Original Investigation

Cutaneous Toxic Effects of BRAF Inhibitors Alone and in Combination With MEK Inhibitors for Metastatic Melanoma

Giuliana Carlos, MBBS; Rachael Anforth, BMed; Arthur Clements, BSc (Med), MBBS; Alexander M. Menzies, MBBS; Matteo S. Carlino, MBBS; Shaun Chou, MBBS; Pablo Fernandez-Peñas, MD, PhD

IMPORTANCE The cutaneous adverse effects of the BRAF inhibitors vemurafenib and dabrafenib mesylate in the treatment of metastatic melanoma have been well reported. The addition of a MEK inhibitor to a BRAF inhibitor improves the blockade of the mitogen-activated protein kinase pathway. The combination of dabrafenib with the MEK inhibitor trametinib dimethyl sulfoxide (CombiDT therapy) increases response rate and survival compared with a BRAF inhibitor alone. Clinical trials have suggested that CombiDT therapy induces fewer cutaneous toxic effects than a single-agent BRAF inhibitor. To our knowledge, a direct comparison has not been performed before.

OBJECTIVE To compare the cutaneous toxic effects of BRAF inhibitor monotherapy and CombiDT therapy in a large cohort of patients.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective cohort study from September 1, 2009, through November 30, 2013. The study population included 185 Australian patients with unresectable stages IIIC and IV melanoma referred from Crown Princess Mary Cancer Care Centre who underwent review at the Department of Dermatology, Westmead Hospital. Of these, 119 patients received dabrafenib; 36, vemurafenib; and 30, CombiDT therapy. Data analysis were performed in December 2013.

MAIN OUTCOMES AND MEASURES Multiple cutaneous adverse effects between BRAF inhibitor monotherapy and CombiDT therapy were identified and compared in a cohort of patients who underwent the same dermatologic assessment.

RESULTS The most common cutaneous adverse effects seen in patients receiving the single-agent BRAF inhibitor dabrafenib or vemurafenib included Grover disease (51 patients [42.9%] and 14 [38.9%], respectively [$P = .67$]), plantar hyperkeratosis (47 [39.5%] and 14 [38.9%], respectively [$P = .95$]), verrucal keratosis (79 [66.4%] and 26 [72.2%], respectively [$P = .51$]), and cutaneous squamous cell carcinoma (31 [26.1%] and 13 [36.1%], respectively [$P = .54$]). Photosensitivity was more common with vemurafenib (14 patients [38.9%]) compared with dabrafenib (1 [0.8%]; $P < .001$). Compared with dabrafenib, CombiDT therapy showed a higher frequency of folliculitis (12 patients [40.0%] vs 8 [6.7%]; $P < .001$) and a significant decrease of cutaneous squamous cell carcinoma (0 vs 31 [26.1%]; $P < .001$), verrucal keratosis (0 vs 79 [66.4%]; $P < .001$), and Grover disease (0 vs 51 [42.9%]; $P < .001$).

CONCLUSIONS AND RELEVANCE This study confirms that the prevalence of cutaneous toxic effects differs among vemurafenib, dabrafenib, and CombiDT therapies. Cutaneous squamous cell carcinoma is the most concerning cutaneous toxic effect related to BRAF inhibitor monotherapy that did not appear with CombiDT therapy. Although CombiDT therapy has an improved profile of cutaneous toxic effects, continuous dermatologic assessments should be provided for all patients when receiving these treatments.

JAMA Dermatol. 2015;151(10):1103-1109. doi:10.1001/jamadermatol.2015.1745
Published online July 22, 2015.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Pablo Fernandez-Peñas, MD, PhD, Department of Dermatology (Building D, Level 5, Ward A), Westmead Hospital, Darcy Road, Westmead, New South Wales, Australia 2145 (pablo.fernandezpenas@sydney.edu.au).

The BRAF inhibitors vemurafenib and dabrafenib mesylate have revolutionized the treatment of stage IV metastatic melanoma with a survival benefit over dacarbazine chemotherapy in BRAF-mutant melanoma.[1,2] The MEK inhibitor trametinib dimethyl sulfoxide has also shown a survival benefit in the same population.[3] The combination of dabrafenib and trametinib improves the response rate and progression-free survival compared with dabrafenib alone and overall survival compared with vemurafenib.[4] These agents are associated with a number of cutaneous toxic effects, many of which are reduced when BRAF and MEK inhibitors are given concurrently.[5] Cutaneous squamous cell carcinomas (SCCs) constitute the toxic effect of most concern associated with BRAF inhibitor monotherapy and have been reported with the use of vemurafenib and dabrafenib,[6] whereas acneiform eruptions are more frequent with the use of the MEK inhibitor trametinib.[7] In this study, we describe the cutaneous toxic effects arising in a large cohort of patients treated with a single-agent BRAF inhibitor (dabrafenib or vemurafenib) or a combination of dabrafenib and trametinib (CombiDT) for metastatic melanoma at a single institution.

Methods

We reviewed the medical records from all patients (n = 211) with advanced melanoma referred from Crown Princess Mary Cancer Care Centre for treatment at the Department of Dermatology, Westmead Hospital, from September 1, 2009, through November 30, 2013, for inclusion into the study. Patients with unresectable stages IIIC and IV melanoma who were treated with the BRAF inhibitor vemurafenib or dabrafenib alone or CombiDT therapy were included (N = 185). All patients were recruited according to the clinical trial protocols, which were approved by the Westmead Hospital independent ethics committee and performed in accordance with good clinical practice guidelines. All patients provided written and verbal informed consent. Data for the analyses were deidentified.

Patients underwent full-body skin examinations by a dermatologist (P.F.-P.); 55 of 185 patients (29.7%) had an assessment before treatment and then every 4 to 8 weeks or earlier if deemed clinically necessary. On examination, any lesion suggestive of a cutaneous malignant neoplasm was photographed and underwent biopsy for further histologic evaluation. If confirmed as potentially malignant, the lesion was completely excised.

Data analysis was performed in December 2013. We performed statistical analysis using JMP 8 software (SAS Institute Inc). Owing to multiple comparisons, the Bonferroni correction method was applied to determine statistical significance (level of significance, <.0023).[8]

Results

Patient Characteristics

We included a total of 185 patients in the study. One hundred fifty-five patients were treated with a single-agent BRAF inhibitor (119 with dabrafenib and 36 with vemurafenib), and 30 patients were treated with CombiDT therapy.

We found no statistically significant differences in sex distribution between vemurafenib (27 of 36 patients [75.0%] were men), dabrafenib (84 of 119 patients [70.6%] were men), and CombiDT therapy (16 of 30 patients [53.3%] were men). Patients treated with vemurafenib were significantly older than those treated with dabrafenib (60 vs 53 years of age; $P = .045$), but no significant differences were found between other treatment groups. We found no statistically significant differences in treatment duration, with the median treatment duration of 26 (range, 7-98) weeks for vemurafenib, 33 (range, 3-211) weeks for dabrafenib, and 42 (range, 7-145) weeks for CombiDT therapy.

Cutaneous Toxic Effects

The BRAF inhibitor–induced cutaneous toxic effects were near universal for patients treated with BRAF inhibitor monotherapy (142 of 155 patients [91.6%]). They were also prevalent in those treated with CombiDT therapy (23 of 30 patients [76.7%]).

BRAF Inhibitor Monotherapy

Common cutaneous toxic effects seen in patients receiving BRAF inhibitor monotherapy included verrucal keratosis, Grover disease, plantar hyperkeratosis, cutaneous SCC, and actinic keratosis (**Table 1**). Approximately three-quarters of patients treated with BRAF inhibitor monotherapy developed adverse effects resulting from paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway and subsequent keratinocyte hyperproliferation (eg, cutaneous SCC, verrucal keratosis, and plantar hyperkeratosis) (Table 1).

Verruciform keratotic squamoproliferative lesions or verrucal keratosis[9] constituted the most common adverse effect in more than 60% of patients treated with a single-agent BRAF inhibitor in this study (79 [66.4%] treated with dabrafenib and 26 [72.2%] treated with vemurafenib). These lesions presented as early as 7 days after the start of treatment and continued to occur throughout the treatment period (**Figure**, A).

The next most frequent skin eruption seen in patients treated with single-agent BRAF inhibitor was Grover disease (Figure, B). Fifty-one patients receiving dabrafenib (42.9%) and 14 patients receiving vemurafenib (38.9%) developed scattered hyperkeratotic papules with variable degrees of itch and inflammation on the trunk.

The most relevant cutaneous adverse event, always reported as a grade 3 toxic effect in clinical trials, was the development of cutaneous SCCs. All lesions suggestive of SCC underwent biopsy or excision with clinical borders according to Australian guidelines.[10] All biopsy specimens were sent to the Department of Tissue Pathology and Diagnostic Oncology, Westmead Hospital for histopathologic evaluation and confirmation. Although we found that 13 vemurafenib-treated patients (36.1%) and 31 dabrafenib-treated patients (26.1%) developed a cutaneous SCC, the difference was not statistically significant.

Photosensitivity (Figure, C) is a prevalent skin eruption in patients receiving vemurafenib that occurred in 14 of our

Table 1. Dermatologic Adverse Effects of Dabrafenib vs Vemurafenib

Effect	BRAF Inhibitor Therapy, No. (%) of Patients		*P* Value
	Dabrafenib Mesylate (n = 119)	Vemurafenib (n = 36)	
Acneiform reaction	9 (7.6)	1 (2.8)	.31
Actinic keratosis	32 (26.9)	11 (30.6)	.67
Angioma or hemangiomas	14 (11.8)	2 (5.6)	.28
BCC	18 (15.1)	7 (19.4)	.54
Gray or curly hair	15 (12.6)	6 (16.7)	.53
Cutaneous SCC	31 (26.1)	13 (36.1)	.24
Drug reaction	1 (0.8)	4 (11.1)	.002[a]
Eczema	8 (6.7)	6 (16.7)	.07
Folliculitis	8 (6.7)	5 (13.9)	.17
Granuloma annulare	1 (0.8)	0	.58
Grover disease	51 (42.9)	14 (38.9)	.67
Hair loss	17 (14.3)	7 (19.4)	.45
Hyperkeratosis NOS[b]	12 (10.1)	3 (0.38)	.76
Inflammation NOS[b]	8 (6.7)	4 (11.1)	.39
Keratosis pilaris	2 (1.7)	2 (5.6)	.20
Panniculitis	3 (2.5)	4 (11.1)	.03
Photosensitivity	1 (0.8)	14 (38.9)	.0001[a]
Plantar hyperkeratosis	47 (39.5)	14 (38.9)	.95
Primary melanoma	3 (2.5)	0	.34
Verruca vulgaris	14 (11.8)	8 (22.2)	.12
Verrucal keratosis	79 (66.4)	26 (72.2)	.51
Vitiligo	5 (4.2)	1 (2.8)	.70

Abbreviations: BCC, basal cell carcinoma; NOS, not otherwise specified; SCC, squamous cell carcinoma.

[a] Significant at Bonferroni correction $P < .0023$.

[b] Conditions presented with hyperkeratosis or inflammation but did not meet the diagnostic criteria of a specific condition.

36 patients (38.9%). Only 1 patient receiving dabrafenib (0.8%) developed facial and trunk erythema after minimal sun exposure.

Plantar hyperkeratosis occurred similarly in both single-agent BRAF inhibitor groups, accounting for 47 patients treated with dabrafenib (39.5%) and 14 patients treated with vemurafenib (38.9%). Plantar hyperkeratosis usually occurred at points of friction and was also seen infrequently on the hands.

Follicular changes were a common but generally asymptomatic adverse effect noted in these patients. Localized folliculitis was present in 5 vemurafenib-treated patients (13.9%) and in 8 dabrafenib-treated patients (6.7%). Keratosis pilaris has also been reported to occur in patients treated with vemurafenib[11,12] and occurred in 5 vemurafenib-treated patients (5.6%) and 2 dabrafenib-treated patients (1.7%). Other less-investigated follicular changes included scalp and body alopecia (17 dabrafenib-treated patients [14.3%] and 7 vemurafenib-treated patients [19.4%]) and gray or curly hair (15 patients [12.6%] and 6 patients [16.7%], respectively).

Changes in melanocytic nevi such as hyperpigmentation, regression, and new primary melanomas were also noted. Three dabrafenib-treated patients (2.5%) developed new primary melanomas, and patients receiving both single-agent BRAF inhibitors had changes in nevi size and color.

Acneiform reactions occurred in 9 dabrafenib-treated patients (7.6%) and 1 vemurafenib-treated patient (2.8%). One patient receiving single-agent dabrafenib also developed a cystic acneiform eruption on the face, chest, and back.

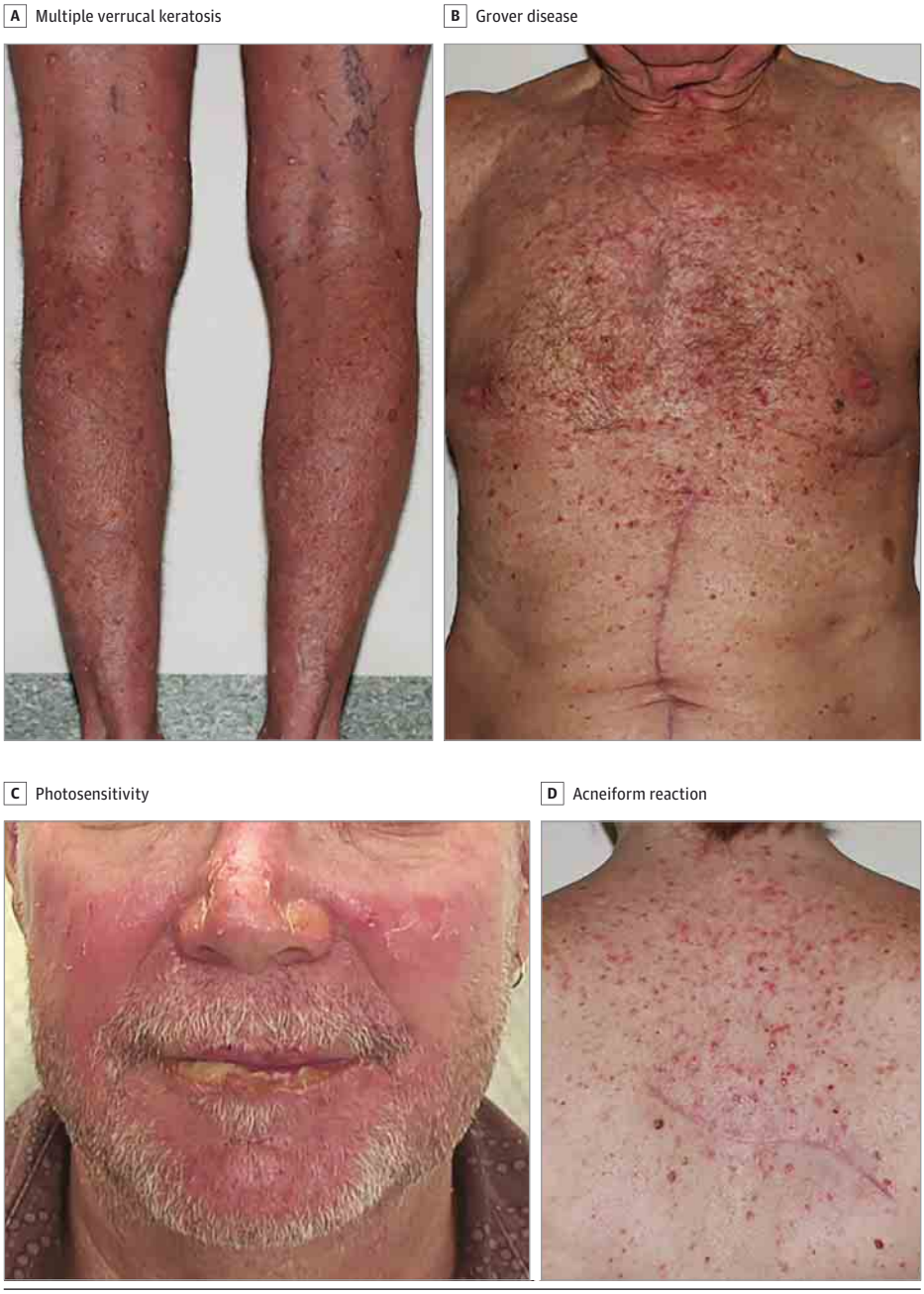
In our study, the type of single-agent BRAF inhibitor (vemurafenib or dabrafenib) did not appear to affect the frequency of cutaneous toxic effects. Photosensitivity, which was more common with vemurafenib than dabrafenib treatment (14 patients [38.9%] vs 1 [0.8%], respectively $P < .001$), was the exception (Table 1).

In patients receiving dabrafenib, age was a significant factor for the development of a number of cutaneous toxic effects (**Table 2**). The mean age of patients who developed verrucal keratosis, Grover disease, cutaneous SCC, basal cell carcinoma, actinic keratosis, and eczema ranged from 57 to 67 years; for the patients developing folliculitis, the mean age was 42 years. No significant differences between sexes were noted.

CombiDT Therapy

The CombiDT group had a different profile of cutaneous adverse effects when compared with single-agent dabrafenib (**Table 3**). No verrucal keratosis, cutaneous SCC, or Grover disease were seen in any patients receiving CombiDT therapy ($P < .001$ for all). The most common adverse effect noted in patients receiving CombiDT therapy was folliculitis (12 of 30 patients [40.0%]), which was more frequent than in patients receiving single-agent dabrafenib (8 of 119 patients [6.7%]; $P < .001$), but the clinical presentation was similar (Figure, D). Plantar hyperkeratosis and acneiform reactions each occurred in 5 patients receiving the CombiDT treatment (16.7% for each). Only 1 CombiDT-treated patient (3.3%) developed facial and trunk erythema after minimal sun exposure.

Figure. Representative Cutaneous Adverse Effects of Study Drugs



A, Multiple verrucal keratosis. Widespread presence of hyperkeratotic papules on both lower extremities in a patient treated with vemurafenib. B, Grover disease. The trunk of a patient with extensive itchy erythematous papules appearing after vemurafenib treatment. C, Photosensitivity. Moderate facial erythema localized to the nose, malar areas, and lips after minimal sun exposure in a patient treated with vemurafenib. No blisters were present. D, Acneiform reaction. Multiple comedones and pustules on the back of a patient treated with combined dabrafenib mesylate and trametinib dimethyl sulfoxide. No cysts were present.

Three patients treated with CombiDT (10.0%) developed localized or whole-body maculopapular eruptions or drug reactions with the concomitant use of penicillin, methotrexate, and anticonvulsants. Seven of the patients treated with CombiDT had been treated previously with dabrafenib and 1 had been treated previously with vemurafenib. After switching to CombiDT therapy, 2 of these patients experienced a reduction in frequency and 6 experienced resolution of cutaneous SCC, verrucal keratosis, Grover disease, and plantar hyperkeratosis.

Discussion

We compared the cutaneous toxic effects of BRAF inhibitor monotherapy and CombiDT therapy in a large cohort of patients who have undergone comparable dermatologic assessments. Benign and malignant squamous proliferative disorders related to vemurafenib and dabrafenib have been recognized and reported in the literature.[9,13,14] Both drugs are associated with the development of cutaneous SCC and other

Table 2. Mean Age at Development of Cutaneous Toxic Effects of Dabrafenib[a]

Effect	Age, Mean, y		P Value
	Development of Adverse Effects		
	Yes	No	
Actinic keratosis	59	50	.004
BCC	60	51	.02
Eczema	67	52	.006
Folliculitis	42	54	.04
Grover disease	59	48	<.001
Cutaneous SCC	61	50	<.001
Verrucal keratosis	57	44	<.001

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

[a] Indicates dabrafenib mesylate.

Table 3. Dermatologic Adverse Effects of Dabrafenib vs CombiDT Therapy

Effect	No. (%)		P Value
	Dabrafenib Mesylate (n = 119)	Dabrafenib & Trametinib (n = 30)	
Acneiform reaction	9 (7.6)	5 (16.7)	.13
Actinic keratosis	32 (26.9)	4 (13.3)	.12
Angioma or hemangiomas	14 (11.8)	2 (6.7)	.42
BCC	18 (15.1)	3 (10.0)	.47
Gray or curly hair	15 (12.6)	1 (3.3)	.14
Cutaneous SCC	31 (26.1)	0	.002[a]
Drug reaction	1 (0.8)	3 (10.0)	.006
Eczema	8 (6.7)	7 (23.3)	.007
Folliculitis	8 (6.7)	12 (40.0)	<.001[a]
Granuloma annulare	1 (0.8)	0	.61
Grover disease	51 (42.9)	0	<.001[a]
Hair loss	17 (14.3)	1 (3.3)	.10
Hyperkeratosis NOS[b]	12 (10.1)	5 (16.7)	.31
Inflammation NOS[b]	8 (6.7)	6 (20.0)	.03
Keratosis pilaris	2 (1.7)	1 (3.3)	.56
Panniculitis	3 (2.5)	3 (10.0)	.06
Photosensitivity	1 (0.8)	1 (3.3)	.29
Plantar hyperkeratosis	47 (39.5)	5 (16.7)	.02
Primary melanoma	3 (2.5)	0	.38
Verruca vulgaris	14 (11.8)	0	.048
Verrucal keratosis	79 (66.4)	0	<.001[a]
Vitiligo	5 (4.2)	1 (3.3)	.83

Abbreviations: BCC, basal cell carcinoma; CombiDT, combined dabrafenib mesylate and trametinib dimethyl sulfoxide; NOS, not otherwise specified; SCC, cutaneous squamous cell carcinoma.

[a] Significant at Bonferroni correction $P < .0023$.

[b] Not otherwise specified (these conditions presented with hyperkeratosis or inflammation but did not meet the diagnostic criteria of a specific condition).

squamoproliferative disorders thought to be the result of paradoxical activation of the MAPK pathway in wild-type BRAF keratinocytes.[15,16] The addition of a MEK inhibitor reduces the activation of ERK and consequently leads to a reduction in squamoproliferative toxic effects to the skin.[5,17]

Verrucal keratoses are the most common cutaneous toxic effects related to single-agent BRAF inhibitor use. These hyperkeratotic premalignant lesions may be a marker of increased risk for development of BRAF inhibitor–induced cutaneous SCC.[18] Although they occurred in 105 of the 155 patients receiving single-agent therapy (67.7%), they are much less frequently reported throughout the medical literature, which may be a result of their misclassification as a nonspecific rash or hyperkeratosis.[1,19,20] Patients were treated according to their clinical presentations, with cryotherapy and shave biopsies being the most common therapies. From our data, verrucal keratosis development occurred independently of the patient's sex but increased with increasing age.

Although rates of cutaneous SCC have been reported to be higher in patients receiving vemurafenib vs dabrafenib,[21] and although we found that 36.1% of vemurafenib-treated and 26.1% of dabrafenib-treated patients developed a cutaneous SCC, the difference was not statistically significant. This result could be owing to the small sample size and the statistically significant difference in age between vemurafenib-treated (mean age, 60 years) and dabrafenib-treated (mean age, 53 years) patients ($P = .045$).

Another underreported skin eruption is Grover disease, which has been associated previously with the use of dabrafenib[9] and vemurafenib,[22] but may have also been misclassified as a nonspecific rash. The etiology of Grover disease is unknown but, given the significant difference be-

tween its frequency in BRAF inhibitor monotherapy (65 of 155 patients [41.9%]) and CombiDT (0 patients; $P < .001$), the MAPK pathway might play a role. Most of our patients who developed Grover disease responded to topical emollients or corticosteroids, with only a few severe cases requiring oral corticosteroids or retinoids (acitretin). No patients required cessation of the study drug therapy at any time. Follicular changes were less frequent, requiring minimal treatment in the form of antibacterial washes and topical moisturizers.

Vemurafenib UV-A–dependent phototoxic effects have been well recognized[23,24] and remain a challenge in the Australian environment. Although 38.9% of our vemurafenib-treated patients developed phototoxic reactions, other studies have reported figures as high as 52% for vemurafenib-treated patients.[25] Despite patients being advised about sun-protective measures at every visit, most of the affected patients developed a spectrum from mild sun-related erythema to severe sunburn with or without associated blistering in the presence of minimal or indirect sun exposure. Treatment varied according to the extensiveness and severity of the phototoxic effects. The use of topical moisturizers and mild topical corticosteroids was sufficient in most cases. One case needed oral corticosteroids and protective dressings for severe sunburn.

The reported incidence of trametinib-induced acneiform reactions is 80%,[3,7] with much lower rates noted when trametinib is combined with dabrafenib.[5] Uribe et al[26] have reported an acneiform reaction emerging after cessation of CombiDT treatment, which was proposed to be a result of trametinib's longer half-life. In our patients, acneiform reactions were localized to the face and trunk, both areas with a high presence of sebaceous glands. Topical treatments (clindamycin hydrochloride) and oral doxycycline hydrochloride were sufficient in most of our cases, with only 1 patient receiving single-agent dabrafenib requiring oral retinoid (isotretinoin). For this specific case, the symptoms were controlled, but the condition did not resolve completely.

No cases of palmar-plantar erythrodysesthesia occurred despite it being reported in approximately 10% of patients treated with vemurafenib.[27] Conversely, plantar hyperkeratosis or keratoderma was a very common and painful condition occurring in 61 of 155 patients treated with a single BRAF inhibitor (39.4%) compared with 5 of 30 CombiDT-treated patients. The most severe cases were in patients receiving a single BRAF inhibitor. Patients were advised to avoid friction by wearing thick socks and well-fitted shoes. Topical keratolytics (urea) were also applied daily.

Zimmer et al[28] and Yagerman et al[29] have reported new primary melanomas with single-agent BRAF inhibitor therapy. Whether these new melanomas are a result of the medication or the increased risk for developing new primary melanomas in this patient population remains unknown[30]; new primary melanomas in BRAF inhibitor–treated patients have been reported not to harbor a BRAF mutation (wild-type BRAF).[28] Therefore, paradoxical activation of the MAPK pathway may also play a role. Hyperpigmentation, regression, and new nevi were also noted in a large number of our patients. Testing for a BRAF mutation was not performed in our patients who developed new primary melanomas during BRAF inhibitor therapy.

Conclusions

Patients treated with BRAF inhibitors alone or in combination with the MEK inhibitor trametinib require careful and ongoing dermatologic monitoring throughout their treatment. CombiDT therapy has an improved profile of cutaneous toxic effects compared with BRAF inhibitor monotherapy. In the spectrum of squamoproliferative disorders, cutaneous SCC remains the most concerning cutaneous toxic effect related to BRAF inhibitor monotherapy and requires accurate clinicopathologic diagnosis and appropriate management in a timely manner. Recognition of the variety of cutaneous toxic effects associated with these different therapies, including the predisposing risk factors for their development, is important with the purpose of ensuring appropriate rapid intervention and thereby abrogating the need to delay or even withhold these essential treatments.

ARTICLE INFORMATION

Accepted for Publication: May 4, 2015.

Published Online: July 22, 2015. doi:10.1001/jamadermatol.2015.1745.

Author Affiliations: Department of Dermatology, Westmead Hospital, Sydney, Australia (Carlos, Anforth, Fernandez-Peñas); University of Sydney Medical Faculty, Sydney Medical School, University of Sydney, Sydney, Australia (Carlos, Anforth, Clements, Menzies, Carlino, Fernandez-Peñas); Westmead Institute for Cancer Research, Westmead Hospital, Westmead, Australia (Clements, Menzies, Carlino); Department of Medical Oncology, Westmead and Blacktown Hospitals, Sydney, Australia (Clements, Menzies, Carlino); Melanoma Institute Australia, Sydney, Australia (Clements, Menzies, Carlino); Department of Tissue Pathology and Diagnostic Oncology, Westmead Hospital, Westmead, Australia (Chou).

Author Contributions: Drs Carlos and Fernandez-Peñas had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Carlos, Anforth, Clements, Menzies, Fernandez-Peñas.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Carlos, Clements, Fernandez-Peñas.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Carlos, Fernandez-Peñas.
Administrative, technical, or material support: Anforth, Clements, Carlino, Fernandez-Peñas.
Study supervision: Clements, Menzies, Fernandez-Peñas.

Conflict of Interest Disclosures: Ms Anforth receives a scholarship from the University of Sydney. Drs Menzies and Carlino receive travel support from GSK and Novartis. Dr Fernandez-Peñas serves as consultant or in an advisory role to Roche. No other disclosures were reported.

Funding/Support: The Fotofinder device used in our clinics was donated by the Westmead Medical Research Foundation.

Role of the Funder/Sponsor: Westmead Medical Research Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We acknowledge Vicky Wegener, MHlthSc, the clinical trials team, and the Department of Medical Oncology, Westmead Hospital; Marina Ali, PhD, and the Department of Dermatology and OncoDermatology Research Teams, Westmead Hospital; and the patients and their families. Neither named contributor received compensation for their roles.

REFERENCE

1. Chapman PB, Hauschild A, Robert C, et al; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507-2516.

2. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-365.

3. Flaherty KT, Robert C, Hersey P, et al; METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107-114.

4. GSK. Trametinib (Mekinist™) and dabrafenib (Tafinlar™) combination demonstrated overall survival benefit compared to vemurafenib: phase III BRAF V600-mutant metastatic melanoma study stopped early. http://us.gsk.com/en-us/media/press-releases/2014/trametinib-mekinist-and-dabrafenib-tafinlar-combination-demonstrated-overall-survival-benefit-compared-to-vemurafenib-phase-iii-braf-v600-mutant-metastatic-melanoma-study-stopped-early/. Accessed July 2014.

5. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367(18):1694-1703.

6. Anforth R, Fernandez-Peñas P, Long GV. Cutaneous toxicities of RAF inhibitors. *Lancet Oncol*. 2013;14(1):e11-e18. doi:10.1016/S1470-2045(12)70413-8.

7. Anforth R, Liu M, Nguyen B, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. *Australas J Dermatol*. 2014;55(4):250-254.

8. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310(6973):170.

9. Anforth RM, Blumetti TC, Kefford RF, et al. Cutaneous manifestations of dabrafenib (GSK2118436): a selective inhibitor of mutant BRAF in patients with metastatic melanoma. *Br J Dermatol*. 2012;167(5):1153-1160.

10. Cancer Council Australia. Clinical practice guide: basal cell carcinoma, squamous cell carcinoma (and related lesions)— a guide to clinical management in Australia. 2008. http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/Basal_cell_carcinoma_Squamous_cell_carcinoma_Guide_Nov_2008-Final_with_Corrigendums.pdf. Accessed July 2013.

11. Huang V, Hepper D, Anadkat M, Cornelius L. Cutaneous toxic effects associated with vemurafenib and inhibition of the BRAF pathway. *Arch Dermatol*. 2012;148(5):628-633.

12. Ma L, Dominguez AR, Collins GR, Kia KF, Cockerell CJ. Hidradenitis suppurativa, eruptive melanocytic nevi, and keratosis pilaris-like eruption in a patient treated with vemurafenib. *Arch Dermatol*. 2012;148(12):1428-1429.

13. Belum VR, Fischer A, Choi JN, Lacouture ME. Dermatological adverse events from BRAF inhibitors: a growing problem. *Curr Oncol Rep*. 2013;15(3):249-259.

14. Curry JL, Torres-Cabala CA, Kim KB, et al. Dermatologic toxicities to targeted cancer therapy: shared clinical and histologic adverse skin reactions. *Int J Dermatol*. 2014;53(3):376-384.

15. Heidorn SJ, Milagre C, Whittaker S, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell*. 2010;140(2):209-221.

16. Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature*. 2010;464(7287):431-435.

17. King AJ, Arnone MR, Bleam MR, et al. Dabrafenib: preclinical characterization, increased efficacy when combined with trametinib, while BRAF/MEK tool combination reduced skin lesions. *PLoS One*. 2013;8(7):e67583. doi:10.1371/journal.pone.0067583.

18. Anforth R, Fernandez-Penas P. BRAF inhibitor induced verrucal keratosis [comment]. *Am J Dermatopathol*. 2014;36(2):192.

19. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010;363(9):809-819.

20. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-Mutant Melanoma Metastatic to the Brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(11):1087-1095.

21. Sharma A, Shah SR, Illum H, Dowell J. Vemurafenib: targeted inhibition of mutated BRAF for treatment of advanced melanoma and its potential in other malignancies. *Drugs*. 2012;72(17):2207-2222.

22. Chu EY, Wanat KA, Miller CJ, et al. Diverse cutaneous side effects associated with BRAF inhibitor therapy: a clinicopathologic study. *J Am Acad Dermatol*. 2012;67(6):1265-1272.

23. Gelot P, Dutartre H, Khammari A, et al. Vemurafenib: an unusual UVA-induced photosensitivity. *Exp Dermatol*. 2013;22(4):297-298.

24. Vanneste L, Wolter P, Van den Oord JJ, Stas M, Garmyn M. Cutaneous adverse effects of BRAF inhibitors in metastatic malignant melanoma, a prospective study in 20 patients. *J Eur Acad Dermatol Venereol*. 2015;29(1):61-68.

25. Boussemart L, Routier E, Mateus C, et al. Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. *Ann Oncol*. 2013;24(6):1691-1697.

26. Uribe P, Anforth RM, Kefford RF, Fernandez-Peñas P. Acneiform eruption in a patient with metastatic melanoma after ceasing combination dabrafenib/trametinib therapy. *Melanoma Res*. 2014;24(5):501-503.

27. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012;366(8):707-714.

28. Zimmer L, Hillen U, Livingstone E, et al. Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. *J Clin Oncol*. 2012;30(19):2375-2383.

29. Yagerman S, Flores E, Busam K, Lacouture M, Marghoob AA. Overview photography and short-term mole monitoring in patients taking a BRAF inhibitor. *JAMA Dermatol*. 2014;150(9):1010-1011.

30. Zimmer L, Haydu LE, Menzies AM, et al. Incidence of new primary melanomas after diagnosis of stage III and IV melanoma. *J Clin Oncol*. 2014;32(8):816-823.