]

"The survival curves were better for those with prominent rash than for those with minimal rash," Dr.

Burtness confirmed. Therefore, managing the rash and keeping patients on EGFR inhibitor therapy should be the goal instead of interrupting or reducing the dose of therapy, she suggested.

Periungual and nail alterations develop in about 12% to 16% of patients treated with targeted therapies, stated Dr. Burtness. Affecting both fingernails and toenails, these complications usually occur after 4 to 8 weeks of therapy, and topical steroids and silver nitrate have been used to improve these conditions, she added. The nail disease paronychia is the result of a bacterial, viral, or fungal infection; Dr. Burtness emphasized the role of culturing these infections and appropriately administering oral antibiotics.

Fissures represent a postinflammatory symptom, which may respond to protective coverings and topical steroids. Cyanoacrylate adhesive dressing may help to relieve pain and promote skin healing. Fissures appear to be less likely with cetuximab and accelerated radiotherapy for head and neck cancer but more common with long-term single-agent cetuximab for colorectal cancer, observed Dr. Burtness. "With cetuximab and erlotinib, paronychial fissures are later events, whereas rash predominantly develops early," she remarked.

Targeted therapies may affect patients' hair in the form of alopecia. Early alopecia is characterized by a mixed inflammatory infiltrate. Late alopecia is not associated with scarring, but the hair becomes curly and brittle. This affects between 4% and 11% of patients after 2 to 3 months of treatment, noted Dr. Burtness.

Dr. Burtness suggested that reactive treatment of skin complications is typically sufficient, although she noted that several small trials have looked at the role of prophylactic treatment.[3,4] In one randomized trial of about 50 patients, the use of oral minocycline, topical tazarotene, or both to reduce or prevent cetuximab-related acneiform rash was evaluated.[3] Prophylaxis with oral minocycline was somewhat effective in reducing the number of facial lesions, but the investigators did not recommend tazarotene, as it caused significant skin irritation.[3]

The STEPP trial compared preemptive and reactive skin treatment on panitumumab-related skin toxicities and quality of life in almost 100 patients who concomitantly received FOLFIRI (folinic acid, fluorouracil, and irinotecan) or irinotecan.[4] The preemptive strategy included skin moisturizer, sunscreen, a low-potency topical steroid, and doxycycline. The investigators found that fewer patients had grade 2 or higher skin toxicity in the preemptive treatment group than in the reactive treatment group (29% vs 62%). However, this benefit came at the cost of increased gastrointestinal toxicity.

In closing, prophylactic treatment of dermatologic toxicity associated with targeted therapy may be helpful in delaying the development of grade 2 or higher skin rash. However, Dr. Burtness explained that patients would respond to these same agents if they in fact did develop skin rash, and so she questioned whether the increase in gastrointestinal toxicity would be worth the benefit. Thus, the issue of prophylactic versus reactive treatment remains debatable among both practitioners and patients at this time.

A Glimpse at Ocular Toxicity and EGFR Inhibitors

Dr. Burtness briefly reviewed the effect of EGFR inhibitors on the eyes (Figure 1). Among the reported ocular side effects are conjunctivitis, blepharitis, trichomegaly, corneal erosion, and dry eye. She also discussed some of the symptoms associated with these side effects.

Eyelash changes include patchy eyelash loss and abnormally long eyelashes. Misdirected eyelashes may cause corneal microerosions or tearing, requiring trimming or permanent removal with diathermy by an ophthalmologist, stated Dr. Burtness, although trimming these eyelashes on follow-up appointments generally is sufficient. With blepharitis, the patient may experience soreness of the eyelid margin and crusting, and matting of the eyelashes on waking. The most common tear film change is dysfunction tear syndrome, in which patients may complain of burning or grittiness in the eyes or vision fluctuation with blinking.

Dr. Burtness cautioned against the routine use of a steroid-containing eyedrops. "This is one situation where I would probably have an ophthalmologist involved every time. If there were a suprainfection, the use of a topical steroid might actually make things much worse," she cautioned.

Other Targeted Agents: Beyond EGFR Inhibitors

EGFR inhibitors are not the only targeted agents that may cause dermatologic toxicities. Cutaneous

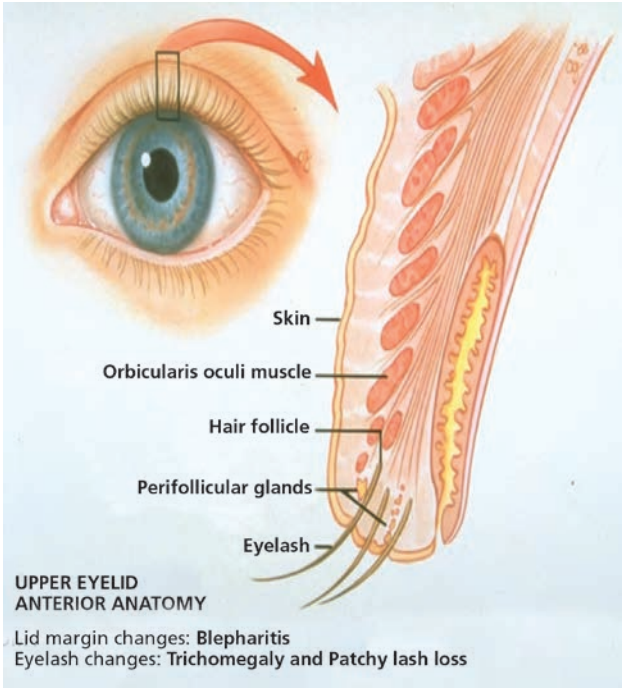

Figure 1 Eyelid changes with EGFR inhibition.

toxic effects have been reported with both BRAF and mTOR inhibitors as well.[5,6] BRAF inhibitors, such as sorafenib and vemurafenib, have been associated with hand-foot skin reaction (HFSR),[5] and the newer BRAF inhibitor regorafenib "has some pretty dramatic skin manifestations," noted Dr. Burtness. mTOR inhibitors, such as temsirolimus and everolimus, may cause stomatitis with ulceration and an erythematous halo, which clinically resembles aphthous stomatitis, as well as yellow, fragile nails (Figure 2), she added.

Huang et al[5] reported on the cutaneous toxic effects associated with vemurafenib in patients treated for advanced melanoma. Among the plethora of complications that appeared after 1 month of treatment were keratosis pilaris–like eruptions, abundant facial cystic cutaneous lesions, and HFSR with hyperkeratotic plaques. "The chronic granulomatous eruption noted with the BRAF inhibitors differs from the pustular, infected skin manifestations of the EGFR inhibitors," clarified Dr. Burtness. The most dramatic complication with BRAF inhibitors is the development of new skin cancers, such as eruptive squamous cell carcinomas.[5] "We need to be aggressive about managing these skin cancers with resection and close follow-up," she recommended.

The novel tyrosine kinase inhibitor regorafenib was the subject of a recent meta-analysis to determine the incidence and risk of developing HFSR in patients with cancer.[6] Erythema and edema over the pressure areas (soles) and hyperkeratosis (forefeet) consistent with a grade 2 HFSR have been linked to the use of regorafenib, stated Dr. Burtness. The investigators found that the incidence and risk of developing HFSR with regorafenib are high and may vary significantly with tumor type.[6] "Interestingly, the HFSR [with regorafenib] seems to be more common in those with renal cell carcinoma than in those with colorectal cancer," she remarked.

Finally, patients who are treated with lenalidomide or the immune checkpoint inhibitor ipilimumab may be at risk of developing a skin rash.[7,8] Usually occurring within the first 2 weeks of treatment, the rash often has a maculopapular or morbilliform pattern, and exfoliative skin lesions are rare, according to Dr. Burtness. Along with high rates of rash with the use of ipilimumab,[8] Dr. Burtness mentioned that pruritus, vitiligo (depigmentation of the parts of the skin), generalized erythema, erythematous macules, and heme-crusted papules have also been noted. Furthermore, PD-1 inhibitors, such as nivolumab, may be associated with Stevens-Johnson syndrome or toxic epidermal necrolysis, she added.

Figure 2 Skin effects of mTOR inhibitors. (A) Typical mTOR inhibitor–associated stomatitis with ulceration and erythematous halo clinically resembling aphthous stomatitis. (B,C) Yellow fragile nails, distal onycholysis.

Dermatologic Effects Are More Than Skin Deep

The dermatologic toxicities associated with the use of targeted therapies affect more than just a patient's skin. The quality of daily living can be seriously impacted by the cutaneous complications of treatment with EGFR inhibitors, in particular. Dr. Burtness briefly mentioned 2 quality-of-life measures—the Skindex-16 and the FAST-EGFRI (Functional Assessment of Side Effects to Therapy with EGFR Inhibitors)—that help patients and their health care team identify the most significant factors affecting a patient's health-related quality of life.

The Skindex-16 is a dermatology-specific, patient-reported quality-of-life questionnaire. The study results of almost 60 patients who completed the Skindex-16 showed a correlation between the NCI-issued CTCAE (Common Terminology Criteria of Adverse Events) grade of papulopustular rash and the dermatology-specific quality of life.[9] In addition, not only did those with higher grades of rash have an increase in skin symptoms, they also had an increase in emotional and functional impairment.

The FAST-EGFRI is a patient-reported outcomes measure to assess the skin-related symptom burden and health-related quality of life indictators among patients receiving an EGFR inhibitor. In one small study, 18 patients with cancer and 11 expert clinicians completed the FAST-EGFRI to determine the most concerning health-related quality-of-life factors.[10] The symptoms reported frequently by both the patients and clinicians were painful, burning, itchy skin; pain in the fingers and toes; and increased facial hair. In addition, depression affecting patients' social life signaled the psychosocial component of these dermatologic side effects.

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