Review

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Melanoma Management

Management of the cutaneous adverse effects of antimelanoma therapy

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Practice points

- Clinicians should be familiar with potential cutaneous toxicities in order to council patients prior to initiation of therapy, and to avoid unwarranted dose reduction, treatment interruption or cessation of therapy.
- Collaborative care with a multidisciplinary team is recommended. This includes dermatologist review, with baseline skin examination and 3–6 monthly follow-up to ensure prompt diagnosis and management of cutaneous eruptions.
- Pruritus is a common cutaneous adverse effect reported in all melanoma therapies and can impact significantly on quality of life. Clinical treatment options include:
  - The provision of dry skin management information, such as taking only short lukewarm baths, frequent application of emollients and using soap-free body wash.
  - First-generation antihistamines and topical antipruritic medications such as menthol and camphor.
  - Medium potency topical corticosteroid and urea creams.
  - Finally, oral gabapentin, pregabalin, mirtazapine, doxepin or low-dose corticosteroids for symptomatically persistent or severe cases.
  - Consideration of aprepitant for refractory patients.
  - Dose interruption or discontinuation is rarely required.
- Lichenoid reactions are the most common cutaneous skin reaction seen in PD-1 antibody therapy. Eruptions present as violaceous papules and plaques distributed on the body. Generally, lichenoid reactions can be managed with medium potency topical corticosteroid, emollients and antihistamine. Severe toxicity may be managed with systemic prednisone or acitretin, though consideration of temporary treatment cessation may be necessary.
- Hyperkeratotic lesions commonly occur in patients on BRAF inhibitor therapy, though this rate decreases with the addition of MEK inhibitors. These hyperkeratotic lesions can include cutaneous squamous cell carcinomas and keratocanthomas – hence eruptions should be reviewed and managed by a dermatologist.
- Blistering or erosion of the skin and lesions in the oral mucosa are rare adverse effects of antimelanoma therapies, but are a red flag for clinicians, who should consider a diagnosis of Steven–Johnson syndrome and toxic epidermal necrosis. These severe reactions are associated with high mortality, and patients suspected of being affected need prompt hospitalization and specialist review. It may be kept in mind that there are a variety of other vesiculobullous reactions described in patients on anti-PD-1 antibody therapy, including bullous pemphigoid, bullous lichenoid reactions and bullous lichen planus-like reactions.

The advent of targeted therapy and immunotherapy has revolutionized the management of advanced melanoma. However, these novel therapies are associated with adverse effects (AEs), of which cutaneous toxicities are the most frequently observed. These cutaneous AEs can exert significant morbidity and impact on patient quality of life, hence the recognition and management of AEs is fundamental in preventing interruption or cessation of survival-prolonging treatments. Additionally, knowledge of these AEs are necessary in order for healthcare professionals to counsel patients when starting treatment and in the initiation of AE prophylaxis. The incidence and clinical presentation of the cutaneous toxicities of novel melanoma therapies will be discussed, and treatment guidelines provided.

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Future Medicine

Prior to the advent of targeted therapy and immunotherapy, metastatic melanoma was associated with a particularly poor prognosis, with median survival ranging from 8 to 18 months [1]. While these novel therapies have revolutionized the management of advanced melanoma, they have also been associated with adverse effects (AEs); of which cutaneous toxicities are the most frequently observed [2]. These cutaneous AEs range from benign keratotic lesions to severe reactions like toxic epidermal necrolysis [3]. However, even mild AEs can exert significant patient morbidity and impact quality of live, which may lead to treatment interruptions or cessation of treatment. Prompt recognition, review and management of these AEs allow patients to continue on their survival-prolonging treatments. In this review, we will examine the cutaneous toxicities of novel melanoma therapies and provide management recommendations that may be utilized in conjunction with collaborative care by dermatologists. For conditions mentioned in Common Terminology Criteria for Adverse Events (CTCAE), treatment guidelines are provided with management according to severity [4].

Hyperkeratotic, keratinocytic lesions

Cutaneous squamous cell carcinomas & keratoacanthomas

Cutaneous squamous cell carcinomas (cuSCC) frequently occur in patients treated with BRAF inhibitors (BRAFi) as single agent, though this incidence decreases with the addition of MEK inhibitors (MEKi; 19 vs 7%, respectively) [5]. The majority of these cuSCC occurs in the first 3 months of therapy and is not exclusive to locations with high ultraviolet (UV) exposure [6]. Most cuSCC are well-differentiated cuSCC or are cuSCC of the keratoacanthoma type [7].

Oral acitretin has been reported as a chemopreventive agent, and has been used to significantly reduce the development of new cuSCC [8,9]. In one case, acitretin reverted multiple cuSCC of the keratoacanthoma type [10].

Excision is the standard of treatment of cuSCC, and is associated with a high level of cure. A 4-mm margin of excision is recommended in lesion less than 2 cm, while tumors greater than 2 cm may require margins up to 10 mm to ensure adequate local control [11]. However, cuSCC induced by BRAFi may be treated more conservatively than typical UV-induced cuSCC [12]. Thin lesions may be managed with the use of deep shave biopsy and subsequent electrodessication and curettage, or aggressive and frequent cryotherapy [13].

Topical therapies such as 5-fluorouracil [14] and conventional photodynamic therapy [15] may be trialed to decrease the burden of superficial SCCs to allow for better differentiation of lesions that require surgical management. This is especially useful when patients have had an eruption of multiple lesions, or have lesions affecting cosmetically sensitive areas such as the face and scalp. These topical therapies have been shown to be well tolerated and to minimize cuSCC recurrence on follow-up [16].

Evidence of the role of viruses like HPV in BRAFi-induced secondary lesions has also led to the suggestion of topical antiviral therapies such as cidofovir as a possible future therapeutic option [17], but the results of these therapies have not been published. It may be noted that imiquimod has additionally been found to be an effective agent in BRAFi-induced keratoacanthomas (KAs), resulting in subsequent dermatoscopic resolution following treatment [18].

Verrucal keratosis

Verrucal keratoses are a common cutaneous AE associated with single-agent BRAFi treatment. These lesions present as hyperkeratotic or smooth papules, often with a similar appearance to keratocathomas or warts. Up to 49% of patients develop these lesions, and they present as early as 7 days after initiation of therapy [12]. They have the same mutations and immunohistological profile of cuSCCs, and as such are considered premalignant lesions [19] that should be monitored. Acitretin can be used as a chemopreventive agent [14]. Lesions may be treated with liquid nitrogen cryotherapy, but lesions suspicious of CuSCC should be excised [20]. The addition of an MEKi to BRAFi therapy greatly reduces its incidence [5].

Actinic keratosis

Actinic keratosis are lesions with a low potential of transformation to cuSCC that occur in sun-exposed skin. Initiation of BRAFi therapy is associated with a marked increase in the development of actinic keratosis. Timely monitoring of skin with regular skin checks is therefore recommended, with appropriate destructive treatment modalities such as cryotherapy or field treatments such as photodynamic therapy or 5-fluorouracil to be utilized when required [13]. Laser ablation has also been trialed [21].

Grover's disease

Grover's disease is one of the most common cutaneous eruption in single-therapy BRAFi treatment, with 39% of patients on vemurafenib [5] and 45% of patients on dabrafenib [22]. They present as rapid-onset pruritic papules often with a crusted top that develop on the trunk, and infrequently, limbs [23]. Grover's disease should be treated symptomatically with emollients, topical steroids, topical keratolytics like urea or salicylic acid and oral antihistamines. Particularly severe cases may be managed with short-term oral prednisone for flares or long-term acitretin [23].

Palmar–plantar erythrodysesthesia syndrome

'Hand-foot syndrome' can at times be used to describe two distance entities – palmar–plantar erythrodysesthesia and plantar keratoderma. Palmar–plantar erythrodysesthesia syndrome is a reaction seen in up to 77% of patients treated with the multikinase inhibitor sorafenib [24]. These lesions present as bilateral erythematous lesions, that can evolve forming blisters, on the palms and soles, and can have significant effect on the patient's quality of life. This reaction occurs usually within the first 46 days of initiation [25], and its severity appears dose related [26]. Preventative measures include the use of orthotics and emollients, as well as patient education in regards to avoiding friction – such as wearing wide, flexible shoes and cotton socks [27]. Patients should be assessed for pre-existing areas of friction, and hyperkeratotic areas treated with keratolytics such as urea 10–50% or salicylic acid 2–5% [23,24]. Early palmar–plantar erythrodysesthesia should be treated with similar principles [27]. Lesions severe enough to cause pain and limit instrumental activities of daily living should be managed with appropriate analgesia, cooling measures such as cold water or ice blocks and potent corticosteroid-like clobetasol [27,28]. A 50% dose reduction may be considered until symptoms are controlled [29]. In instances where there are severe skin changes, and symptoms are limiting self-care activities of daily living, oral corticosteroids or pyridoxine may be added to management [27,28]. Treatment should be ceased until symptoms are controlled, and therapy restarted at a lower dose, if at all [23,29], see Figure 1.

Plantar keratoderma

Plantar keratoderma has been observed in patients treated with BRAFi or combination BRAFi and MEKi. They are a distinct entity from the palmar–plantar erythrodysesthesia seen in patients treated with sorafenib, as they only present in areas of pressure or friction, and both blisters and palm involvement are infrequent. However, these lesions may be quite tender and can still severely affect quality of life. Early treatment with topical keratolytics such as urea or salicylic acid should be initiated, and patients should be advised on techniques to avoid friction, as mentioned previously [23].

Cutaneous exanthemas

'Rashes' are often characterized as a common AE for cancer immunotherapy and targeted therapy, which clinicians often treat with broad principles of management. However, care must be taken, as a 'rash' is a clinical sign and not a diagnosis. Such a description may encompass a variety of dermatoses, such as bullous pemphigoid, lichenoid reactions, Sweet syndrome, eczema, psoriasis and so on. Failing to obtain a diagnosis hinders not only early treatment and symptom control but may necessitate the disruption of life-saving therapy [30]. Several cutaneous eruptions associated with antimelanoma therapy will be discussed below.

Maculopapular exanthema

Maculopapular exanthemas can occur in all antimelanoma therapies with varying frequency. In the case of anti-PD-1 therapy and anti-CTLA-4 therapy [16], this eruption appears as an exanthema composed of red erythematous papules coalescing into plaques [31], which develop soon after treatment initiation [16].

Treatment depends upon the body surface area involved, and severity of symptoms such as pruritus (see Figure 2). The presence of mucosal involvement or blisters or erosions in the body should trigger the concern of a very severe drug reaction, such as Steven–Johnson syndrome and toxic epidermal necrosis (SJS/TEN). Initial management includes the use of emollients, mid-potency topical steroids, topical calcineurin inhibitors and antihistamines. In recalcitrant cases, and in extensive or highly symptomatic eruptions, a course of oral corticosteroid may be necessary. A tapering dose of 0.5–1 mg/kg of oral prednisone daily weaned over a month has been used effectively in ipilimumab [32], though physicians should be wary of recurrence or exacerbation of symptoms resulting from rapid weaning [33]. While some clinicians may feel hesitant to use an immunosuppressant such as oral steroid in the

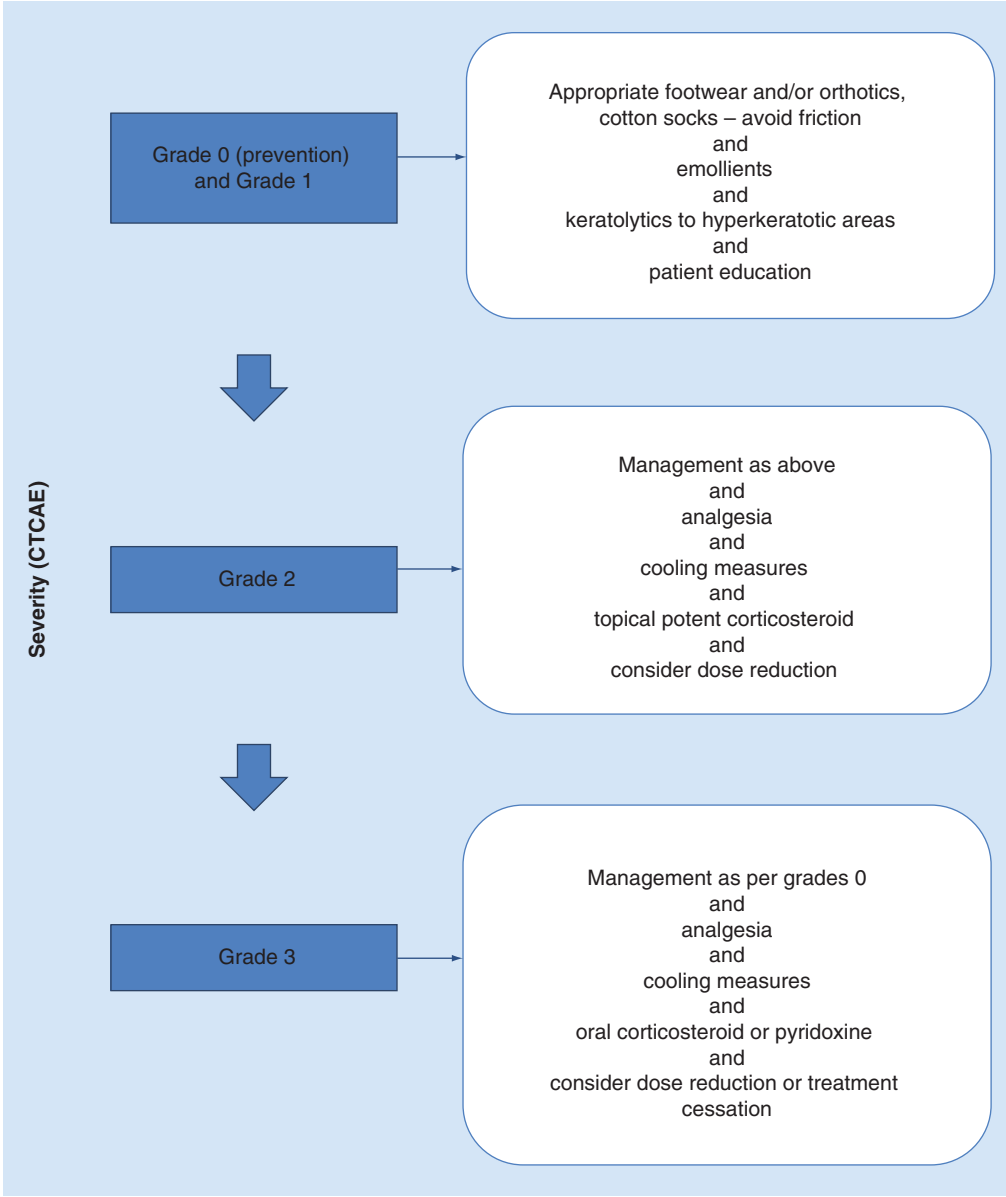

Figure 1. Management of palmar–plantar erythrodysesthesia syndrome.
CTCAE: Common Terminology Criteria for Adverse Events.

context of melanoma immunotherapy, a recent retrospective study demonstrated that in patients on ipilimumab, treatment with systemic immunosuppression was not associated with any difference in overall survival or treatment failure compared with those who were not [34]. Indeed, patients on ipilimumab treated with high-dose steroids continued to exhibit antitumor effect [35]. Emulsifying ointment wet dressings are also an effective addition to management. Dose adjustment or cessation of treatment should be considered in severe eruptions [20].

Acneiform eruptions

Acneiform eruptions are the most common cutaneous AE associated with MEKi monotherapy, with up from 57 to 82% of patients developing these lesions [36,37], which appear in a seborrheic distribution (face, scalp, upper chest and back) [13]. These eruptions are usually inflammatory (papular, pustular and erythematous, but typically without comedones) as opposed to cystic [38], with an appearance similar to EGFR inhibitor eruptions.

Prevention of acneiform eruptions can be achieved by prophylactic oral tetracyclines such as doxycycline 100 mg two-times a day or minocycline 100 mg two-times a day [21,31]. Symptomatic control of associated pruritus, burning

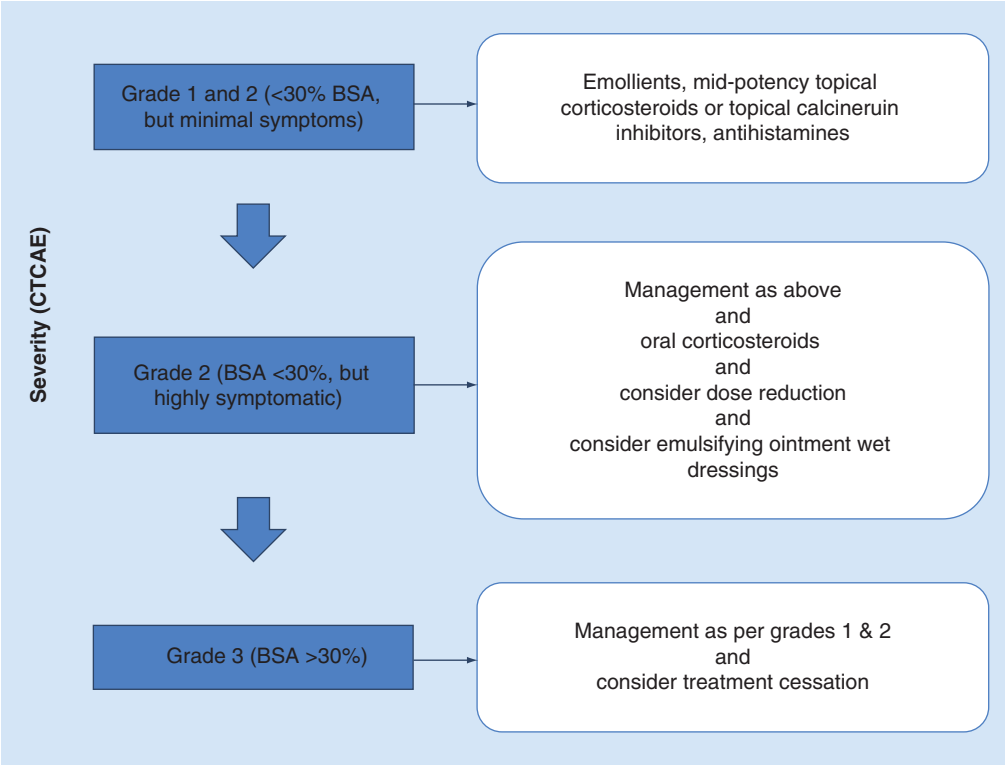

Figure 2. Management of maculopapular eruptions.
BSA: Body surface area; CTCAE: Common Terminology Criteria for Adverse Events.

and pain may be achieved with topical corticosteroid, topical antibiotics such as clindamycin or oral doxycycline [20]. Oral isotretinoin or oral corticosteroid, and dose adjustment and treatment cessation may be required for severe eruptions [13] (see Figure 3). The addition of BRAFi to the therapy regime reduces the incidence of acneiform eruptions.

Secondary infections are commonly present, and clinicians should have a low threshold to culture lesions that appear atypical or do not respond to standard therapy with systemic antibiotics [13]. Bleach baths may also be utilized in this context to decrease skin bacterial burden and hence reduce inflammation [39].

Psoriasiform eruptions

Psoriasiform eruptions in patients with no past history of psoriasis as well as flares in patients with history of psoriasis have been reported in patients treated with anti-PD-1 and anti-CTLA-4 therapies [40–42]. These lesions have been effectively managed with both topical and oral corticosteroids, as well as topical vitamin D analogs [35]. Oral retinoids have also been used for patients where extensive plaques are present and treatment with methotrexate has also been described in some case reports [40,41].

Folliculitis

Folliculitis occurs in approximately 9% of patients on BRAFi therapy [23], and approximately 40% of patients on combination BRAFi and MEKi therapy [5]. Most folliculitis are mild, and can be treated with antiseptic washes such as triclosan or chlorhexidine [20]. Moderate to severe cases may require oral antibiotic/anti-inflammatory therapy such as doxycycline [23].

Lichenoid reaction

Lichenoid reactions have been reported infrequently in patients treated with ipilumumab [43], and in approximately 33% of patients within 14 months of commencing anti-PD-1 antibodies [3]. It is, therefore, the most frequently observed symptomatic cutaneous eruption in those undergoing PD-1 therapy.

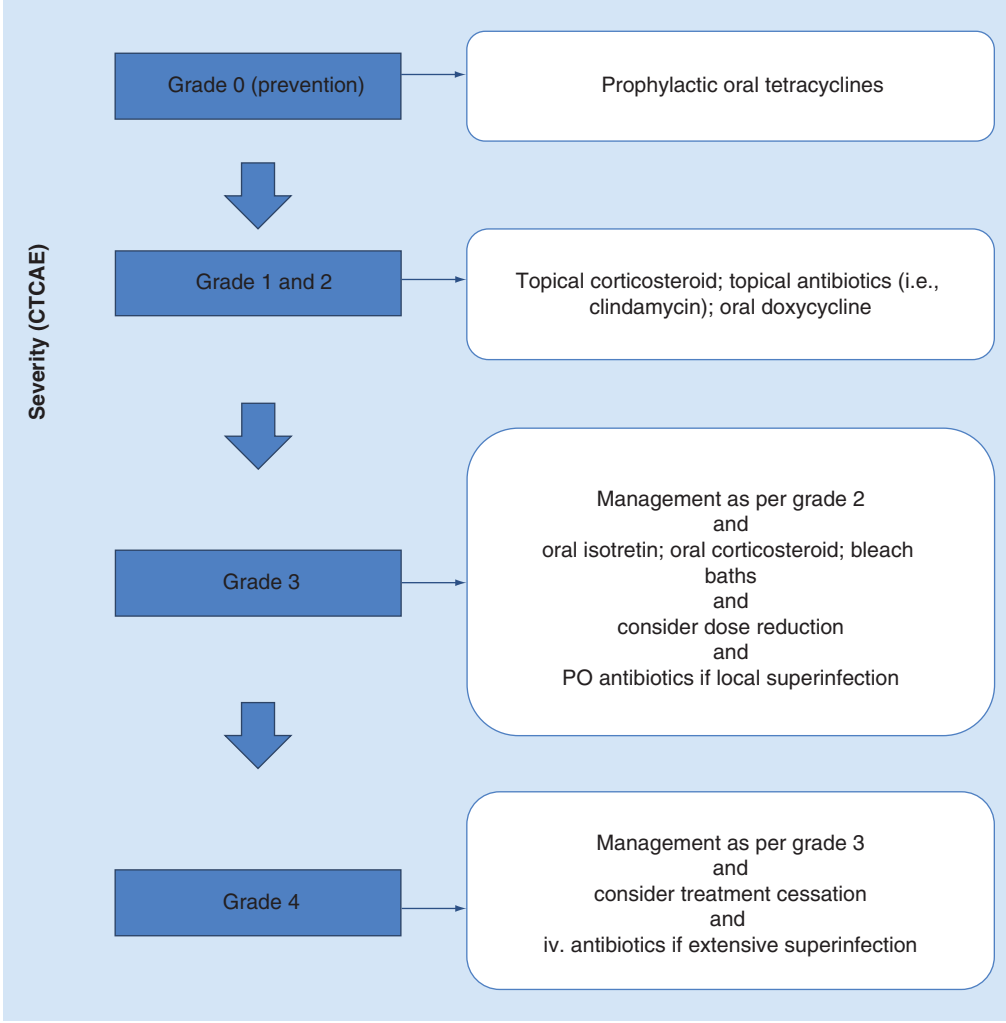

Figure 3. Management of acneiform eruptions.
CTCAE: Common Terminology Criteria for Adverse Events; iv.: Intravenous.

This eruption presents as violaceous pruritic papules and plaques resembling lichen planus, predominately distributed on the body, with minimal involvement of the mucosal surfaces [3]. Often the onset is delayed, with only approximately a quarter of patients developing lesions in the first 8.3 months [3]. Generally, lichenoid reactions can be managed with a medium potency topical corticosteroid, emollients and antihistamines [44] without the need for dose adjustment for therapy [45]. In cases of severe toxicity, the use of systemic prednisone or acitretin [20] may be necessary along with consideration of temporary treatment cessation [13].

Sweet syndrome/pyoderma gangrenosum

There have been reported cases of sweet syndrome and pyoderma gangrenosum-like ulcerations in patients being treated receiving anti-CTLA-4 antibodies and BRAFi therapy [46,47]. Sweet syndrome is characterized by sudden onset tender erythematous papules, plaques and nodules that is often associated with systemic features such as fever, malaise and neutrophilia [48]. Pyoderma gangrenosum is also a neutrophilic dermatoses, but presents as a tender, rapidly growing ulcer [49]. In the case of ipilimumab, these neutrophilic dermatoses occurred after 3–6 weeks after initiation of treatment, and was dose dependent [50]. Treatment includes aggressive wound care and high-dose oral corticosteroid [31,47].

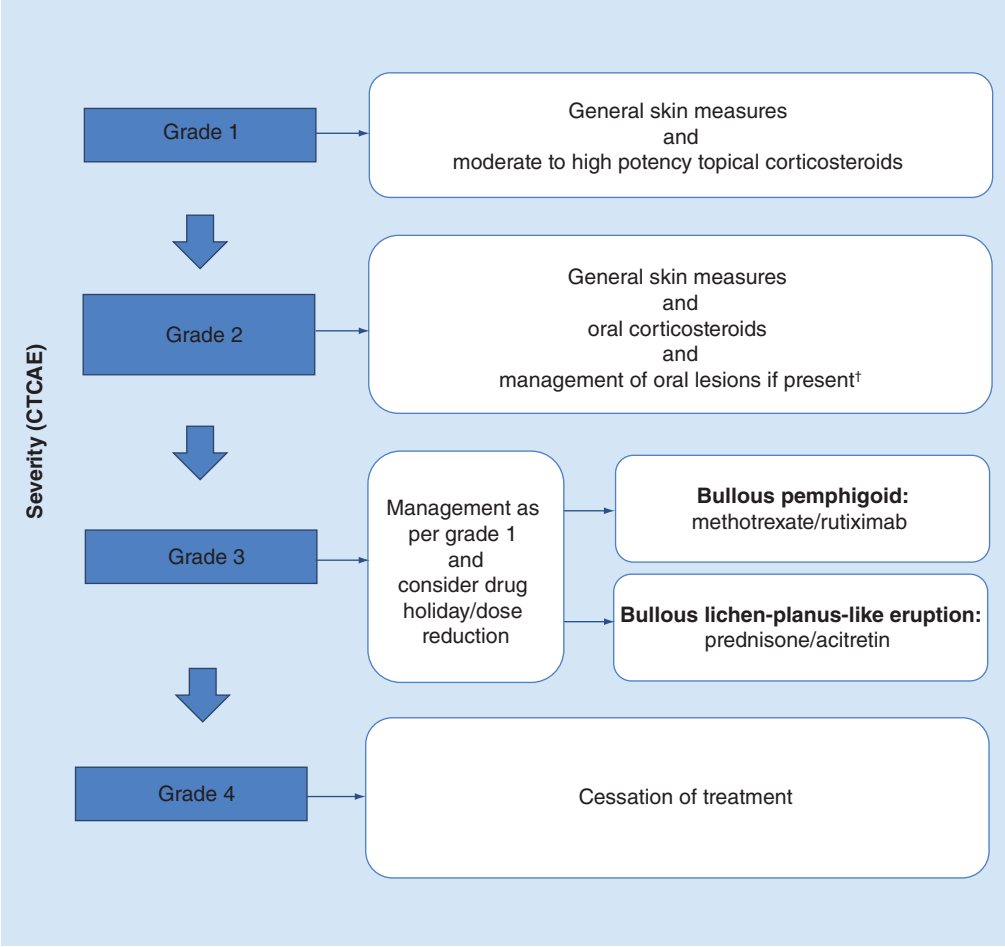

Figure 4. Management of vesiculobullous eruptions.
†Mucosal erosions can be managed with triamcinolone acetonide, oral tacrolimus ointment and dexamethasone mouthwash.
CTCAE: Common Terminology Criteria for Adverse Events.

Panniculitis

Reports in the literature exist of BRAFi-induced panniculitis, particularly the erythema nodosum type [13], with a reported frequency of 2.5% for dabrafenib and 11% for vemurafenib [5]. Panniculitis typically presents as tender, firm nodules and plaques with erythematous overlying skin [51]. This can be managed symptomatically with nonsteroidal anti-inflammatory drugs, systemic prednisone or potassium iodine. Temporary cessation of BRAFi therapy was necessary in one case [52].

Vesiculobullous reactions/bullous pemphigoid

Multiple reports in the literature describe vesiculobullous reactions such as bullous pemphigoid [53,54], bullous lichenoid reactions and bullous lichen planus-like reactions [55] occurring in patients treated with anti-PD-1 antibodies. Onset of the eruption ranges from 1-month post start of therapy [55] to 18 months after initiation [54]. No formal consensus has been met in regards to standard treatment, and multiple management methods have been described (see Figure 4) including the use of topical or oral corticosteroid and cessation of anti-PD-1 antibody in severe cases [53]. Methotrexate has been successfully utilized in anti-PD-1-induced bullous pemphigoid [53,56], along with rituxumab [57]. Acitretin has been used in bullous lichen-planus like eruptions [55]. Mucosal erosions have been treated with triamcinolone acetonide [55] as well as oral tacrolimus ointment and dexamethasone mouthwash [58].

DRESS

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug reaction that is characterized by a clinical presentation with high fever, extensive skin exanthema and organ involvement, with frequent presence of lymphadenopathy and eosinophilia [59]. There have been three reported cases of vemurafenib (BRAFi)-induced DRESS syndrome and one case of ipilimumab-associated DRESS [60]. All cases of vemurafenib-induced DRESS occurred soon therapy initiation, between 8 days to 4 weeks [61]. There have also been two cases resembling DRESS in patients administered with vemurafenib following anti-PD-1 therapy [62]. In these reports, the eruption occurred 7 and 9 days following vemurafenib treatment, leading the authors to hypothesis that anti-PD-1 antibodies may prime the immune system, and hence increase the risk of DRESS [62]. As the disease can potentially have a fatal evolution, permanent discontinuation of the medication is required, hence early recognition on presentation and immediate withdrawal of the suspect drug is necessary.

There are no validated treatment guidelines for DRESS, but general management recommendations include supportive therapy in specialized units, systemic corticosteroid or cyclosporine [61,63]. Alternative steroid-sparing therapies that have also been reported in the literature include adjunctive high-dose intravenous immunoglobulin, plasmapharesis and immunosuppressive drugs such as cyclophosphamide, interferons, muromonab-CD3, mycophenolate mofetil and rituximab [59].

Acute generalized exanthematous pustulosis

Acute generalized exanthematous pustulosis is a serious cutaneous reaction characterized by nonfollicular sterile pustules on an edematous erythematous base, effecting predominately the flexures and face [64]. Acute generalized exanthematous pustulosis has been reported in patients treated with ipilimumab, combination ipilimumab and nivolumab therapy, and sorfenib [65–68]. Treatment includes prompt cessation of the responsible drug, along with intravenous or oral corticosteroid [65–67].

Steven–Johnson syndrome & toxic epidermal necrosis

SJS/TEN are severe cutaneous reactions characterized by sheets of epidermal detachment and erosions of mucous membranes [69], and associated with high mortality [70]. SJS and TEN exist on a spectrum, and are classified based on the extent of skin detachment. TEN has been described in BRAFi [71,72], anti-PD-1 treatment [73] and TEN/SJS has been reported in less than 1% of patients treated on CTLA-4 therapy [33]. Evidence-based standard treatment protocols do not exist for SJS/TEN given its rarity [74], but important treatment principles include prompt and permanent cessation of the culprit medication, hospital admission in early referral to specialized units with supportive care (such as burn units) and close monitoring [72,73]. Systemic steroids, intravenous immunoglobulin, plasmapharesis, along with other treatments such as cyclosporine [74], cyclophosphamide and anti-TNFα antibodies should also be considered [75].

Changes in pigmentation

Vitiligo-like depigmentation

Vitiligo presents as depigmentated patches or macules that are bilaterally distributed, characterized by the presence of Koebner's phenomenon and can be distinguished from hypopigmentation by its fluorescence under a wood's lamp [13]. Vitiligo is not a rare phenomenon in patients with melanoma, with an approximate prevalence of 3.7% in melanoma patients not on systemic therapy [76].

Interestingly, a recent study examining depigmentation in eight patients treated with anti-PD-1 therapy has described these lesions to be clinically and biologically distinct from vitiligo. The vitiligo-like lesions were observed only on photoexposed areas that were noted to have pre-existing actinic lentigos – areas such as the forehead, dorsum of the hand and forearms. Additionally, the Koebner phenomenon was absent, as was a history of previous autoimmune disease [77]. However, another study of 17 patients found that the majority had a generalized vitiligo distribution, defined by a bilateral symmetrical form including acrofacial vitiligo, diffuse vitiligo vulgaris and universal vitiligo – more in keeping with classic vitiligo [78]. Vitiligo-like depigmentation has also been known to develop around sites of primary melanoma or areas of cutaneous metastasis among patients treated with antimelanoma therapy [13].

Approximately 2–11% of patients treated with ipilimumab [31] and 8–24% of patients on anti-PD-1 therapy reported a loss in pigmentation [3,79–80]. Multiple studies have reported on the possible association between

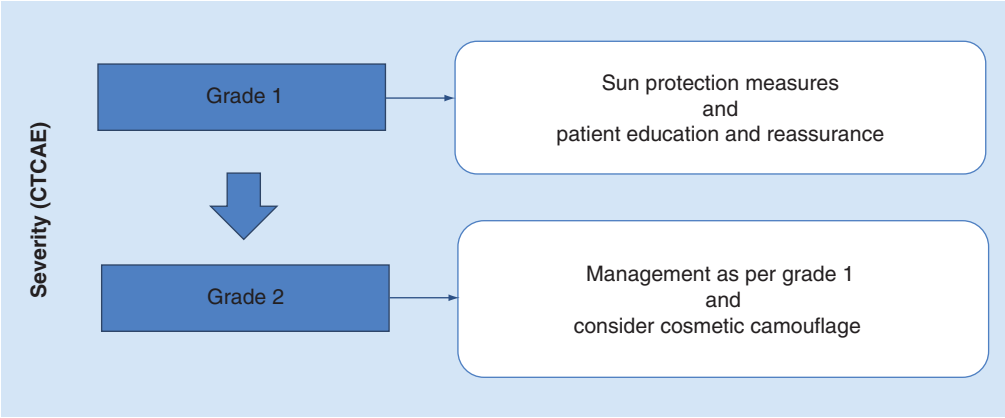

Figure 5. Management of vitiligo-like depigmentation.
CTCAE: Common Terminology Criteria for Adverse Events.

vitiligo/vitiligo-like depigmentation and survival benefit [81] in both anti-CTLA-4 [31,35] and anti-PD-1 therapies [78,80,82]. It must be noted, however, that there are statistical fallibilities associated with these studies [83].

Patients who develop these lesions are more susceptible to sunburn, and should therefore be counseled on sun-protection measures [33,43]. There is no standard protocol for managing vitiligo, but cosmetic camouflage may be considered for patients who feel the lesions are impacting their quality of life or self esteem [84] (see Figure 5).

New primary melanomas

Some groups have found that the administration of BRAFi is associated with new primary melanomas [85] that can present as either new lesions or rapid change in pre-existing lesions [86]. Reports on the frequency of a second primary melanoma lesion in patients treated with BRAFi vary from 1.6 [87] to 21% [88]. Mutational analyses of these new melanomas demonstrate BRAF wild-type proliferations, possibly from increased MAPK activity induced by BRAF inhibition [89]. Some authors have questioned the high rate of melanoma [90]. In any case, patients undergoing melanoma cancer therapies should undergo serial dermatological examinations, and any lesions that appear atypical should be appropriately excised for histopathological analysis [85].

Change in melanocytic naevi

This is a frequent event with most antimelanoma therapy. BRAFi have been associated with naevi involution, new atypical pigmentation and eruptive naevi [85,86]. A recent study demonstrated that patients on BRAFi monotherapy have increased rates of darkening nevi, while those on combination BRAFi and MEKi demonstrated increased rates of nevi lightening, along with those on anti-PD-1 and anti-CTLA-4 therapies [91]. Again, this reiterates the importance of regular skin checks for patients on antimelanoma therapy, preferably in specialized clinics with the means to closely monitor nevi changes, using technology such as total body photography and sequential digital dermoscopy.

Other

Pruritus/xerosis

Pruritus is a common cutaneous AE that has been reported in all melanoma therapies, and can significantly impact on a patient's quality of life [92]. Approximately 13–30% of patients being treated with BRAFi develop pruritus [23,93], which is often associated with drug-induced xerosis or Grover's disease [23,43]. MEKi also frequently cause pruritus and xerosis – 45 and 23% of patients managed, respectively [31]. 12% patients on anti-PD-1 therapy [79] and 31% of patients on ipilimumab have reported pruritus [92]. In the instance of ipilimumab, pruritus can occur without the presence of cutaneous lesions or xerosis [31], and is thought to be the result of immune activation [92]. Patients who develop xerosis may go on to develop xerotic eczema – an event that occurs more frequently in those treated with anti-PD-1 therapy [3].

Management depends on the severity of symptoms (see Figure 6) – generally, patients should be given information regarding dry skin management, such as taking only short lukewarm showers, frequent application of emollients,

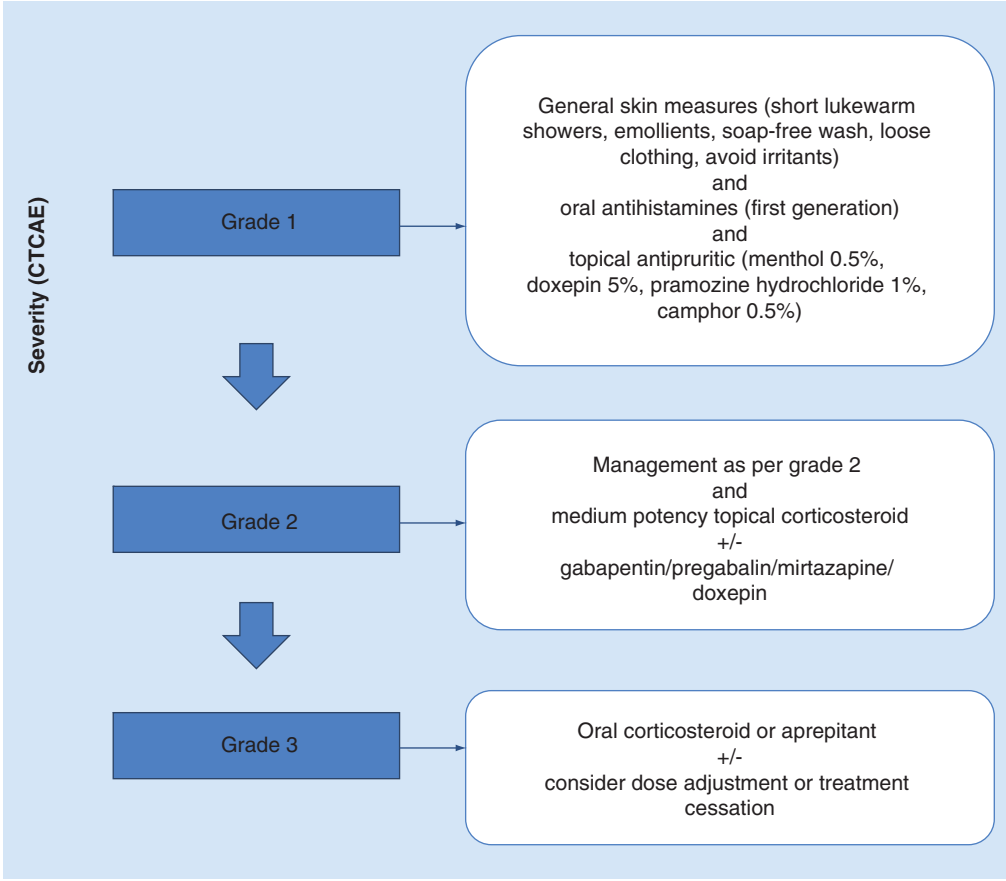

Figure 6. Management of pruritus/xerosis.
CTCAE: Common Terminology Criteria for Adverse Events.

avoidance of skin irritants, wearing lose clothing, using soap-free body wash and maintaining a cool ambient environment [43]. First-generation oral antihistamines such as diphenhydramine HCL or hydroxyzine HCL have also proven effective [33]. Topical antipruritic medications such as menthol 0.5%, doxepin 5%, pramoxine hydrochloride 1%, camphor 0.5% [32], medium potency topical corticosteroid and urea creams [20] can also be used. Oral gabapentin, pregabalin, mirtazapine [94], doxepin and short courses of low-dose corticosteroids [20] have also been effective. Aprepitant, a neurokin receptor inhibitor, can also be considered for refractory patients. Pruritus rarely requires dose interruption or discontinuation [95].

Photosensitivity

UVA-induced photosensitivity is a common cutaneous side effect associated with BRAFi, with approximately 52% of patients treated with vemurafenib [23], and 0.8% of patients on dabrafenib [5] develop photosensitive reactions. While most dabrafenib-induced photosensitivity are grade 1 and 2 reactions (i.e., pink and red erythema of sun-exposed skin) [5], patients undergoing vemurafenib therapy are more likely to develop severe reactions characterized by a severe sunburn with possible blistering that may cause pain and significantly impair daily activities [13]. Indeed, around 92% of patients on vemurafenib are reactive to light on phototesting [96]. A painful burning sensation can develop within 10 min of exposure of light [23], and eruptions occur even when patients are behind windows, as UVA can penetrate glass.

Prevention of photosensitive reactions includes strict sun avoidance and the use of photoprotective clothing and the application of broad-spectrum chemical sunscreens that protect against UVA and UVB, even when indoors [13]. Vitamin D supplementation should be considered in patients with undergoing extended or strict sun avoidance [97], (see Figure 7).

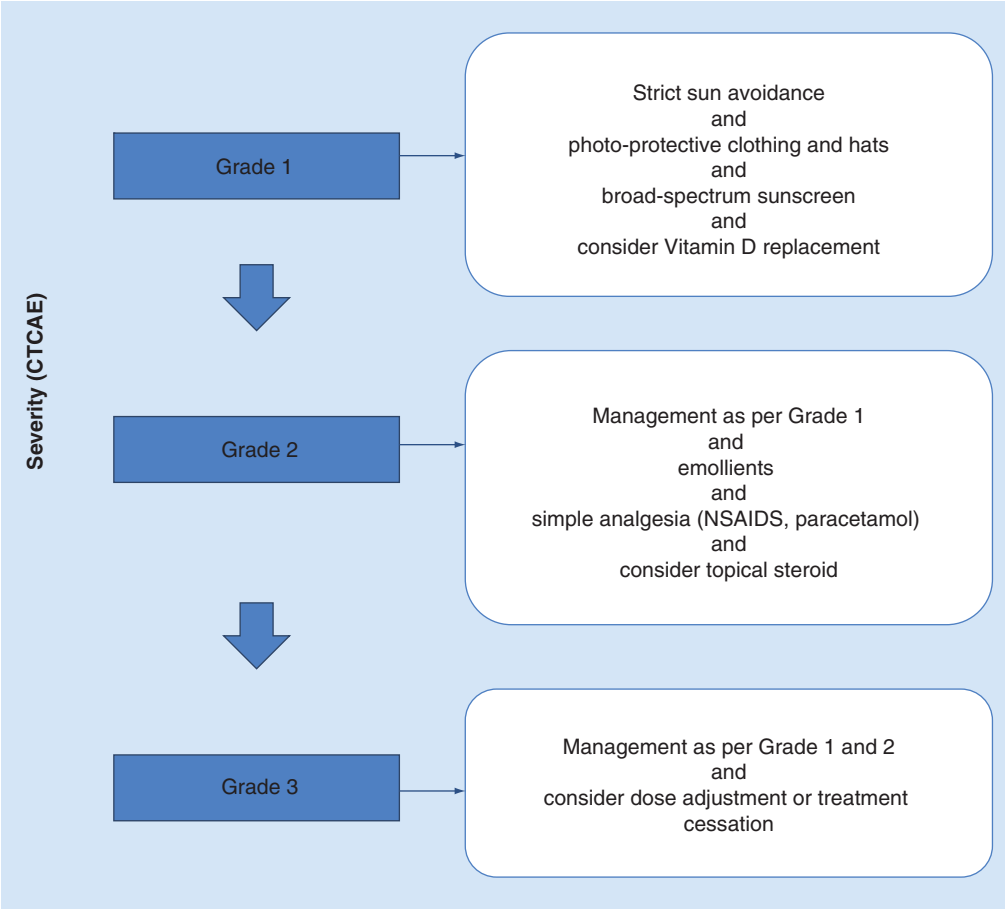

Figure 7. Management of photosensitivity.
CTCAE: Common Terminology Criteria for Adverse Events.

Management for photoreactive reactions involves symptomatic relief in the form of emollients and simple analgesia. Cold compresses or soaks in cool water can also be used to provide relief. Topical steroids can be considered for significantly symptomatic eruptions. Care should be taken to identify and treat any secondary infection [98].

Hair follicle changes

A variety of hair follicle changes have been described in patients undergoing BRAFi therapy including alopecia, changes in the structure of hair (such as straight to curly hair or hair turning gray) and keratosis pilaris-like eruptions [23]. In Phase II trials of vemurafenib, 36% of patients reported hair loss [99], whereas 8% of patients were affected in Phase III trials [100]. On dabrafenib, 20% of patients reported hair loss, and 17% reported changes in hair structure [22]. Keratosis pilaris is reported to be frequent all BRAFi therapy, but the incidence is unknown [23]. Supportive care for alopecia involves identification of co-morbidities that may contribute to their loss, such as thyroid function, zinc and iron levels, and camouflaging methods such as sprays, powders, hairpieces and wigs [101]. Keratosis pilaris-like reactions are best treated with mild keratolytics such as lactic acid, salicylic acid or urea, topical corticosteroids for pruritus and gentle exfoliation [21].

Conclusion

Immunotherapy and targeted therapy in the treatment of melanoma has significantly improved overall survival for patients. However, cutaneous AEs are common and practitioners should be able to pre-emptively counsel patients on anticipated skin toxicities, recognize reactions and understand treatment principles. Collaborative patient care with a dermatologist where possible is recommended; with a baseline skin examination and regular three monthly follow-

up and prompt review if cutaneous AEs are suspected. This ensures accurate diagnosis and management, ensuring patients' quality of life and allowing for the continuation of life-prolonging treatment. Long-term monitoring even following treatment cessation is recommended, given the likely high-risk nature of patient populations, the slow resolution times of some cutaneous SE and the possibility of delayed reactions.

Future perspective

As the field of antimelanoma therapy evolves, there is an expected increase of the utilization of novel immunotherapy and targeted therapies, in addition to new combination regimes and the development of new therapies. New drug combinations may lead to increased severity of cutaneous toxicities (such as in the case of combined ipilimumab and nivolumab) or decreased frequency of adverse events (such as with combined BRAFi and MEKi therapy). Regardless, the off-target effects of these medications warrant further study, and ongoing management by dermatologists. Understandably, the involvement of a dermatologist may be difficult due to distance or a scarcity of specialists familiar with oncodermatology. However, improving technology and the rise of teledermatology may increase the availability of specialist care in the management of cutaneous toxicities.

Current management guidelines such as those provided in this review are often a description of best practice, sometimes based on practitioner preference and case reports. Clarification of evidence-based medicine should be conducted, with further research through clinical trials and cohort studies.

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