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Review Article

Cutaneous adverse effects of targeted therapies

標靶治療的皮膚不良反應

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Novel antineoplastic therapy has evolved and shifted to molecularly targeted agents. They are designed to block specific cancer cell processes. However, many of these agents, particularly those interfering with signal transduction (e.g., epidermal growth factor receptor [EGFR] inhibitors, multitargeted tyrosine kinase inhibitors [TKIs]), frequently cause cutaneous adverse events. The dermatological adverse reactions not only affect cosmetically, but may also lead to poor treatment adherence, dose reduction or even discontinuation of treatment. In this article, we will describe key clinical features of common dermatological adverse reactions among the common targeted therapies, focusing mainly on skin toxicity, as well as to discuss the pathology and suggested treatments for these reactions.

新型抗腫瘤治療已發展並轉向分子標靶性藥物。它們旨在阻止特定的癌細胞過程。然而當中不少，特別是那些通過干擾訊息傳遞的藥物（例如表皮生長因子受體抑製劑、多重標靶性酪氨酸激酶抑製劑）經常會引起皮膚不良反應。皮膚不良反應不僅影響儀容，而且可能減低治療依從性、或需調低劑量甚至停止治療。本文中，我們將描述常見標靶治療中常見皮膚不良反應的關鍵臨床特徵，主要聚焦在皮膚毒性上，並討論這些反應的病理和建議的治療方法。

Keywords: Cutaneous adverse reaction, epidermal growth factor inhibitors, multi-targeted tyrosine kinase inhibitors, targeted therapy

關鍵詞：皮膚不良反應、表皮生長因子抑製劑、多重標靶性酪氨酸激酶抑製劑、標靶治療

Introduction

There has been a rapid emergence of targeted therapy in treating various malignancies over the last decade. They are designed to block specific cancer cell processes and the safety profile is better when compared to conventional chemotherapies. Although these agents are better tolerated, cutaneous adverse reactions are not uncommon because some target molecules also present in the skin e.g, epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR). The intensity and severity of the skin toxicities may lead to poor treatment compliance, dose reduction and even discontinuation of the targeted therapies.[1]

In the light of life-saving nature of the targeted therapy, it is important for dermatologists to

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recognise the common targeted therapy-induced skin toxicities and provide effective clinical management. To allow for uniform reporting and proper cataloging of side effects between specialists caring for cancer patients, a standardised grading system: Common Terminology Criteria for Adverse Events (CTCAE) has been adopted. The management is based on the disease severity and broadly divided into general, preemptive and reactive approach. In this article, we provide an overview of the most common skin toxicities related to the targeted therapy, including the clinical presentation and management strategies.

A. Epidermal growth factor receptor (EGFR) inhibitors

EGFR inhibitors are used in treating different types of malignancy e.g, colorectal, non-small cell lung and breast cancer. Since EGFRs are largely expressed in the epidermis and its appendages, they commonly cause skin toxicities including papulopustular eruption, xerosis and pruritus, hair and nail changes and mucositis (Table 1).[2,3]

Papulopustular rash

Papulopustular rash is also known as acneiform eruption. It presents as papules and pustules in a seborrheic distribution but lacks comedones and nodulocysts. It is the most common and earliest cutaneous adverse event, in over 75% of patients it occurs after 1-2 weeks initiation of EGFR inhibitor therapy. The EGFRs are abundantly expressed in the epidermis and its appendages. Unlike acne vulgaris which is characterised by androgen-activated sebaceous gland hypertrophy and increase sebum production, comedone development and immunological reactivity to colonisation by Propionibacterium acnes, the pathogenesis is believed to be the alteration in growth and differentiation of the epidermis leading to altered corneocyte terminal differentiation.[4]

Common Terminology Criteria for Adverse Events grading depends on the body surface area (BSA) and the influence over the activities of daily living (ADL)(Table 2). Since the degree of the skin toxicity positively correlate with the treatment response, it is important to educate the patient about the potential of cutaneous adverse events. Although supporting clinical evidence is lacking, sunscreens are recommended as flare up induced by sun exposure has been reported.[5] Hot water baths should be avoided and moisturising cream and gentle cleansers are advised.

For Grade 1 eruption, low potency topical steroid with or without topical antibiotics are recommended. As the underlying pathphysiology is different, traditional acne treatment may not be useful and can be irritative. For Grade 2 and 3 eruptions, oral antibiotics such as doxycycline 100 mg, tetracycline 500 mg and minocycline 100 mg can be added.[6]

Xerosis and pruritus

Xerosis and pruritus are dose-dependent and appear 4-12 weeks after treatment (Table 3). Over 35% of patients receiving EGFR inhibitors report progressive skin dryness, which later may evolve into fissure and eczema. Superimposed secondary

Table 1. Summary of cutaneous reactions associated with epidermal growth factor receptor inhibitors

Drugs	Reported cutaneous effects
Cetuximab	Papulopustular (acneiform) rash
Panitumumab	Abnormal scalp, facial hair, and / or eyelash growth
Necitumumab	
Erlotinib	Paronychia with / without pyogenic granuloma
Gefitinib	
Lapatinib	Telangiectasias
Afatinib	Xerosis
Osimertinib	Pruritus
	Purpuric xerotic dermatitis
	Alopecia
	Hand-foot-skin reaction

infection with *Staphylococcus aureus* or herpes simplex has been reported.[7] Frequent moisturising with emollients can help to improve xerosis. Oral anit-histamines can be used to relieve pruritus.

Hair alterations

Changes in hair quality, texture and growth pattern are associated with the use of EGFR inhibitor after 8-12 weeks of treatment. Alopecia can occur over scalp and body and the severity is usually mild (Table 4). However, both scarring and non-scarring inflammatory scalp alopecia have been described.[8,9] Hypertrichosis and trichomegaly have also been reported.[10] When such changes occur over the eyelashes, it can cause inward curling of the lash hairs resulting in keratitis.[11]

For scalp hair, frequent brushing may help loosening kinkiness, making it easier to style and less brittle. Inflammatory alopecia may require early treatment with high potency topical steroids. For eyelash curling, trimming the eyelashes may be needed to prevent keratitis and referral to the opthalmologist for further treatment.[7]

Table 2. The National Cancer Institute Common Terminology Criteria for Adverse Events (NI CTCAE) acneiform rash

	1	2	3	4	5
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.	Papules and/or pustules covering 10-30% BSA, associated with psychosocial impact; limitation of instrumental ADL.	Papules and/or pustules covering >30% BSA; limiting self-care ADL; associated with local superinfection requiring oral antibiotics.	Papules and/or pustules covering any % BSA, associated with extensive superinfection requiring IV antibiotics. Life-threatening consequences.	Death

BSA=body surface area; ADL=activities of daily living; IV=Intravenous

Table 3. NI CTACE dry skin

	1	2	3
Xerosis	Covering <10% BSA and no associated erythema or pruritus.	Covering 10-30% BSA and associated with erythema or pruritus; limiting instrumental ADL.	Covering >30% BSA and associated with pruritus; limiting self-care ADL.

BSA=body surface area; ADL=activities of daily living

Table 4. NI CTACE alopecia

	1	2
Alopecia	Hair loss of <50%, not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but wig or hair piece not required.	Hair loss of >/=50%, readily apparent to others; a wig or hair piece as required by the patient. Associated with psychosocial impact.

Mucositis

Mucosal complications are reported in the use of EGFR inhibitor and multikinase inhibitors.[12] Oral mucosa is the most common site of involvement, presenting with xerostomia, mucositis, stomatitis and aphthous ulcers. Genital involvement is less common and may present with balanitis, vulvovangitis and genital erosion.

Mucositis is usually mild and resolves without specific treatment. Aphthous ulcers are treated with topical steroids or antiseptic washes and lubricants can relieve the discomfort caused by mucosal dryness.[13]

Nail changes

Nail abnormalities are common and can cause significant debilitation. Depending on the nail units affected, it can present with onycholysis, subungual haemorrhage (nail bed), dyspigmentation, brittle nails (nail plate) and paronychia (nail fold). Nailfold inflammation can affect all fingernails and toenails, particularly the great toes. The inflammation may evolve from erythema, oedema and tenderness of the nail fold initially, eventually progressing to pyogenic granuloma-like lesions. Superimposed bacterial or fungi infection may occur (Table 5).[14,15]

Advice for avoiding trauma and ill-fitting shoes should be given. Topical treatments include antiseptic soaks and wet dressings to the affected nails. Topical corticosteroid or intralesional triamcinolone can be used if there is nailfold inflammation. Oral doxycycline 100 mg daily or twice daily for 6 months may help to reduce peri-ungual inflammation. While paronychia is sterile at the beginning, if there is increased purulence and pain, septic work-up is needed and systemic antibiotics / anti-fungal treatment may be considered. Other medical interventions such as silver nitrate, electrocautery and nail avulsion can be used to remove excessive granulation tissue (Table 6).[16-18]

B. Multikinase inhibitors

Multi-targeted kinase inhibitors are generated from the bcr-abl fusion protein, c-Kit and platelet-derived growth factor receptors (PDGFRs). They affect many tyrosine kinase systems and hence result in a variety of dermatological adverse effects (Table 7).

Table 5. NI CTACE mucositis

	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated.	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated.	Severe pain; interfering with oral intake.	Life-threatening consequences; urgent intervention indicated.	Death

Table 6. NI CTACE paronychia

	1	2	3
Paronychia	Nail fold oedema or erythema; disruption of the cuticle.	Nail fold oedema or erythema with pain; associated with discharge or nail plate separation.	Surgical intervention or IV antibiotics indicated;
		Localised or oral intervention indicated; limiting instrumental ADL	Limiting self care ADL.

IV=Intravenous; ADL=activities of daily living

Hand-foot skin reaction (HFSR)

Hand-foot Skin Reaction often occurs during the early weeks e.g. 2-6 weeks after starting multikinase inhibitors targeting VEGFR. They are frequently reported with the use of sorafenib, sunitinib and pazopanib. It initially presents with hyperkeratotic plaques, causing pain and sometimes blistering. Pressure points e.g. balls of the feet are the most common sites of involvement (Table 8). The pathophysiology of HFSR is not fully understood.[19] The most relevant histopathological finding is keratinocyte damage, which presents as keratinocyte vacuolar degeneration and confluent keratinocyte necrosis leading to intra-epidermal cleavage.[20]

Patients should be informed of the dose-dependent reaction of HFSR and preventative treatment can be started as early as the initiation of the target therapy. Any pre-existing hyperkeratotic plaques should be referred to podiatrist and insole / flexible shoes are advised. Ten percent urea cream is prescribed at the start of treatment for a moisturising and keratolytic effect.

Table 7. Summary of cutaneous reactions associated with multikinase inhibitors

Drugs	Reported cutaneous effects
Imatinib	Hand-foot skin reaction
Dasatinib	Inflammatory, appendageal and
Nilotinib	neoplastic skin toxicities overlap with
Bosutinib	other drug categories
Ponatinib	

The treatment of HFSR depends on the severity: Grade 1: emollients and topical corticosteroids; Grade 2: potent topical corticosteroids, target therapy dose may be reduced to 50%; Grade 3: Analgesics such as non-steroidal anti-inflammatory drugs or narcotics can be used for pain control, target therapy should be interrupted for at least one week until recovery to grade 0 or 1.[21,23]

Inflammatory eruption

Various skin eruptions have been described. Dasatinib may cause localised and generalised erythema, papular eruptions. Severe cutaneous adverse reactions like acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) have been associated with imatinib therapy.[22]

Others

Development of genital eruption with involvement of the inguinal area can occur with multikinase inhibtors. Oedema due to target therapy is usually superficial but occasionally may cause central fluid retention. Pigmentary changes including localised or diffuse hypopigmentation and depigmentation are caused by inhibition of C-kit which regulates melanocytes development. Hyperpigmentation has been reported far less frequently, and is due to the deposition of drug metabolites containing melanin and iron, similar to minocycline and anti-malarial drugs.[23]

Table 8. NI CTACE Palmar-plantar erythrodysaesthesia syndrome

	1	2	3
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis without pain. (e.g. erythema, oedema, or hyperkeratosis)	Skin changes (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting instrumental ADL.	Severe skin changes (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting self-care ADL.

ADL=activities of daily living

Conclusion

With the increasing use of targeted therapies, cutaneous adverse effects will be expected to occur more often. Although several reports and recommendations have been published, standard evidence-based therapies are still lacking. As a dermatologist, it is important to recognise the dermatological complications and provide appropriate treatments. Otherwise, the skin toxicities may lead to poor oncological treatment adherence, dose interruption and discontinuation of targeted therapies.

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