Unveiling cutaneous adverse events and prognosis in immunotherapy for melanoma and squamous cell carcinoma

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The introduction of immune checkpoint inhibitors (ICIs) has marked a transformative era in cancer therapy, particularly in melanoma and cutaneous squamous cell carcinoma (cSCC), showcasing remarkable efficacy vs. traditional chemotherapy. Despite the generally favourable safety profiles of ICIs, the advent of immune-related adverse events (irAEs) – notably in combined anti-programmed cell death protein 1/anti-cytotoxic T-lymphocyte associated protein 4 regimens – demands vigilant management. Recent investigations have scrutinized the impact of irAEs on prognosis, with a specific focus on the cutaneous district.[1,2] The comprehensive multi-institutional study led by Wan *et al.*, encompassing a robust cohort of >3000 patients, has highlighted a significantly elevated risk of cutaneous irAEs (cirAEs) in patients with melanoma and cSCC treated with ICIs.[1] Notably, this heightened risk translates into an adjusted survival benefit, unveiling a novel dimension of therapeutic outcomes. The study delves into the potential biologic mechanisms of this, exploring both vitiliginous and nonvitiliginous cirAEs. Regarding the former, it is suggested that the immune response targeting primary epitopes may extend to other distinct epitopes within the same tissue type, potentially enabling the elucidation of the antigenic overlap between neoplastic and normal melanocytes that leads to the destruction of normal melanocytes.[3] With regard to the latter, the authors propose a plausible explanation in the form of a tissue-homing process. Dendritic cells, recognizing tumour antigens in melanoma and cSCC, may migrate to secondary lymphoid organs, activating naïve T cells and transforming them into effector T cells. Subsequently, these activated T cells return to the skin – the tissue of origin – initiating a more widespread immune response. While these mechanisms warrant further scrutiny, their implications are intriguing and merit in-depth exploration. Recent evidence underscores a correlation between cancers with a high tumour mutational burden (TMB), such as melanoma, and an increased incidence of irAEs vs. low TMB cancers.[4] This observation may be explained by the varying neoantigenic load of different cancer types and the phenomenon of antigen spreading secondary to tumour cell death, activating lymphocytes against wild-type antigens in healthy tissues.

As cirAEs emerge as predominant adverse events in immunotherapies, clinicians should be aware that such trends may intensify with increasing drug utilization and the development of new drug combinations.[5] Despite mainly being managed on an outpatient basis, cirAEs have a substantial impact on patients' lives and pose an economic burden on hospitals.[6] Swift identification and management of cirAEs is vital, given their impact on patients' quality of life and the potential for treatment discontinuation. Hence, collaboration between oncologists and dermatologists is crucial, emphasizing the essential role of a multidisciplinary approach, particularly in settings lacking dedicated derma-to-oncologists.

The growing evidence highlights the need for an update of the Common Terminology Criteria for Adverse Events (CTCAE) grading system for skin reactions.[6] The current system, which relies mainly on surface area involvement, may potentially underestimate severe cutaneous toxicities and overestimate milder ones. The observed survival advantages could enhance the clinical identification of patients with favourable outcomes, positively impacting on patients struggling with visible cutaneous events, which often bear more emotional significance than laboratory-based alterations. In the evolving cancer care landscape, these discoveries emphasize the persistent need for better prognostic indicators in patients treated with ICIs.[7,8] The need for enhanced collaboration across specialisms, personalized approaches and accurate assessment of irAEs remains crucial.

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