

SKIN REACTIONS SECONDARY TO ANTICANCER AGENTS

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ABSTRACT

In recent decades, new chemotherapeutic agents have been introduced in cancer therapy. The skin is often the target for the toxicity of these drugs. Skin side-effects may decrease the compliance and the quality of life of these patients. To cure and to prevent these side-effects dermatologists can cooperate with oncologists. In this paper we propose a brief review of the main toxic skin events caused by chemotherapeutic agents, in particular linked to the epidermal growth factor receptor (EGF-R) inhibitor.

Keywords: Skin reaction, chemotherapy, EGF-R inhibitors, radiodermatitis.

INTRODUCTION

New Antineoplastic Agents and Skin Toxicities

In recent decades, new chemotherapeutic agents have been introduced for cancer treatments, with various different side-effects: in particular the use of molecular target therapy has shown evidence of significant skin side-effects.¹ New drugs and new therapeutic schedules have brought many malignancies to a better prognosis and a longer survival. But sometimes many side-effects occur, reducing the compliance of the patients and decreasing their quality of life.^{2,3} Sometimes it is necessary to interrupt the therapy. The aim of the dermatological research is to identify the correct prevention and therapy of these skin reactions. Common skin reactions undergoing chemotherapy include alopecia, papulopustular rash, hand-foot syndrome, paronychia and mucositis.⁴ Alopecia and mucositis are very well-known side-effects of chemotherapy. No data will be presented in this review. Additional information on papulopustular follicular

rash, hand-foot syndrome and paronychia are described below.

EGFR INHIBITORS AND THE PAPULOPUSTULAR FOLLICULAR RASH

Among the innovative therapeutic strategies in chemotherapy, the epidermal growth factor receptor (EGFR) inhibitors (cetuximab, panitumumab, erlotinib, gefitinib) approved for lung and colon-rectum tumours showed an increasing skin toxicity, causing widespread skin dryness (in >90% of patients) and a papulopustular follicular rash which can be complicated by pruritus, pain and infections.^{3,5} The papulopustular follicular rash, very often involves the seborrhoeic areas, scalp and chest, and less frequently, the extremities and the back, with papule and pustules. For these reasons it is also defined as an acneiform rash but the pathogenesis and histology is completely different from acne.⁶ Its peculiar characteristic is the association of a typical sebaceous gland disease with a marked xerosis, suggesting

the keratinocyte itself is involved in the pathogenesis.¹ EGFR is expressed in epidermal keratinocytes, in hair follicle epithelium and in the sweat glands. Its activation plays a crucial role in keratinocyte proliferation and differentiation.⁷ Its inhibition induces growth arrest and apoptosis, decreasing cell migration, increasing cell attachment and differentiation, and stimulating inflammation.⁸

Although the rash has been defined as 'acneiform,' distinctions should be done. The EGFRi (EGFR-inhibitor)-induced papulopustular eruption does not present comedones. In acne, the primary process is sebaceous hyperplasia and lipid release into the follicular lumen; it leads to comedo formation and overgrowth of *Propionibacterium acnes* that result in follicular

wall rupture, stimulating neutrophil chemotaxis and pustule formation. On the other hand, in EGFRi rash the primary event is the damage of sebaceous glands and follicular epithelium, which leads to alteration in keratinocytes growth and differentiation. This causes the release of cytokines and the infiltration of mononuclear leucocytes ('sterile folliculitis').⁹ The severity of the papulopustular rash is dose-dependent and correlates with an improved tumour response and survival.⁸ The incidence of papulopustular rash varies from 12-35%^{8,10} and it often represents one of the cutaneous aspects persistently influencing the patient's quality of life. Gutzmer et al.¹¹ described cutaneous adverse reaction by targeted therapies (Table 1) and the classification of severity cutaneous adverse events during therapy with various EGFRi (Table 1 and 2).

Table 1. Cutaneous adverse events by targeted therapies.

Target structure (reference)	Main indications	Substances	Cutaneous adverse events	Frequency
EGFR inhibitors	Carcinomas of lung, pancreas, gastrointestinal tract, breast; squamous cell carcinomas of the head and neck	Erlotinib, gefitinib, lapatinib, cetuximab, panitumumab	Papulopustular rash, perifollicular xanthoma, xerosis cutis/prunitus, eczema craquele, fissures/rhagades, paronychia, hypertrichosis, hair follicle abnormalities	++ +/- ++ + ++ ++ + +
Multikinase inhibitors	Renal cell carcinoma, hepatocellular carcinoma	Sorafenib, sunitinib, pazopanib	Maculo-papular rash, hand-foot syndrome, hair discoloration, skin discoloration, xerosis cutis/prunitus, facial erythema, alopecia, epithelial skin tumours, subungual splinter haemorrhages	++ ++/pazopanib + ++/sorafenib - ++ (only sunitinib) + + + + (only sorafenib) +
BCR/ABL O-kit	Certain leukaemia entities, gastrointestinal stomal tumour	Imatinib, nilotinib, dasatinib	Maculo-papular rash, periorbital oedema, xerosis cutis/prunitus, light sensitivity, alopecia, pigmentation disorders, pustules/folliculitis	++ ++ (only imatinib) + + + + +/-
Mutated BRAF	In clinical trials, with focus on melanoma	Vemurafenib (PLX4032, RG7204, RO5185426), GSK2118436	Maculo-papular rash, light sensitivity, epithelial skin tumours, alopecia, hand-foot syndrome	++ ++(only vemurafenib) ++ + +
MEK	In clinical trials, with focus on melanoma	Selumetinib (AZD6244) GSK1120212 CI-1040 (PD184352)	Papulopustular rash, xerosis/prunitus, paronychia, fissures/rhagades	++ + + +

(++ very frequent [≥10%], + frequent [≥1%], +/- occasionally [≥0.1%], - seldom/never [<0.1%])

Adapted from Gutzmer et al.¹¹

Table 2. Classification of severity of cutaneous adverse events (as defined by the National Cancer Institute Common Toxicity Criteria, version 4.03).

	Papulopustular (acneiform) rash	Maculo-papular rash	Hand-foot syndrome
Grade 1	<10% body-surface area, with or without symptoms of pruritus or tenderness	<10% body-surface area, with or without symptoms (e.g. pruritus, tightness, or burning)	Minimal skin changes (e.g., erythema, oedema, or hyperkeratosis) without pain
Grade 2	10-30% body-surface area, with or without symptoms of pruritus or tenderness; with psychosocial impact; limiting instrumental activities of daily living	10-30% body-surface area, with or without symptoms (e.g. pruritus, tightness, or burning), limiting instrumental activities of daily living	Skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting practical activities
Grade 3	>30% body-surface area, with or without symptoms of pruritus or tenderness; limiting self-care activities of daily living; associated with local superinfection with oral antibiotics indicated	>30% body-surface area, with or without associated symptoms; limiting self-care activities of daily living	Severe skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting self-care activities
Grade 4	Covering any percent of the body-surface area; with or without symptoms of pruritus or tenderness; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences		
Grade 5	Death		

Adapted from Gutzmer et al.¹¹

Recently, Curry et al.¹² divided skin reactions into two groups: cutaneous inflammations and cutaneous epithelial proliferations, but the classification of Gutzmer fits the aim of the investigation better. EGFRi (such as cetuximab) and MEK inhibitors (such as selumetinib and trametinib) showed papulopustular rash with a suppurative folliculitis in 83%, 93%, and 80% of the patients on therapy, respectively.¹²

HAND-FOOT SYNDROME AND MULTIKINASE INHIBITORS

Hand-foot syndrome (HFSR) is one of the most common skin reactions, occurring in 30-60% of patients in therapy with EGFRi erlotinib and tyrosine kinase inhibitor sorafenib.¹²⁻¹⁴ The HFSR often requires cessation or reduction of the dose of sorafenib therapy. Although the specific mechanisms underlying the sorafenib-induced HFSR are unknown, vascular endothelial growth factor receptor (VEGFR) was reported to be

primarily responsible for this side-effect.¹³⁻¹⁷ Sunitinib, like sorafenib, is a multikinase inhibitor used for kidney and liver cancers: it is associated with bullous manifestation and HFSR, which can also be used as a marker of drug efficacy;¹⁸ inflammatory actinic keratosis has also been observed with these two drugs.^{18,19} Other multikinase inhibitors in addition to HFSR also induce skin changes, such as facial erythema and subungual splinter haemorrhages.²⁰ RAF inhibitors such as vemurafenib were also associated with a variety of cutaneous epithelial proliferations (keratosis pilaris, seborrheic keratosis, verruca vulgaris, actinic keratosis, keratoacanthoma, and squamous cell carcinoma).¹²

BRAF inhibitors can lead to the development of rashes and cutaneous keratinocytic neoplasms, for which patients should be closely monitored. Finally, MEK/ERK inhibitors induce similar skin toxicities to EGFRi, such as papulopustular rashes, skin xerosis and paronychia.¹⁹⁻²¹ Multikinase inhibitors used in haematology, such as imatinib,

dasatinib and nilotinib, frequently cause skin toxicity, such as exfoliative dermatitis, associated with fever¹⁸ and frequently with oedema. The phosphoinositide 3-kinase (PI3K)/serine-threonine protein kinase Akt pathway is a vital transduction cascade that is connected with many essential cellular activities, such as growth and survival. PI3K inhibitor BKM120 and AKT inhibitor MK2206, used in patients with ovarian cancer, produced maculopapular eruptions.¹²

NAIL DAMAGE AND EGFR

Paronychia and periungual pyogenic granuloma-like lesions are observed in 10-30% of patients receiving EGFR therapy, developing after 2 or more months of drug exposure. Paronychia is characterised by oedematous inflammation of the nail folds and usually affects the first digits. Periungual pyogenic granuloma-like lesions are characterised by easily bleeding, friable vascular tissue overgrowth on lateral nail folds.²² The pathogenesis of paronychia is due to the traumatic conflict between the thin tissues around the nail and the nail itself. In fact, changes in growth and differentiation of the nail are responsible for the retention of squama in the nail folds, which act as foreign bodies, causing an inflammatory reaction.²³

RADIATION THERAPY AND SKIN REACTION

Up to 60% of patients with cancer receive radiotherapy treatment. One of the main side-effects of this treatment is an acute skin reaction, which may range in severity from a mild erythema to very severe radiodermatitis. Different treatments are proposed.²⁴⁻²⁸ Skin radiotherapy (RT) reactions can be divided into acute and chronic. Radiation-induced acute skin reactions are traditionally assessed using the Radiation Therapy Oncology Group (RTOG) toxicity criteria.²⁴⁻³¹ To treat severe acute radiation skin reactions (ARSR) such as radiodermatitis, the data show that, among the topical products analysed, calendula, corticosteroids, topical sodium hyaluronate, urea, and allantoin have shown significant protective effects.²⁵ In the expert opinion from the Cancer Care Ontario's Supportive Care Guidelines Group (SCGG) the use of a plain, non-scented, lanolin-free hydrophilic cream may be helpful in preventing radiation skin reactions. In addition, a low dose (i.e. 1%) corticosteroid

cream may be beneficial in the reduction of itching and irritation.³² To reduce the risk of severe acute radiation skin reaction some authors suggest that it can be useful to stop smoking during RT because smoking is an independent risk factor for ARSR.²⁴

Among the skin reactions it can be useful to signal the Erythema Multiforme associated with Phenytoin and Cranial radiation Therapy (EMPACT) syndrome. Phenytoin is commonly used as an antiepileptic medication for seizure prophylaxis in patients with brain metastases;³³ it can, rarely, cause side-effects when associated with radiotherapy. The EMPACT syndrome is characterised by erythematous macular eruption on the scalp within the radiation field in patients under phenytoin therapy; that usually dramatically extends after a few days to involve extensive areas of the face, trunk and extremities. Significant mucocutaneous blistering and desquamation with conjunctival suffusion can also develop.³³ The pathogenesis of the EMPACT syndrome is still unclear. Studies in mice have shown that brain radiation can induce the increase of TNF- α , TNF- β , ICAM-1, and cytokines that could induce cellular autoimmunity. Moreover, radiation can alter the metabolism of phenytoin and anticonvulsant drugs. Normally, phenytoin and other anticonvulsants induce microsomal cytochrome P450 3A (CYP3A) and produce oxidative intermediates that are later detoxified by epoxide hydrolase. In the case of therapy with phenytoin/phenobarbital and radiation therapy, a deficiency of this enzyme can develop. Oxidative intermediates, which cannot be metabolised, have direct toxicity for cells, and/or they can bind cell macromolecules and behave as haptens. These mechanisms can stimulate a new immune response and be responsible for skin manifestations. Fabbrocini et al.³³ described two interesting cases of EMPACT syndrome, caused by the combination of phenobarbital and cranial radiotherapy.

CONCLUSIONS

In these last years, new cancer therapies have led to the increase of anticancer therapy success, but several skin reactions have emerged. These negatively impact on the quality of life of these patients. The dermatologist plays a critical role in the management of these adverse effects. A strong relationship between dermatologists and oncologists is important to make the best

decisions for patients and to choose anti-toxicity interventions with minimal side-effects. During and after radiation therapy it is particularly necessary to have a close follow-up in order to identify and monitor precancerous lesions occurring in these patients.

Take-Home Messages:

- New chemotherapeutic agents increase survival, but can lead to several skin reactions, worsening the quality of life of patients.
- The EGFR (such as cetuximab, panitumumab, erlotinib, and gefitinib) showed increasing skin toxicity, causing widespread skin dryness and the papulopustular follicular rash.

- HFSR occurred in 30-60% of patients in therapy with EGFRs erlotinib and sorafenib.

- Paronychia and periungual pyogenic granuloma-like lesions could be observed in patients receiving EGFR therapy.

- It is necessary to pay attention to cranial radiation therapy and neuroleptic drugs such as phenobarbital and phenytoin that can cause skin reaction such as EMPACT syndrome.

- Hydration, antimicrobial, sterile tissue, protective ointment, and specific dermocosmetological treatments can reduce the side-effects of chemo and radiotherapy.

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