

Letter to the Editor

Breaking barriers: The impact of targeted cancer treatments on skin health

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Dear Editor,

Targeted cancer therapies have revolutionised oncology by improving survival rates while reducing systemic toxicities compared to conventional chemotherapy. These therapies, designed to selectively inhibit molecular pathways crucial for tumour progression, include epidermal growth factor receptor inhibitors (EGFRIs), immune checkpoint inhibitors (ICIs) and B-Raf proto-oncogene, serine-threonine kinase/mitogen-activated protein kinase (BRAF/MEK) inhibitors. Despite their oncologic benefits, these agents frequently induce cutaneous adverse effects, significantly affecting patients' quality of life and treatment adherence.^[1,2]

The skin barrier, primarily maintained by the stratum corneum, serves as a critical defence against transepidermal water loss, microbial invasion and environmental insults. Disruptions to this barrier increase susceptibility to xerosis, pruritus, inflammatory eruptions and secondary infections, all of which are commonly observed in patients undergoing targeted therapies.^[3,4] Cutaneous toxicities may necessitate dose modifications or therapy discontinuation, highlighting the need for early recognition and effective management strategies. This manuscript critically examines the impact of targeted therapies on skin barrier function, elucidates underlying mechanisms of dermatologic toxicity and discusses evidence-based approaches for mitigation.

MECHANISMS OF SKIN BARRIER DYSFUNCTION IN TARGETED CANCER THERAPY

EGFRIs

EGFRIs such as erlotinib, gefitinib, cetuximab and panitumumab are integral in the management of non-small cell lung cancer, colorectal cancer and head-and-neck malignancies. Epidermal growth factor receptor (EGFR) signalling plays a fundamental role in keratinocyte proliferation, differentiation and epidermal homeostasis. Inhibition of this pathway disrupts epidermal renewal, leading to impaired wound healing, reduced sebum production and alterations in the stratum corneum composition. The hallmark dermatologic adverse event associated with EGFRIs is an acneiform eruption, typically presenting within the first 2–4 weeks of treatment. Unlike acne vulgaris, this papulopustular rash lacks comedones and is characterised by significant inflammation and compromised skin integrity.^[5,6]

In addition, EGFRIs have been associated with PRIDE syndrome - an acronym describing papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching and dryness due

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to EGFR inhibitors. PRIDE complex reflects a constellation of cutaneous toxicities that collectively underscore EGFR's role in epidermal maintenance and repair.^[7]

ICIs

ICIs, including programmed cell death-1 inhibitors (nivolumab and pembrolizumab) and cytotoxic T-lymphocyte-associated protein 4 inhibitors (ipilimumab), modulate immune responses to enhance antitumor activity. These agents are associated with immune-mediated dermatologic toxicities, including lichenoid dermatitis, psoriasis-like eruptions and severe eczema. The underlying mechanism involves immune system hyperactivation, resulting in increased inflammation and epidermal barrier dysfunction. Studies indicate that ICIs downregulate filaggrin expression, leading to defective stratum corneum integrity, increased permeability and heightened susceptibility to allergens and irritants.^[8,9]

BRAF and MEK inhibitors

BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib and cobimetinib) are widely used in melanoma patients harbouring BRAF mutations. These agents paradoxically activate the mitogen-activated protein kinase pathway in keratinocytes, leading to hyperkeratosis, keratosis pilaris and an increased risk of secondary cutaneous malignancies, particularly squamous cell carcinoma. In addition, BRAF and MEK inhibitors interfere with epidermal lipid metabolism, contributing to severe xerosis, fissuring and increased susceptibility to infections.^[10,11]

Clinical manifestations of skin barrier dysfunction

Targeted therapy-induced barrier dysfunction manifests clinically with a variety of dermatologic findings. Common presentations include xerosis, pruritus, acneiform and eczematous eruptions and increased infection susceptibility. The severity of these conditions often correlates with therapy duration and specific drug class. For instance, EGFRIs predominantly cause papulopustular rashes, whereas ICIs are more frequently linked with lichenoid and psoriasiform eruptions.

Grading of dermatologic toxicities: the common terminology criteria for adverse events (CTCAE) version 5.0 provides a standardised grading system for cutaneous toxicities. Skin rash, pruritus, xerosis and other adverse effects are graded on a scale from 1 (mild) to 5 (death related to toxicity), enabling clinicians to make informed decisions regarding treatment continuation, dose adjustment or discontinuation.^[12]

Management strategies for dermatologic toxicity

Optimising the management of dermatologic adverse effects is crucial for maintaining treatment adherence and patient comfort.

1. Hydration and barrier repair: The use of emollients enriched with ceramides, humectants (urea and glycerine) and occlusive agents is essential for restoring epidermal barrier function and preventing xerosis^[13]
2. Topical corticosteroids and immunomodulators: Low- to mid-potency corticosteroids effectively mitigate inflammation associated with rashes and eczematous dermatitis. Calcineurin inhibitors (tacrolimus and pimecrolimus) serve as alternative steroid-sparing agents
3. Oral antihistamines and anti-inflammatory agents: These pharmacologic interventions help alleviate pruritus and inflammatory manifestations of ICIs and EGFRIs^[14]
4. Prophylactic and therapeutic antibiotics: Tetracyclines, such as doxycycline and minocycline, are commonly employed to manage EGFRi-induced papulopustular rash and prevent secondary bacterial infections^[15]
5. Photoprotection: Patients on BRAF inhibitors must adhere to stringent sun protection measures to minimise photosensitivity reactions and secondary malignancies^[16]
6. Preventive strategies Proactive management includes pre-treatment counselling, initiation of emollients from day 1 of therapy, use of gentle cleansers and prompt intervention for early signs of toxicity. Education on skin hygiene and avoidance of irritants (e.g., alcohol-based products) enhances outcomes.^[17]

CONCLUSION

Targeted cancer therapies have transformed the oncologic landscape, yet their deleterious effects on skin barrier function pose significant clinical challenges. Dermatologic toxicities such as xerosis, inflammatory eruptions and secondary infections are common, often necessitating treatment modifications. Early dermatologic intervention, including barrier repair strategies, anti-inflammatory agents and prophylactic antibiotics, is critical for minimising these adverse effects and ensuring optimal patient outcomes. The use of standardised grading tools like CTCAE and a preventive approach further enhances the quality of care for affected patients. Further research is warranted to develop targeted dermatologic interventions that preserve skin integrity while maintaining the efficacy of cancer therapies.

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