Curr. Treat. Options in Oncol. (2016) 17: 57
DOI 10.1007/s11864-016-0434-0

Skin Cancer (BY Kwong, Section Editor)

Cutaneous Complications of Targeted Melanoma Therapy

Emily de Golian, MD[1]
Bernice Y. Kwong, MD[1]
Susan M. Swetter, MD[1,2]
Silvina B. Pugliese, MD[1,*]

Address
[*,1]Department of Dermatology, Cutaneous Oncology, Stanford University Medical Center and Cancer Institute, 780 Welch Road, CJ220F, Palo Alto, CA, 94304-5779, USA
Email: spugliese@stanford.edu
[2]Dermatology Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Published online: 19 September 2016

This article is part of the Topical Collection on *Skin Cancer*

Keywords Supportive dermato-oncology · Oncodermatology · Ipilimumab · Vemurafenib · Dabrafenib · Trametinib · Cometinib · Nivolumab · BRAF inhibitor · MEK inhibitor · CTLA-4 antibody · PD-1 antibody · Checkpoint inhibitors · Morbilliform rash · Verrucal keratoses · Keratoacanthoma · Squamous cell carcinoma · Vitiligo · Autoimmune dermopathy · Pruritus · Xerosis

Opinion statement

The landscape of advanced and metastatic melanoma therapy has shifted dramatically in recent years. Since 2011, eight drugs (ipilimumab, vemurafenib, dabrafenib, trametinib, cometinib, pembrolizumab, nivolumab, and talimogene laherparepvec) have received FDA approval for the treatment of advanced or metastatic melanoma, including combination regimens of both small molecule kinase and immune checkpoint inhibitors. These therapies have revolutionized the management of unresectable regional nodal and distant melanoma, providing hope of extended survival to patients. As the use of novel agents has increased, so have the cutaneous toxicities associated with these medications. While most skin reactions are low-grade and can be managed conservatively with topical therapies, malignant lesions and more serious or life-threatening drug reactions can arise during therapy, requiring prompt dermatologic recognition and treatment in order to improve patient outcome. Given the survival benefit attributed to these new agents, treating skin toxicity and maintaining patient quality of life is of paramount importance. Oncologists should be aware of the common cutaneous toxicities associated with these medications and should be encouraged to involve dermatologists in the collaborative care of advanced melanoma patients. Close communication between oncologists and dermatologists can help to avoid unnecessary dose reduction or treatment discontinuation and identify situations when treatment cessation is truly warranted.

Introduction

Improved understanding of the immunologic and molecular basis of melanoma has led to the development of BRAF inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib, cometinib), and antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab), programmed death-1 (PD-1) (pembrolizumab, nivolumab) and its ligand programmed death ligand-1 (PD-L1), which are each associated with a variety of cutaneous adverse events (AEs). These cutaneous AEs range from common entities, such as morbilliform eruptions, to unique toxicities, such as development of cutaneous squamous cell carcinoma (cuSCC) and severe photosensitivity in patients undergoing treatment with BRAF inhibitor monotherapy, papulopustular eruptions in patients receiving MEK inhibitors, and lichenoid dermatitis in patients receiving PD-1 and PD-L1 inhibitors. Life-threatening drug reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) may occur and warrant prompt recognition and appropriate management. In this review, we will focus on both common and uncommon cutaneous toxicities associated with currently approved, novel melanoma therapies, as well as provide treatment recommendations that can be utilized by oncologists – in conjunction with collaborative care by dermatologists

Dermatologic Complications of BRAF Inhibitors

Approximately 50 % of melanoma patients harbor an activating mutation in BRAF [1]. Vemurafenib and dabrafenib are $BRAF^{V600}$ inhibitors that are FDA-approved for the treatment of metastatic melanoma in patients with BRAF mutation-positive melanoma. Prolonged survival has been observed in various subsets of metastatic melanoma patients receiving BRAF inhibitor monotherapy [2]. Cutaneous toxicity is observed in 92–99 % of patients on BRAF inhibitor monotherapy (e.g., vemurafenib, dabrafenib) [3], with the most common AE being the development of hyperproliferative epidermal neoplasms. Therapy with vemurafenib or dabrafenib has resulted in the frequent development of verrucal keratoses (72.2 and 66.4 % incidence, respectively), plantar hyperkeratosis (38.9 and 39.5 %, respectively), Grover's disease (38.9 and 42.9 %, respectively), actinic keratoses (30.6 and 26.9 %, respectively), and cutaneous squamous cell carcinoma (36.1 and 26.1 %, respectively) [4••].

Verrucae Vulgaris, Verrucal Keratoses, Actinic Keratoses, Keratoacanthomas (KAs), and Cutaneous Squamous Cell Carcinomas (cuSCCs)

White, hyperkeratotic, verrucous (wart-like) growths can develop as early as 1 week into BRAF inhibitor monotherapy [4••] but are more commonly seen 6–12 weeks into the treatment course. They present in both sun-exposed and sun-protected areas [5]. These BRAF inhibitor-related verrucal keratoses may differ from common viral warts (verruca vulgaris) in that they may not exhibit viral inclusions on pathology review and have not been associated with human papillomavirus [6]. Although verrucal keratoses are not considered malignant, they may rarely progress to cuSCC and should generally be treated, typically with liquid nitrogen cryotherapy [7].

Actinic keratoses are considered "pre-cancerous" lesions, although individual rates of AK transformation to cuSCC are low [8]. They occur on sun-exposed

skin and are most prevalent on the scalp, face, and extremities. Sun-damaged patients on BRAF inhibitor monotherapy may demonstrate marked increase in the development of AKs. As such, all patients who will be treated with a BRAF inhibitor are recommended to have a baseline total body skin examination performed by a dermatologist experienced in the management of cutaneous complications of targeted therapy prior to initiation of BRAF inhibitor monotherapy and then every 4 weeks thereafter. During the initial visit, baseline AKs and smaller hyperkeratotic lesions are preemptively treated with destructive modalities (e.g., cryotherapy, electrodessication and curettage) and can also be treated with ablative laser [5]. For patients with numerous lesions, topical field therapies may be utilized (e.g., salicylic acid, tretinoin, 5-fluorouracil, imiquimod, photodynamic therapy). Larger lesions are biopsied if symptomatic, erythematous, or clinically atypical as compared to surrounding lesions. KAs are crateriform skin tumors that grow rapidly and may also spontaneously involute. KAs are considered to be a well-differentiated, low-grade subtype of cuSCC and are generally treated similarly. Both KAs and cuSCCs occur in sun-exposed skin and are more prevalent in patients 49 years or older, with a median age of 62 [3, 5, 9]. The median time to cuSCC/KA presentation is 8 weeks for vemurafenib, occurring in 4–31 % of patients, and 16 weeks for dabrafenib, occurring in 6–11 % of patients [10]. Development of cuSCC is believed to result from RAF inhibition of wild-type BRAF cells, coupled with oncogenic RAS mutations present in photodamaged skin [5]. Importantly, metastatic SCC has not yet been reported, to our knowledge, in patients who are treated with vemurafenib or dabrafenib monotherapy. Dose adjustment is not necessary in the setting of appropriate management of cuSCC, and treatment can be more conservative than that for typical ultraviolet radiation-induced cuSCC in other patients [10, 11••]. While the latter are generally treated with full fusiform excisions, the former are most often treated with a deep (saucerization) shave biopsy followed by electrodessication and curettage. They can also be treated with aggressive and frequent cryotherapy. For extensive or eruptive lesions, fluorouracil (topical or intralesional), photodynamic therapy, and low-dose acitretin may be utilized [5, 10] with proper patient counseling regarding the risks of photosensitivity and other significant adverse events that may occur with use of these medications.

In addition to baseline skin examination, we follow these patients at least once per month for repeat full skin examination. Although most verrucal keratoses, AKs, and cuSCCs occur within the first 6 months of treatment [9], they have been reported to develop after 1 year of therapy [11••], making ongoing dermatologic assessment critical throughout treatment.

Hand-Foot Skin Reaction

Hand foot skin reaction is a dose-dependent [12] reaction presenting as painful erythema of palms and soles, with tender hyperkeratotic plaques developing at pressure-bearing sites (e.g., heels). It occurs on high-friction areas of skin (e.g., lateral feet) [13] and may be associated with development of bullae. This eruption can be exquisitely painful, adversely impacting quality of life and limiting the patient's ability to walk. Recommended treatment regimens depend upon severity of the reaction, and they

generally consist of a combination of topical keratolytic agents (ammonium lactate, urea cream, or lotion), thick moisturizers (petroleum jelly), topical anesthetics (lidocaine 2–5 % gel or cream), high-potency topical corticosteroids (with or without occlusion), gabapentin or pregabalin, and pain medication including NSAIDs and/or narcotics as needed [3, 5, 12]. We encourage our patients to rest their hands and feet, protect them from injury, and wear thick socks and well-fitting shoes (although they should not be tight) to prevent friction. Pre-treatment, patients should be counseled to see a podiatrist, pare existing corns, calluses, and thicker areas of skin, and avoid excess trauma to their hands and feet [5]. Uncontrollable pain and interference with activities of daily living may necessitate dose adjustment or brief drug holidays [5], which are not believed to adversely affect patient outcome [14].

Rash

Morbilliform drug eruptions and keratosis pilaris-like eruptions, which present as spiny protrusions within hair follicles, are also common cutaneous adverse reactions to vemurafenib [3, 5]. These eruptions are generally low-grade, minimally symptomatic (the primary symptom being pruritus), and can be managed with topical corticosteroids, the potency titrated to the severity and extent of the eruption. For patients with extensive or highly symptomatic eruptions (>grade 2–3), oral corticosteroids and/or oral antihistamines may be necessary [5]. These eruptions rarely necessitate BRAF inhibitor interruption.

Keratosis pilaris-like eruptions, which present in a generalized distribution as folliculocentric papules, or "chicken skin", are best treated with keratolytics (e.g., lactic acid, urea), topical corticosteroids for pruritus, gentle exfoliation [5], or with a combination of topical adapelene and pimecrolimus.

Melanocytic Lesions

BRAF inhibitors have been associated with the development of new, eruptive, and/or changing common melanocytic nevi, dysplastic nevi, and new primary melanoma [15]. These melanocytic proliferations are believed to result from increased MAPK activity in wild-type BRAF lesions, which is induced by BRAF inhibition, and biopsy of these nevi (both common and dysplastic) and new primary melanomas reveal that they are BRAF-wild type proliferations [15, 16•]. Clinical trials with BRAF inhibitor monotherapy were associated with new primary melanoma in 8 of 337 (2.3 %) patients [17] and 3 of 187 (1.6 %) patients [18].

Photosensitivity

Ultraviolet A (UVA)-mediated photosensitivity has been reported to occur in 38.9 % of patients treated with vemurafenib and 0.8 % of patients treated with dabrafenib. [4••] Photosensitivity presents as pink or red erythema of sun-exposed skin, with more severe reactions characterized by severe sunburn, including pain, blistering, and impairment of daily

activities. This eruption is UVA-mediated, which is significant because UVA rays can penetrate window glass, and most currently available sunscreens in the USA do not contain ingredients which filter long-wave UVA. Patients can develop severe sunburns with limited and indirect sun exposure and must therefore be counseled to use photoprotective clothing (designed with built in ultraviolet protection factor, or UPF) and broad-spectrum chemical sunscreens that provide both UVA and UVB protection. The most effective UVA blockers in the USA include the chemical avobenzone, which is photostabilized with the addition of octocrylene. Superior, broad spectrum UV filters such as bemotrizinol and bisoctrizole are not yet available in the USA but provide superior protection from UV radiation. Physical sunscreens contain zinc oxide and titanium dioxide, often in micronized forms; however, these agents by themselves do not filter throughout the UV spectrum.

Other Cutaneous Findings

Additional cutaneous adverse events associated with BRAF inhibitor therapy include cystic facial eruptions, non-scarring alopecia, seborrheic dermatitis-like eruptions, Grover's disease, radiation recall, enhanced radiation dermatitis, panniculitis (particularly erythema nodosum type), Sweet's syndrome, cutis verticis gyrata, SJS, and TEN [3, 5, 10, 19, 20]. Grover's disease, also known as transient acantholytic dermatosis, is an intensely pruritic eruption characterized by red to brown keratotic papules that tend to involve the trunk but may be generalized. It is usually treated with mid-potency topical corticosteroid creams, topical menthol and camphor-containing anti-pruritic creams, and oral antihistamines for pruritus. Cystic lesions can be treated with oral tetracycline antibiotics, extraction, and topical or systemic retinoids [21•]. Effective management of radiation recall and radiation dermatitis includes topical cortisteroids, wound care, and symptomatic management with emollients and non-steroidal anti-inflammatory (NSAID) medications [19]. Development of erythema nodosum panniculitis may be managed with NSAIDs, and patients should be informed that these intermittent lesions typically resolve even while continuing therapy, although dose adjustment or discontinuation may be necessary if symptoms are too severe [5].

Due to the number of cutaneous adverse events associated with BRAF inhibitors, dermatologic counseling of patients undergoing treatment with these agents should occur prior to drug initiation. Comprehensive, baseline skin examination, treatment of pre-existing actinic damage and xerosis, discussion of expected cutaneous AEs, and education regarding the appropriateness of continuing treatment despite AEs will contribute to successful side effect management on BRAF inhibitors. Importantly, concomitant MEK inhibitor therapy leads to decreased incidence of BRAF inhibitor-induced cutaneous AEs and addition of this therapy should be considered in patients with intolerable skin reactions. Combination BRAF/MEK inhibitors

are now considered first line in patients with BRAF-mutant melanoma given the increased efficacy of this regimen.

Dermatologic Complications of MEK Inhibitors

In the RAS-RAF-MEK-ERK cell signaling pathway (MAPK pathway), MEK1 and MEK2 act downstream of BRAF. Addition of a MEK inhibitor to a BRAF inhibitor can improve overall survival as compared to BRAF monotherapy [22]. Combined BRAF and MEK inhibition also reduces the incidence of skin toxicity compared with BRAF monotherapy [4••, 23, 24]. Trametinib and cometinib are the two MEK inihibitors currently FDA-approved for melanoma treatment (May 2013 and November 2015, respectively).

Papulopustular Eruption

Papulopustular eruptions are the most common adverse event seen with MEK inhibitor monotherapy and occur in as many as 57–93 % of patients [25]. This eruption is similar in nature to that seen with epidermal growth factor receptor inhibitor (EGFRi) therapy, and management is comparable [26]. Patients develop pruritic papules and pustules in a seborrheic distribution (scalp, face, upper chest, and upper back). These outbreaks tend to be low-grade. Preventative measures for papulopustular eruptions include sunscreen (with sun protection factor [SPF] of at least 30), moisturizer, topical steroids for pruritus, and prophylactic tetracyclines (e.g. doxycycline 100 mg PO BID, minocycline 100 mg PO BID) [5, 27]. Patients should be alerted to potential phototoxicity associated with tetracycline use. Other antibiotics, such as cephalexin, may be utilized for patients at increased risk of phototoxicity. Topical steroid ointments (e.g., hydrocortisone 2.5 % ointment or desonide 0.05 % ointment for the face and triamcinolone 0.1 % ointment for the body) and oils (e.g., fluocinolone 0.01 % oil for the scalp) may effectively manage pruritus, burning, and pain, some of the most debilitating features of papulopustular outbreaks. Providers should have a low threshold for culturing any lesions that appear atypical or which are not improving with standard treatment, as it is common for secondary infection to be present. In addition to systemic antibiotics, dilute bleach baths may be utilized for their antimicrobial effect. Soaks with Dakin's solution (containing sodium hypochlorite) or bleach baths composed of ¼ cup bleach in a full bathtub for 10 minutes daily can be used to decrease surface bacteria and inflammation and may reduce retention hyperkeratosis [19, 28]. Topical antibiotics (e.g., clindamycin, dapsone) can also be added to the treatment regimen [5]. Severe papulopustular eruptions (≥ grade 3) may respond to isotretinoin at a dose of 20–30 mg daily or oral corticosteroids or may necessitate treatment pause or cessation.

Other Cutaneous Findings

Other skin AEs observed with MEK inhibitor treatment include pruritus (45 %), xerosis (23 %), alopecia (9–17 %), peripheral

edema (26–43 %), paronychia, hyperpigmentation, hair depigmentation, trichomegaly, hypertrichosis, telangiectasias, stomatitis, and angular cheilitis [27]. Xerosis and pruritus are common side effects and are generally managed with dry skin education (discontinuation of hot showers, daily application of a thick moisturizer, avoidance of skin irritants) and anti-pruritic agents (including topical steroids, topical doxepin, camphor menthol lotion, oral antihistamines, gabapentin or pregabalin, and aprepitant). Patients also commonly experience morbilliform drug eruptions on MEK inhibitors, which are dose-dependent and commonly managed with topical corticosteroids, not generally requiring oral corticosteroid use. Grade 3–4 morbilliform eruptions may necessitate dose reduction or discontinuation of therapy [5]. Three cases of dusky erythema, urticarial to targetoid in appearance and characterized by central duskiness, have been reported [25]. These cases did not exhibit features of fixed drug eruption, erythema multiforme, or Stevens-Johnson syndrome and were treated with topical and oral corticosteroids.

As previously noted, abrogation of cutaneous AEs occurs when BRAF and MEK inhibitors are combined. In one study of 44 patients treated with BRAF inhibitors (vemurafenib or dabrafenib) monotherapy or BRAF inhibitor/MEK inhibitor (vemurafenib/cometinib or dabrafenib/trametinib), cutaneous AEs were more frequently noted during BRAF inhibitor monotherapy than during combination therapy ($P = .012$). In addition, patients on BRAF inhibitor monotherapy developed cutaneous AEs much earlier than patients on combination therapy, with a median cutaneous AE-free interval of 28 days for BRAF inhibitor monotherapy and 122.5 days for combination therapy [23]. A retrospective cohort study comparing 119 patients receiving dabrafenib to 30 patients receiving dabrafenib/trametinib demonstrated an increased incidence of verrucal keratoses ($P < .001$), cuSCC ($P = .002$), and Grover's disease ($P < .001$) in patients who received dabrafenib monotherapy [4••]. In addition to reducing cutaneous toxicity, combination of BRAF inhibitor with MEK inhibitor increases initial tumor response, reduces treatment resistance, and improves many aspects of a patient's quality of life [29], though increased systemic toxicities have been reported on the dual regimen.

Dermatologic Complications of Immune Checkpoint Blockade with Anti-CTLA-4 Immunotherapy

Cutaneous AEs related to ipiliumumab are dose-related and generally reversible; however, up to 60 % of patients experience immune-related AEs [30], with 40 % developing autoimmune-related dermatologic conditions. These reactions include pruritus (<30 % of patients), morbilliform rash (10–50 % of patients), and vitiligo (more specifically referred to as vitiligo-like melanoma-associated hypopigmentation) [5].

Pruritus

Pruritus related to ipilimumab may not only be associated with xerosis and rash [27] but may also be a result of increased immune system activation [31••]. Treatment options for pruritus include emollients, anti-pruritic lotions, anti-histamines, gabapentin, pregabalin, and mirtazapine [32••]. The neurokinin receptor inhibitor aprepitant [5] should be considered for refractory patients. In a trial of 45 patients, every other day aprepitant dosing for three total doses yielded >50 % reduction in intensity of pruritus in 91 % of patients. Furthermore, pruritus recurred in only 13 % of those treated [33•].

Rash

The common morbilliform eruption presents early, generally within the first 3 to 4 weeks of ipilimumab therapy. It tends to concentrate on the trunk and extremities and is composed of red erythematous papules coalescing into plaques [27]. The rash may be accompanied by peripheral eosinophilia or focused around nevi, which is believed to result from an inflammatory response against melanocytes [5, 32••]. Lacouture et al. [32••] developed a very useful algorithm for management of ipilimumab-associated rash. Grade 1 or 2 eruptions can be treated with topical corticosteroids and oral antihistamines. Grade 3 eruptions may necessitate temporary treatment cessation along with a course of oral corticosteroids. Grade 4 eruptions, rare and characterized by TEN or SJS, necessitate permanent cessation of the drug and hospitalization for prompt multidisciplinary management. A recent retrospective study comparing patients who experienced an immune-related AE to ipilimumab and were treated with systemic immunosuppression (oral corticosteroids or a TNF-alpha inihibitor) to those who did not receive systemic immunosuppression found no difference in overall survival or time to treatment failure between both groups [34]. In a study of prognostic factors related to clinical response in patients receiving ipilimumab, the authors found that patients who necessitated high-dose steroids for management of immune-related AEs continued to exhibit an antitumor effect [35]. Although systemic immunosuppression should not be utilized without careful consideration, it may be necessary in cases of grade 3 or 4 toxicity.

Vitiligo-Like Melanoma-Associated Hypopigmentation

Vitiligo occurs in 2–11 % of patients treated with ipilimumab and portends a favorable response to therapy [27]. This supports the assertion that immune-related adverse events correlate with enhanced antitumor response. Downey et al. showed a significant association between patients who developed an immune-related adverse event and likelihood of response to ipilimumab ($P = 0.00004$) [35]. Vitiligo presents as

asymptomatic depigmented macules or patches, oftentimes surrounding the original melanoma site or sites of metastases, but which can be localized or generalized in distribution. Depigmentation can be distinguished from hypopigmentation (a common post-inflammatory side effect) by examination with a Wood's lamp. Importantly, vitiligo does not resolve after cessation of ipilimumab.

Other Cutaneous Findings

Less common AEs include prurigo nodularis, lichenoid dermatitis, pyoderma gangrenosum-like ulcerations, photosensitivity, radiation recall, alopecia universalis, dermatomyositis, TEN, and drug reaction with eosinophilia and systemic symptoms (DRESS) [5, 27, 36].

Dermatologic Complications of Anti-PD-1 Antibody Immunotherapy

The anti-PD-1 immunotherapies pembrolizumab and nivolumab bind PD-1 receptors, thus blocking attachment to PD-L1 and PD-L2, releasing PD-1 pathway inhibition, and allowing anti-tumor functions to take place [37]. Pembrolizumab was FDA approved in 2014 for the treatment of unresectable and metastatic melanoma, and nivolumab received FDA approval shortly thereafter in 2015.

As with ipilimumab, cutaneous AEs from PD-1 inhibitors tend to be dose-related and reversible. However, most clinical trials of these agents have only noted a poorly characterized "rash," limiting firm conclusions regarding the specific type and duration of associated skin toxicities [5, 27]. In early trials comparing ipilimumab and anti-PD-1 therapy, the most common cutaneous AEs in patients receiving anti-PD-1 therapy were rash in 14.7 % and pruritus in 14.4 %, with no grade 3–5 cutaneous AEs reported in this cohort, compared to <1 % in the ipilimumab group. The incidence of rash was comparable between these drugs, although worse pruritus was observed in patients on ipilimumab, occurring in 25.8 % [38]. In the dermatology literature, skin toxicity has been reported in 18 to 42 % of patients receiving pembrolizumab [39].

Morbilliform Eruption

The most common skin finding in patients receiving PD-1 inhibitor treatment is a maculopapular eruption [40•]. This rash develops early in the course of treatment and can be managed with mid-potency topical corticosteroids (e.g., triamcinolone 0.1 % lotion, cream, or ointment).

Lichenoid Dermatitis

Lichenoid eruptions with varying clinical morphologies have also been noted in patients undergoing treatment with PD-1 inhibitors (Fig. 1). A small Mayo Clinic report described lichenoid dermatitis in three patients. Biopsies of these lesions showed an abundance of CD3+ lymphocytes and few PD-1 positive T cells [41]. A recent immunohistochemical analysis of lichenoid dermatitis in patients receiving PD-1 or PD-L1 inhibitors showed the presence of significant CD163+ histiocytes (as compared to lichen planus and lichen-planus like keratosis), and these cases also exhibited few PD-1 positive T cells [42]. Clinically, these eruptions are low-grade, pruritic, and generally managed with topical corticosteroids. Interestingly, they are often delayed in their onset, occurring many months after initiation of treatment. Continuation of therapy without dose adjustment is usually possible [41]. However, oral corticosteroids and temporary treatment cessation may be necessary in high-grade toxicity.

Vitiligo

Similar to ipilimumab, vitiligo has been reported in melanoma patients receiving pembrolizumab [5, 40•]. In a prospective study of 67 patients receiving pembrolizumab for treatment of unresectable stage III or IV melanoma, 17 (25 %) developed vitiligo. Vitiligo was more commonly generalized and in three cases developed around sites of cutaneous metastasis. The median time to onset was 126 days and all vitiligo patients were alive at 441 days, indicating a possible favorable tumor response in patients who developed vitiligo [43].

Other Cutaneous Findings

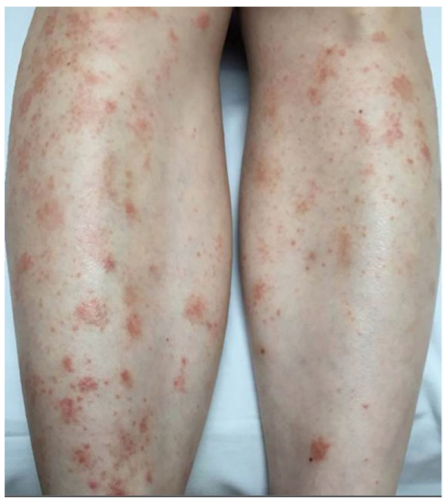

Fig. 1. PD-1 inhibitor-related lichenoid dermatitis. Pruritic, thin, red-brown papules and plaques over the lower extremities in a patient receiving anti PD-1 therapy. Skin biopsy showed a lichenoid infiltrate.

Other reported skin eruptions on PD-1 inhibitors include autoimmune blistering conditions, psoriasiform dermatitis, and systemic cutaneous lupus erythematosus [39, 40•, 44, 45].

Conclusion

In the rapidly evolving field of advanced melanoma therapy, targeted therapies and immunotherapies have been shown to improve both progression-free and overall survival. With increased use and more combinations of these agents being studied, these drugs present new challenges to oncologists and dermatologists. Oncology providers should be aware of cutaneous toxicity associated with these therapies and should work in collaboration with dermatology colleagues to provide pre-emptive counseling of anticipated cutaneous AEs. Early referral to a dermatologist or other provider experienced in managing skin toxicities of cancer therapies can help to expedite correct diagnosis and appropriate management, while preventing unnecessary treatment interruption or cessation of a potentially life-saving drug. As more advanced melanoma patients experience prolonged survival, improving quality of life both during and following treatment is imperative. We encourage a collaborative, team approach to patient care to provide optimal outcomes in melanoma management.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Goldinger SM, Murer C, Stieger P, Dummer R. Targeted therapy in melanoma—the role of BRAF, RAS and KIT mutations. EJC Suppl. 2013;11(2):92–6.
2. Grossman KF, Margolin K. Long-term survival as a treatment benchmark in melanoma: latest results and clinical implications. Ther Adv Med Oncol. 2015;7(3):181–91.
3. Lacouture ME, Duvic M, Hauschild A, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. Oncologist. 2013;18(3):314–22.
4.•• Carlos G, Anforth R, Clements A, et al. Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma. JAMA Dermatol. 2015;151(10):1103–9.

A retrospective cohort study with detailed incidence of cutaneous toxicities comparing vemurafenib to dabrafenib and BRAF inhibitor monotherapy to BRAF inhibitor/MEK inhibitor combination therapy.

5. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: part II: inhibitors of intracellular molecular signaling pathways. J Am Acad Dermatol. 2015;72(2):221–36.
6. Anforth R, Fernandez-Penas P. BRAF inhibitor induced verrucal keratosis. Am J Dermatopathol. 2014;36(2):192.
7. Anforth R, Tembe V, Blumetti T, Fernandez-Peñas P. Mutational analysis of cutaneous squamous cell carcinomas and verrucal keratosis in patients taking BRAF inhibitors. Pigment Cell Melanoma Res. 2012;25(5):569–72.
8. Rigel DS, Stein Gold LF. The importance of early diagnosis and treatment of actinic keratosis. J Am Acad Dermatol. 2013;68(1 Suppl 1):S20–7.
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):1153–60.
10. Anforth R, Fernandez-Peñas P, Long GV. Cutaneous toxicities of RAF inhibitors. Lancet Oncol. 2013;14(1):e11–8.
11.•• Anforth R, Carlos G, Clements A, Kefford R, Fernandez-Peñas P. Cutaneous adverse events in patients treated with BRAF inhibitor-based therapies for metastatic melanoma for longer than 52 weeks. Br J Dermatol. 2015;172(1):239–43.

This study emphasizes the need for long-term monitoring in patients treated with BRAF inhibitors due to the continued development of cutaneous adverse events, including cutaneous squamous cell carcinomas, after 52 weeks of therapy.

12. Lilly E, Burke M, Kluger H, Choi J. Pregabalin for the treatment of painful hand-foot skin reaction associated with dabrafenib. JAMA Dermatol. 2015;151(1):102–3.
13. Miller KK, Gorcey L, McLellan BN. Chemotherapy-induced hand-foot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management. J Am Acad Dermatol. 2014;71(4):787–94.
14. Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. Dermatol Ther. 2011;24(4):386–95.
15. Zimmer L, Hillen U, Livingstone E, Lacouture ME, Busam K, et al. Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. J Clin Oncol. 2012;30(19):2375–83.
16.• Mochel MC, Hammond MR, Frederick DT, et al. Melanocytic nevi excised during B-Raf proto-oncogene (BRAF) inhibitor therapy: a study of 19 lesions from 10 patients. J Am Acad Dermatol. 2015;73(3):491–9.e2.

Histopathologic and immunohistochemical evaluation of excised nevi during BRAFi monotherapy, showing that new/changing nevi are BRAF wild-type lesions.

17. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323–32.
18. 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;380:358–65.
19. Kwong B. Dermatologic toxicities of melanoma drugs. Presented 23 March 2015 at the American Academy of Dermatology 73rd Annual Meeting. Lecture.
20. 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):628–33.
21.• 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):61–8.

Prospective study of twenty patients detailing extent of cutaneous toxicity and accompanied by excellent clinical photographs.

22. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30–9.
23. Sanlorenzo M, Choudhry A, Vujic I, et al. Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma. J Am Acad Dermatol. 2014;71(6):1102–1109.e1.
24. Chen FW, Tseng D, Reddy S, Daud AI, Swetter SM. Involution of eruptive melanocytic nevi on combination BRAF and MEK inhibitor therapy. JAMA Dermatol. 2014;150(11):1209–12.
25. Patel U, Cornelius L, Anadkat MJ. MEK inhibitor-induced dusky erythema: characteristic drug hypersensitivity manifestation in 3 patients. JAMA Dermatol. 2015;151(1):78–81.
26. Balagula Y, Barth Huston K, Busam KJ, et al. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs. 2011;29(5):1114–21.
27. Choi JN. Dermatologic adverse events to chemotherapeutic agents, part 2: BRAF inhibitors, MEK inhibitors, and ipilimumab. Semin Cutan Med Surg. 2014;33(1):40–8.
28. Leung T, Zhang LF, Wang J, et al. Topical hypochlorite ameliorates NF-kB-mediated skin diseases in mice. J Clin Invest. 2013;123(12):5361–70.
29. Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or

metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol. 2015;16(13):1389–98.
30. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
31.•• Ensslin CJ, Rosen AC, Wu S, Lacouture ME. Pruritus in patients treated with targeted cancer therapies: systematic review and meta-analysis. J Am Acad Dermatol. 2013;69(5):708–20.
Detailed analysis of pruritus, an important but often overlooked symptom affecting patient quality of life during cancer therapy.
32.•• Lacouture ME, Wolchok JD, Yosipovitch G, et al. Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol. 2014;71(1):161–9.
Treatment algorithm for rash associated with ipilimumab.
33.• Santini D, Vincenzi B, Guida FM, et al. Aprepitant for management of severe pruritus related to biological cancer treatments: a pilot study. Lancet Oncol. 2012;13(10):1020–4.
A novel and effective therapy for pruritus associated with chemotherapy.
34. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol. 2015;33(28):3193–8.
35. Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res. 2007;13(22 Pt 1):6681–8.
36. Sheik Ali S, Goddard AL, Luke JJ, et al. Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. JAMA Dermatol. 2015;151(2):195–9.
37. Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol. 2001;22(5):265–8.
38. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–32.
39. Totonchy MB, Ezaldein HH, Ko CJ, Choi JN. Inverse psoriasiform eruption during pembrolizumab therapy for metastatic melanoma. JAMA Dermatol. 2016;152(5):590–2.
40.• Sanlorenzo M, Vujic I, Daud A, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. JAMA Dermatol. 2015;151(11):1206–12.
The development of cutaneous adverse events in patients undergoing therapy with pembrolizumab may portend a favorable prognosis, although further studies are necessary.
41. Joseph RW, Cappel M, Goedjen B, et al. Lichenoid dermatitis in 3 patients with metastatic melanoma treated with anti-PD1 therapy. Cancer Immunol Res. 2015;3(1):18–22.
42. Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. J Cutan Pathol. 2016;43(4):339–46.
43. Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol. 2016;152(1):45–51.
44. Carlos G, Anforth R, Chou S, Clements A, Fernandez-Peñas P. A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. Melanoma Res. 2015;25(3):265–8.
45. Naidoo J, Schindler K, Querfeld C, et al. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. Cancer Immunol Res. 2016;4(5):383–9.