Cutaneous adverse effects of targeted therapies

Part II: Inhibitors of intracellular molecular signaling pathways

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Learning objectives
After completing this learning activity, participants should be able to describe the management strategies of cutaneous adverse effects associated with 11 families of targeted therapies currently in prevalent use.

Disclosures
None declared.

The last decade has spawned an exciting new era of oncotherapy in dermatology, including the development of targeted therapies for metastatic melanoma and basal cell carcinoma. Along with skin cancer, deregulation of the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK intracellular signaling pathways contributes to tumorigenesis of a multitude of other cancers, and inhibitors of these pathways are being actively studied. Similar to other classes of targeted therapies, cutaneous adverse effects are among the most frequent toxicities observed with mitogen-activated protein kinase pathway inhibitors, PI3K-AKT-mTOR inhibitors, hedgehog signaling pathway inhibitors, and immunotherapies. Given the rapid expansion of these families of targeted treatments, dermatologists will be essential in offering dermatologic supportive care measures to cancer patients being treated with these agents. Part II of this continuing medical education article reviews skin-related adverse sequelae, including the frequency of occurrence and the implications associated with on- and off-target cutaneous toxicities of inhibitors of the RAS-RAF-MEK-ERK pathway, PI3K-AKT-mTOR pathway, hedgehog signaling pathway, and immunotherapies. (J Am Acad Dermatol 2015;72:221-36.)

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RAS-RAF-MEK-ERK PATHWAY

The RAS-RAF-MEK-ERK (mitogen-activated protein kinase [MAPK]) pathway is one of the most frequently deregulated signaling pathways leading to increased cellular proliferation in a broad spectrum of cancers. Patients who are taking inhibitors of the MAPK pathway frequently present with cutaneous adverse effects (AEs). The extensive interaction of the MAPK pathway with the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway by sharing common inputs and activation through oncogenic RAS (Fig 1) provides a possible mechanism for compensatory signaling and the development of tumor resistance to targeted

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Abbreviations used:

AE:	adverse effect
CIA:	chemotherapy-induced alopecia
CTLA-4:	cytotoxic T lymphocyte–associated antigen 4
EGFR:	epidermal growth factor receptor
HhSP:	hedgehog signaling pathway
MAH:	melanoma-associated hypopigmentation
MAPK:	mitogen-activated protein kinase
MED:	minimal erythema dose
mTOR:	mammalian target of rapamycin
PD-1:	programmed death 1
PTCH1:	patched homologue 1
SCC:	squamous cell carcinoma
SMO:	smoothened homologue
UVA:	ultraviolet A

monotherapy. One approach used to overcome this challenge is to use a dual pathway–targeted approach. However, although this provides increased potential for clinical benefit, it is often accompanied by a greater degree of toxicity, especially to the skin.[1]

RAF INHIBITORS

Key points

- **Cutaneous eruptions, keratotic squamoproliferative lesions, and photosensitivity are among the most debilitating skin-related adverse effects of RAF inhibitors**
- **Preventative measures and conservative treatments generally control most drug-related adverse effects; surgical treatment may be needed for select aggressive neoplasms**
- **Close interval follow-up appointments optimize supportive care for RAF inhibitor patients, because skin toxicities are numerous**

BRAF, an upstream activator in the MAPK pathway, is mutated in approximately 40% to 60% of cutaneous melanomas.[2] In addition, BRAF is one of the most frequently mutated protein kinases found in all human cancers.[3] Malignancies with the highest association with BRAF mutation, the so-called BRAFomas, include hairy cell leukemia (100%), melanoma (~50%), papillary thyroid (~40%), serous ovarian (~30%), colorectal (<10%), and prostate (<10%).[4,5] The majority of BRAF mutant melanomas contain a substitution of glutamic acid for valine at codon 600 (BRAF V600E). This mutation constitutively activates BRAF kinase, resulting in hyperproliferation of melanocytes.[6] Targeted therapies of mutated BRAF, such as vemurafenib and dabrafenib, have emerged as successful treatments for patients with metastatic melanoma, both as monotherapy[7,8] and in combination with MEK inhibition.[9] Cutaneous reactions associated with these agents are common and may be dose-limiting. Treatment considerations are outlined below each AE and summarized in Table I.

Cutaneous eruption

Eruptions may occur in up to 68% of patients taking vemurafenib, with up to 8% experiencing grade 3 symptoms (affecting ≥50% body surface area itching or soreness).[8,10,11] The eruption has most commonly been described as folliculocentric smooth papules that coalesce into broad morbilliform or toxic, erythema-like plaques involving the torso and extremities, with sparing of the head and neck.[12] Associated acute kidney injury has been described.[13] Histopathology reveals features of exanthematous drug eruption.[12] The use of vemurafenib after initial treatment with ipilimumab may be associated with a higher likelihood of severe skin toxicity.[14]

Treatment of eruptions. Emollients and careful observation are sufficient for grade 1 eruptions. Associated symptoms of grade 2 and 3 eruptions can be controlled with antihistamines and topical steroids (class II-III). Severe cases may require a 5- to 7-day course of systemic steroids and/or treatment interruption. If halting treatment is necessitated because of intolerable symptoms, vemurafenib can be reintroduced with a 25% dose reduction after symptoms abate,[15] typically without worsening of the eruption.[8,12] Hospital admission with intravenous fluid resuscitation and immediate drug discontinuance is needed for the rare grade 4 eruption.

Epidermal neoplasms (ie, squamous cell carcinoma, keratoacanthoma, verrucal keratoses)

Keratinocyte proliferation is characteristic of BRAF inhibitor–induced adverse skin reactions and presents as a broad spectrum of cutaneous toxicities from verrucal keratoses to invasive squamous cell carcinoma (SCC; Fig 2). The mechanism for formation of SCC in patients treated with RAF inhibitors has been a subject of active research. Biochemical studies[16-19] have shown that RAF blockade in wild-type BRAF cells, particularly in the presence of oncogenic RAS mutations (eg, sun-damaged keratinocytes in a patient with melanoma), can lead to paradoxical MAPK pathway activation through dimerization of RAF isomers (BRAF-CRAF, BRAF-AFAR, and CRAF-CRAF).[18,20,21] Indeed, studies have shown a high prevalence of RAS mutations in cutaneous SCCs developing in