Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma

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Background: BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi) frequently cause cutaneous adverse events.

Objective: We sought to investigate the cutaneous safety profile of BRAFi versus BRAFi and MEKi combination regimens.

Methods: We performed a retrospective cohort study, collecting data from 44 patients with melanoma treated either with BRAFi (vemurafenib or dabrafenib) or BRAFi and MEKi combination regimens (vemurafenib + cobimetinib or dabrafenib + trametinib). Patient characteristics, and the occurrence and severity of cutaneous adverse events, are described.

Results: The development of cutaneous adverse events was significantly less frequent (P = .012) and occurred after longer treatment time (P = .025) in patients treated with BRAFi and MEKi combination regimen compared with patients treated with BRAFi monotherapy. Among patients who received both BRAFi and the combination of BRAFi and MEKi at different time points during their treatment course, the development of squamous cell carcinoma or keratoacanthoma was significantly less frequent when they received the combination regimen (P = .008). Patients receiving vemurafenib developed more cutaneous adverse events (P = .001) and in particular more photosensitivity (P = .010) than patients who did not.

Limitations: There were a limited number of patients.

Conclusion: Combination regimen with BRAFi and MEKi shows fewer cutaneous adverse events and longer cutaneous adverse event-free interval compared with BRAFi monotherapy. (J Am Acad Dermatol 2014;71:1102-9.)

Key words: cutaneous adverse event; histology; inflammation; rash; squamous cell carcinoma; therapy.

Pharmacologic inhibition of the mitogen-activated protein kinase (MAPK) pathway by targeting the mutant BRAF is a milestone in the management of metastatic melanoma. BRAF inhibitors (BRAFi), such as vemurafenib and dabrafenib, have been associated with prolonged progression-free and overall survival.[1,2] MEK inhibitors (MEKi), such as cobimetinib[3] and trametinib,

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have also been associated with improved progression-free and overall survival in BRAF[4] mutant melanoma and NRAS[5] mutant melanoma. Despite these advances in melanoma treatment, disease progression occurs in approximately 50% of patients within 6 to 7 months of commencing therapy with either a BRAFi or MEKi.[1,2,4,6] This is a result of several mechanisms of resistance, most of which seem to rely on reactivation of the MAPK pathway.[7-9] Therefore, to avoid or delay resistance to a single drug, combination therapies with BRAFi and MEKi have been explored.[10] In phase I and II studies, combination regimens showed improved progression-free survival over single inhibitor therapy.[10] Vemurafenib and dabrafenib are approved by the Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation, as detected by an FDA-approved test. The recommended dosages of vemurafenib and dabrafenib are 960 mg and 150 mg, respectively, both taken orally twice a day (bid). Trametinib is approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E and V600K mutations, as detected by an FDA-approved test, and the recommended dose is 2 mg orally once daily. Ongoing clinical trials are exploring these drugs in an adjuvant setting for patients with stage III (American Joint Committee on Cancer) disease.[11] Treatment with vemurafenib causes a multitude of cutaneous adverse events, such as exanthema, photosensitivity, palmar-plantar dysesthesia or hand-foot syndrome, alopecia, pruritus, keratosis pilaris–like eruptions, actinic keratosis (AK), hyperkeratosis, skin papillomas, keratoacanthomas (KA), and cutaneous squamous cell carcinomas (SCC).[1,6,12-14] The most frequent cutaneous adverse events of dabrafenib are hyperkeratosis, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. Trametinib is more frequently related with the development of acneiform dermatitis or alopecia.[4,15] Less is known about the cutaneous adverse events related to cobimetinib. In a phase Ib trial where cobimetinib was administered in combination with a pan-PI3K inhibitor, 50% of the patients developed a rash.[16] Interestingly, when BRAFi and MEKi drugs are combined, the development of cutaneous adverse events specific for each drug appear to be reduced.[4,10]

The number of patients treated with BRAFi and MEKi combination is increasing, and a better understanding of the type and morphology of related cutaneous adverse events and their management is needed. In this retrospective study, we collected data on 44 patients treated with either a BRAFi alone or the combination of a BRAFi and a MEKi. We have clinically and histologically characterized the cutaneous adverse events of BRAFi monotherapy and of combination regimens.

CAPSULE SUMMARY

- BRAF and MEK inhibitors frequently cause cutaneous adverse events.
- Combination of BRAF and MEK inhibitors shows fewer cutaneous adverse events and longer cutaneous adverse event-free interval compared with BRAF inhibitor monotherapy.
- The knowledge of expected cutaneous adverse events can help clinical decision-making during follow-up.

METHODS

We performed a retrospective cohort study, and included patients with stage IV or unresectable stage III melanoma[17] who received BRAFi monotherapy or BRAFi + MEKi combination therapy. All patients were treated and followed up at the University of California–San Francisco between November 2009 and August 2013. In all, 32 patients received treatment with a BRAFi and 23 patients received BRAFi + MEKi combination. Eleven patients received both BRAFi monotherapy and BRAFi + MEKi regimen at different time points during their treatment. Among the patients treated with a BRAFi: 27 received vemurafenib (PLX4032) at a dose of 960 mg bid (phase III clinical trial, NCT01006980), and 5 received dabrafenib (GSK2118436) at a dose of 150 mg bid (phase III clinical trial, NCT01227889). In the BRAFi + MEKi group, 15 patients received a combination of dabrafenib at 150 mg bid and trametinib (GSK1120212) at 2 mg daily (phase II clinical trial, NCT01072175), and 8 patients received a combination of vemurafenib at 960 mg bid on days 1 to 28 of each cycle and cobimetinib (GDC-0973) at 60 mg daily on days 1 to 21 of each cycle (phase Ib clinical trial, NCT01271803). All treatment decisions were made by the patient's medical oncologist. Collected data included patient demographics, course of the disease, medications (previous chemotherapy and immunotherapy—including interleukin 2, interferon, or anti-CTLA 4 antibodies), cutaneous adverse events, the treatment of those adverse events, and the response to treatment. Patients were evaluated at baseline by a dermatologist with full-body skin examinations and followed up at 4- to 6-week