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REVIEW

Cutaneous Adverse Events of New Anti-melanoma Therapies: Classification and Management

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Abstract Over the past decade, targeted therapies such as BRAF inhibitors, MEK inhibitors and immunotherapies such as anti-CTLA4 and anti-PD1 antibodies have emerged as novel treatments of advanced melanoma. Along with increased use of these therapies, a range of cutaneous adverse events have also emerged, varying from more serious and frequent cutaneous squamous cell carcinoma to mere cosmetic changes such as curly hair or rare severe toxic epidermal necrolysis. Early detection and management of these cutaneous adverse events will aid patients to receive accurate treatment, avoid unnecessary discontinuation of anti-tumour treatment and improve the patient's overall quality of life. This review will describe various cutaneous adverse events of anti-melanoma therapies and its management.

PALABRAS CLAVE
Inhibidores de BRAF;
Inhibidores de MEK;
Anti-CTLA4;
Anti-PD1;
Melanoma metastásico;
Efecto cutáneo adverso

Efectos cutáneos adversos de los nuevos tratamientos para melanoma: Clasificación y Tratamiento

Resumen En la última década han aparecido nuevos tratamientos para el melanoma avanzado, como las terapias contra dianas como los inhibidores de BRAF o MEK, y las inmunoterapias como los anticuerpos contra CTLA-4 y PD1. Debido al uso cada vez más frecuente de estos tratamientos también han aparecido diversos efectos secundarios cutáneos, que van desde efectos graves y frecuentes como el desarrollo de carcinomas espinocelulares, a cambios cosméticos como el pelo rizado, o casos infrecuentes y graves de necrosis epidérmica tóxica. La detección y

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el tratamiento temprano de estos efectos adversos ayudará a los pacientes a recibir mejor tratamiento, a evitar el cese de la terapia antitumoral y a mejorar su calidad de vida. En esta revisión describiremos los efectos cutáneos adversos de los nuevos tratamientos contra el melanoma y su tratamiento.

Introduction

The incidence of malignant melanoma has been increasing in people of European descent over the past decades. Previously the median survival of patients with stage IV metastatic melanoma was only 10 months, and treatment options were limited to cytotoxic chemotherapy with poor prognosis.[1] Over the past number of years, novel melanoma therapies such as targeted therapies and immunotherapies have revolutionised the treatment options for advanced melanoma.[2–6] With increasing use of these therapies, myriads of cutaneous adverse events (AEs) have emerged. These cutaneous AEs range from malignant BRAF inhibitor (BRAFi) induced cutaneous squamous cell carcinoma (cuSCC)[1] to vitiligo observed in patients treated with anti-Programmed cell death protein 1 (PD1) antibodies[2] or very severe rare AE such as toxic epidermal necrolysis.[7] While not all of these AEs are medically concerning, they may significantly affect patient's quality of life and lead to disruption in treatment dosing. Prompt identification of these AEs and initiation of treatment may help avoid this. This review will summarise the various cutaneous toxicity profiles of anti-melanoma treatments and discuss the appropriate management (Table 1).

Cutaneous adverse events of BRAF inhibitors

BRAFi (vemurafenib, dabrafenib) are used to treat stage IV BRAF mutant (V600E/K) metastatic melanoma. While immune modulating agents may have a longer progression free survival (PFS), BRAFi still have an important place in BRAF mutant disease.[8,9]

Mutations within the BRAF kinase have been identified in up to 50% of patients with metastatic melanoma.[10] The most common mutation has been identified at position 600 and results from a substitution of valine to glutamic acid. This subsequently leads to over activation of the mitogen-activated protein kinase pathway (MAPK), which regulates cellular growth, proliferation and survival. BRAFi acts by binding to the BRAF kinase, thereby inhibiting its ability to phosphorylate downstream mitogen-activated extracellular signal-regulated kinase (MEK) and inhibiting cellular proliferation.[11,12]

Keratinocytic malignant and pre-malignant lesions

Cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinoma is the most well-known malignant BRAFi induced cutaneous AE (Fig. 1a). It has been proposed that BRAFi forms a dimer with the wild-type BRAF kinase within the keratinocyte, leading to activation of the MAPK pathway.[13–15] Up to 31% of people treated with a BRAFi will develop a cuSCC (Table 1) and they can appear on both sun exposed and non-sun exposed areas. The peak time for developing a cuSCC is within the first three months of treatment, and elderly patients (>60 years) are at increased risk.[16]

CuSCCs are best excised though other treatment modalities such as photodynamic therapy and 5-flurouracil have been reported.[17,18] In our hands, oral acitretin slows down the development of cuSCC (Table 1).[19,20]

Verrucal keratosis

Verrucal keratosis are pre-malignant hyperkeratotic papules (Fig. 2). They are induced by both vemurafenib and dabrafenib and are common in the early stages of treatment with up to 49% of patients treated with dabrafenib having reported to develop at least one of them.[1] They become less frequent after 52 weeks of treatment, with 18% of patients having reported to develop a lesion.[21]

While these lesion are benign on histopathology, they harbour the same mutations[22,23] and immunohistochemical profile[24] as cuSCC, suggesting that they may have the potential to develop into cuSCCs.[1] Oncogenic human papillomavirus is believed not to be linked with the development of verrucal keratosis.[22] Acitretin may be useful in the prevention of verrucal keratosis.[20] Verrucal keratosis can be treated with cryotherapy and if there are any suspicious features of malignancy, the lesion should be excised (Table 1).[22]

Benign keratotic lesions

''Rash'' was reported in the early clinical trials for both vemurafenib and dabrafenib. While this can take many forms including the classical maculopapular drug-related exanthema,[25] in our experience the most common rash induced by BRAFi's is Grover's disease. This occurs in up to 45% of patients on dabrafenib,[1] and 39% on vemurafenib.[3] It commonly presents on the trunk with the limbs infrequently involved. Treatment varies depending on its severity (Table 1). One group has reported the development of Darier's-like disease[26] that on histology looked similar to Grover's disease.

Plantar keratoderma usually occurs at sites of friction and also on the hands (Fig. 1b). As these lesions are quite tender and interfere with patient's quality of life, early treatment is essential.[1]

Grover's disease and plantar keratoderma can be treated with moisturisers and topical keratolytics (urea or salicylic acid). Oral acitretin has also been reported to be useful

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