DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

Cutaneous side effects of molecularly targeted therapies for the treatment of solid tumors

Daniel I G Cubero[1] MD, PhD, Beatrice Martinez Zugaib Abdalla[2] MD, Jean Schoueri[3], Fabio Iazetti Lopes[3], Karine Corcione Turke[2], Jose Guzman[2] MD, Auro Del Giglio[1] MD, PhD, Carlos D'Apparecida Santos Machado Filho[2] MD, PhD, Vanessa Salzano[2] MD, Dolores Gonzalez Fabra[2] MD

[1]Department of Oncology and Hematology, ABC Foundation School of Medicine, Av Principe de Gales, 821, Santo André/SP – Brazil, ZIP 09060-650; [2]Department of Dermatology, ABC Foundation School of Medicine, Av Principe de Gales, 821, Santo André/SP – Brazil, ZIP 09060-650; [3]ABC Foundation School of Medicine, Av Principe de Gales, 821, Santo André/SP – Brazil, ZIP 09060-650

Abstract

Background: Currently, molecularly targeted drugs are part of the therapeutic arsenal for the treatment of many neoplasms and are responsible for improvements in the quality of life and survival of patients. Although they act on proteins and components within biochemical pathways that are expressed to a greater extent in neoplastic cells, these drugs can also interfere with the activity of normal cells.

Scope: This article reviews the cutaneous side effects of main molecularly targeted cancer therapies for solid tumors.

Findings: The use of these drugs causes side effects, and the skin is one of the most commonly affected organs. In this literature review, we discuss the adverse cutaneous effects caused by molecularly targeted drugs.

Conclusion: The identification of these reactions is important to both dermatologists and oncologists so that they properly diagnose the reaction and administer adequate treatment, which would allow greater adherence to the oncological treatment and improve patients' quality of life.

Keywords: adverse reactions, chemotherapy, dermatology, drug-related side effects, immunotherapy, oncology, skin, targeted therapy.

Citation

Cubero DIG, Abdalla BMZ, Schoueri J, Lopes FI, Turke KC, Guzman J, Del Giglio A, Machado Filho CDS, Salzano V, Fabra DG. Cutaneous side effects of molecularly targeted therapies for the treatment of solid tumors. Drugs in Context 2018; 7: 212516. DOI: 10.7573/dic.212516

Introduction

Currently, molecularly targeted drugs are part of the therapeutic arsenal for the treatment of many neoplasms and are responsible for improvements in the quality of life and survival of patients. Unlike traditional chemotherapeutic agents, which generally act on dividing cells, molecularly targeted drugs are being developed to function predominantly in neoplastic cells. These drugs interfere with biochemical proteins or components of pathways that are overexpressed or overactivated in neoplastic cells.

However, such molecular targets are not unique to neoplastic cells. Since they originate from normal cells, neoplastic cells share many of the biochemical proteins and pathways with normal tissues.

In particular, cell-proliferation-related pathways, which are the target of many of these drugs, are activated in tissues with high turnover rate such as the skin. For this reason, we commonly observe adverse cutaneous effects related to molecularly targeted therapies. Such adverse reactions may make continuity of treatment impossible, or they may interfere greatly in the quality of life of patients.[1–3]

This article aims to review the literature on the main adverse cutaneous effects related to this group of drugs and the recommendations for their management.

Methods

This is a nonsystematic literature review (integrative review) on articles available on PubMed/Medline regarding the main adverse cutaneous effects linked to the use of molecularly targeted drugs. Relevant research papers from the last 20 years have been included to elucidate the progress such drugs have been through.

Classification of molecularly targeted drugs

Antineoplastic molecularly targeted drugs can be classified into small or large molecules based on their molecular weight.

Small molecules act inside cells by inhibiting specific biochemical pathways. The main representatives of this group are tyrosine-kinase inhibitors (TK inhibitors). These drugs act on a diversified group of enzymes located in the intracellular environment, just below the transmembrane receptors. When these receptors are inhibited, the signaling cascade between the membrane receptor and the cell nucleus is disrupted. Thus, even if the membrane receptor is activated, it will not send the corresponding signal.

Other important drugs that belong to the small molecule group are the inhibitors of the BRAF protein (BRAF inhibitors), inhibitors of the mitogen-activated protein kinase enzymes (MEK [MAPK/ERK] inhibitors), and inhibitors of the mechanistic target of rapamycin (mTOR inhibitors). Each will inhibit a specific biochemical pathway that belongs to a particular signaling cascade, that is, a specific part of the pathway located between the membrane receptor and the cell nucleus.

Large molecules, especially those represented by monoclonal antibodies, act on circulating proteins (ligands) or proteins present on the surface of cells (transmembrane receptors) within the extracellular environment. In most cases, the proteins that constitute therapeutic targets are overexpressed or overactivated on the surface of neoplastic cells and exhibit a growth receptor function (e.g. epidermal growth factor receptor [EGFR] or human epidermal growth factor receptor [HER]).

Recently, a new class of 'immune checkpoint inhibitor' drugs has been approved for the treatment of certain neoplasms. Although they are monoclonal antibodies, they exhibit their function in a manner different from the other members of this group. They do not act by direct cytotoxic action on neoplastic cells, but rather, they bind to proteins that are associated with the process of immune response modulation; these proteins are present on the surface of T lymphocytes or on neoplastic cells. In this way, they reduce the threshold of activation of the individual's own immune system in order to activate it against the neoplasm. As a result, these drugs are often responsible for the onset of autoimmune diseases, including those of the skin.[4]

Table 1 lists the main molecularly targeted drugs used in the treatment of solid tumors.

Table 1. Main molecularly targeted drugs used in solid tumors.[1–4]

Drugs	Molecular target pathway	Class	Commercial name	Disease
Erlotinib	EGFR	TK inhibitor	Tarceva®	NSCLC
Gefitinib	EGFR	TK inhibitor	Iressa®	NSCLC
Afatinib	EGFR	TK inhibitor	Gilotrif®	NSCLC
Osimertinib	EGFR	TK inhibitor	Tagrisso®	NSCLC
Cetuximab	EGFR	Monoclonal antibody	Erbitux®	Colorectal cancer; head and neck cancer; NSCLC
Panitumumab	EGFR	Monoclonal antibody	Vectibix®	Colorectal cancer
Vemurafenib	BRAF	BRAF kinase inhibitor	Zelboraf®	Melanoma; NSCLC
Dabrafenib	BRAF	BRAF kinase inhibitor	Tafinlar®	Melanoma; NSCLC
Cobimetinib	MEK	MEK inhibitor	Cotellic®	Melanoma
Trametinib	MEK	MEK inhibitor	Mekinist®	Melanoma; NSCLC
Everolimus	mTOR	mTOR kinase inhibitor	Afinitor®	Renal cell cancer
Temsirolimus	mTOR	mTOR kinase inhibitor	Torisel®	Renal cell cancer
Lapatinib	HER-2	TK inhibitor	Tykerb®	Breast cancer
Trastuzumab	HER-2	Monoclonal antibody	Herceptin®	Breast cancer; gastric cancer
Pertuzumab,	HER-2	Monoclonal antibody	Perjeta®	Breast cancer
Ado-trastuzumab emtansine	HER-2	Antibody drug conjugate	Kadcyla®	Breast cancer
Sunitinib	VEGF	TK inhibitor	Sutent®	Renal cell cancer; GIST
Sorafenib	VEGF	TK inhibitor	Nexavar®	Renal cell cancer; hepatocellular cancer; thyroid cancer
Pazopanib	VEGF	TK inhibitor	Votrient®	Renal cell cancer; soft tissue sarcoma
Axitinib	VEGF	TK inhibitor	Inlyta®	Renal cell cancer; thyroid cancer

Table 1. (*Continued*)

Drugs	Molecular target pathway	Class	Commercial name	Disease
Cabozantinib	VEGF	TK inhibitor	Cabometyx® Cometriq®	Renal cell cancer; medullary thyroid cancer
Lenvatinib	VEGF	TK inhibitor	Lenvima®	Renal cell cancer; thyroid cancer; hepatocellular carcinoma
Bevacizumab	VEGF	Monoclonal antibody	Avastin®	Colorectal cancer; renal cell cancer; breast cancer, NSCLC
Ipilimumab	Immune checkpoint inhibitor (target CTLA-4)	Monoclonal antibody	Yervoy®	Melanoma
Nivolumab	Immune checkpoint inhibitor (target PD-1)	Monoclonal antibody	Opdivo®	Melanoma; NSCLC; head and neck cancer; colorectal cancer with mismatch repair deficiency; hepatocellular carcinoma; renal cell cancer; urothelial carcinoma
Pembrolizumab	Immune checkpoint inhibitor (target PD-1)	Monoclonal antibody	Keytruda®	Melanoma; NSCLC; head and neck cancer; microsatellite instability-high cancer; gastric cancer
Atezolizumab	Immune checkpoint inhibitor (target PD-L1)	Monoclonal antibody	Tecentriq®	NSCLC; urothelial carcinoma

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GIST, gastrointestinal stromal tumor; HER-2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; NSCLC, nonsmall cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TK inhibitor, tyrosine-kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFr, vascular endothelial growth factor receptor.

Cutaneous side effects

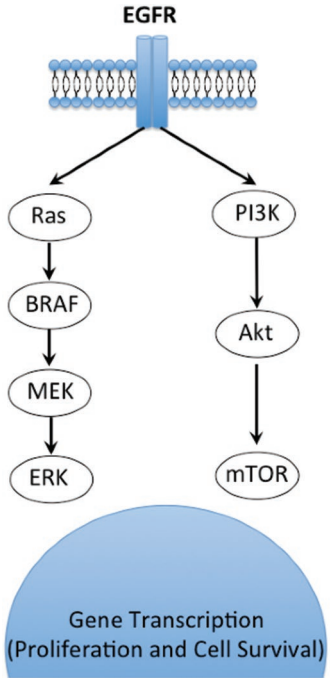
The skin is one of the organs that is most commonly affected by molecularly targeted drugs. This is because the skin is in a constant state of cell proliferation/renewal, and therefore, certain proliferation pathways are always activated.

One such pathway is the EGFR pathway, which is a cascade reaction of biochemical pathways that begins at the transmembrane receptor called EGFR and relays to the cell nucleus. Its activation is directly related to the transcription of proteins related to cell proliferation.

Under normal conditions, as in cutaneous tissue, this activation occurs in an orderly and controlled manner. In neoplastic tissues, however, the overactivation of this pathway due to changes in its components (mutations in genes responsible for EGFR, BRAF, or MEK proteins) leads to unbridled proliferation.

Drugs that inhibit such components will have an antineoplastic effect but will also invariably affect the normal function of cutaneous tissue. The fact that these proteins are largely parts of the same signaling pathway explains why these drugs share side effects that involve the skin[4–6] (Figure 1).

Figure 1. EGFR pathway diagram.



EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase.

EGFR/HER inhibitors

EGFR belongs to the HER family. EGFR inhibitors block the proliferation, migration, and angiogenesis of tumor cells.

This receptor is expressed in 30–100% of solid tumors. Cutaneous reactions are common because EGFRs are expressed in basal keratinocytes, sebocytes and endothelial cells. The common reactions can be summarized as follows: papulopustular eruption, paronychia, capillary alterations, pruritus, and xerosis.[5,6]

Three examples of drugs that belong to this category are cetuximab, erlotinib, and panitumumab. EGFR inhibitors inhibit their target receptor in normal basal keratinocytes, interfere with cell renewal in the epidermis, and disturb sebaceous and sweat glands.[7] By perturbing normal epidermal physiology, EGFR inhibitors create alterations in the skin barrier, which may lead to xerosis and follicular plugin as well as nail dystrophy and cutaneous acneiform reaction.[8]

EGFR inhibitors also induce abnormal keratinocyte differentiation with a thinner stratum corneum, decreased loricrin, and a reduced ability to retain moisture.[9]

Papulopustular eruption

Papulopustular eruption is clinically similar to acne but does not have comedones. This condition occurs due to neutrophil folliculitis,[10] but secondary infection by *Staphylococcus aureus* may also occur. Secondary infection should be suspected when the appearance of a honey-colored crust, a papulopustular condition outside the classical pattern, is observed.[11,12]

Approximately 90% of patients who use EGFR inhibitors experience early papulopustular eruption, which may be accompanied by symptoms such as pruritus or pain that, depending on the degree, may have an impact on daily activities and quality of life.[13]

This condition primarily affects the face, scalp, and upper part of the thorax (seborrheic areas). The associated rash is aggravated by sun exposure. Moreover, this condition tends to decrease up to the eighth week (with improvement without drug withdrawal), but recurrence periods during treatment are not uncommon.[13,14]

The development of the rash is dose-dependent, and its severity is positively correlated with treatment response.[15,16] Eruption may serve as a marker of efficacy, but clinical management is essential to ensure adherence to treatment and to allow an antineoplastic response.[17] The reaction is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute version 4.0[18] (Table 2). The current concept for the therapeutic approach of these patients includes, in addition to the treatment of the reactions, the use of strategies for a prophylactic approach from the beginning of the treatment.[17]

Table 2. Grade of acneiform lesions according to the CTCAE of the National Cancer Institute and their corresponding treatment.[13]

Degree	Affected area	Management
1	<10% of the body area, with complaints of discomfort and mild pruritus in the lesions	Topical drugs such as erythromycin, clindamycin, metronidazole, topical creams, and corticosteroids Patients are advised to camouflage the lesions with appropriate nonocclusive makeup and sunscreen
2	10–30% of the body area, with psychosocial impact and impact on daily activities	Cyclins are indicated due to their anti-inflammatory action Tetracyclines, 100–200 mg/day, oxytetracyclines, 500–1000 mg/day, doxycycline, 100–200 mg/day, and lymecycline, 150–300 mg/day, are used as first-line therapies Treatment is usually given during the first 4–8 weeks In some patients, however, a maintenance dose of 50–100 mg/day should be continued in the long term
3	>30% of the body area, with a psychosocial impact and impact on daily activities and/or associated local superinfection	Change of dose and/or anti-EGFR interval Treat with tetracycline or derivatives, associated systemic corticosteroid (prednisone 0.5 mg/kg/day) for 3–5 days and antihistamines (hydroxyzine 25 mg PO up to 6/6 h) if itching occurs
4	Any body area with extensive superinfection associated with blisters and exulceration	Temporarily suspend the anti-EGFR treatment Assess need for hospitalization, antibiotic therapy and/or intravenous corticosteroids
5	Death	-

EGFR, epidermal growth factor receptor; PO, per os.

Table 3. CTCAE xerosis grade and therapeutic recommendations.[13]

Grade	Affected area	Management
1	<10% of body surface area and no associated erythema or pruritus	Follow guidelines for bathing and use of sanitizers. Keep skin moisturized with moisturizing creams and topical corticosteroids for a limited time if needed
2	10–30% of body surface area with associated erythema or pruritus; limitation of instrumental activities of daily living	Follow guidelines for bathing and use of sanitizers. Keep skin moisturized with moisturizing creams and topical corticosteroids for a limited period if needed. If more severe involvement occurs, use systemic corticosteroid therapy for a limited period of time. Use hydroxyzine to relieve itching
3	>30% of the body surface area with associated pruritus; limitation of daily activities	Follow the same guidelines as in the previous grade; the addition of gabapentin, 300–600 mg/day, and aprepitant, 120 mg, on the first day, followed by 80 mg on the third and fifth days can be used if the pruritus is refractory to hixizine. If superinfection occurs, use systemic antibiotics

Xerosis and pruritus

Nearly 30% of patients experience itchy, dry skin approximately 1–3 months after treatment is started. Xerosis occurs due to alterations in the keratinocyte differentiation process and is associated with abnormal functioning of the sebaceous glands, which results in alterations of the epidermal barrier and consequent transepidermal loss of excess water. Generally, it is a diffuse condition that causes painful fissures in the extremities. Associated eczema and secondary impetiginization may also occur.[14]

Guidance is given regarding baths, soaps and the frequent use of barrier moisturizers. In cases of eczema, the topical corticosteroids used should be creams. Cracks can be treated with semisolid Vaseline®. Superinfection should be treated with appropriate topical and oral antibiotics. Pruritus occurs frequently and may be associated with xerosis and/or acneiform eruption. Emollient creams associated with antihistamines, such as hydroxyzine, are useful in the management of pruritus. In cases that are more severe and refractory to doxepin, one may use gabapentin and pregabalin. Some have reported on the use of aprepitant for the treatment of refractory pruritus.[19]

The summary of the xerosis grade according to the CTCAE as well as the therapeutic recommendations is available in Table 3.

Hair changes

During antineoplastic treatment, hair all over the body becomes hardened. On the scalp, it can become curly and difficult to comb. Hypertrichosis, hirsutism, and androgenetic pattern alopecia may occur. Eyelashes may grow and bend (trichomegaly), and trichiasis (eyelashes curl toward the eyeball) and corneal ulceration may occur.[4]

For trichomegaly of the eyelashes with EGFR inhibitor use, trimming of the eyelashes may be necessary to prevent keratitis and blepharitis. It also helps to brush hair frequently if it is newly kinky or curly, trimming of the eyelashes is often required; for facial hypertrichosis or unwanted hair, eflornithine can be used topically daily. Patients can also consider laser hair removal or electrolysis for permanent hair removal. For nonscarring alopecia, a trial of topical minoxidil 5% daily for women and twice daily for men can be used.[20]

Paronychia

Paronychia is a late and persistent phenomenon that affects 10–20% of patients after several weeks and even months of treatment.[21] In addition to erythema and oedema of the nail folds, a pyogenic granuloma appears. The use of comfortable shoes to avoid trauma, as well as topical antibiotics, white vinegar baths diluted 50% in water or topical applications of trichloroacetic acid are recommended. In resistant cases, electrocoagulation of the granuloma, besides the partial removal of the nail, may be useful.[22]

Inhibitors of the RAS/BRAF/MEK/ERK signaling pathway

Cutaneous manifestations related to RAF and/or MEK inhibitors' are like those observed with EGFR inhibitors[23] including acneiform eruptions, xerosis cutis, paronychia and hair dystrophy. BRAF and MEK both represent major downstream mediators of EGFR signaling[23] inhibition of the mitogen-activated protein kinase (MAPK) pathway in keratinocytes, either at the level of EGFR or at the level of MEK, can result in keratinocyte cell death, decreased cell migration, and inflammation, which can cause dermatologic toxicity.[24] Most recently, BRAF inhibitors were shown to induce apoptosis in cells through regulation of endoplasmic reticulum stress-related genes.

Skin infection by opportunistic bacteria can be present because of disturbed skin barrier through inhibition of EGFR signaling. Also, suboptimal MAP-dependent epithelial wound healing aggravates the maintenance of skin barrier.[25]

RAF inhibition induces paradoxical activation of the MAPK signaling pathway in cells that do not carry BRAF mutation, resulting in the appearance of skin tumors such as keratoacanthoma and squamous cell carcinoma (SCC).[26] Cotargeting of MEK together with RAF has been proposed to reduce or prevent their formation.[27]

BRAF inhibitors: vemurafenib and dabrafenib

Patients who use BRAF inhibitors may present papulopustular eruption in 15–18% of cases with vemurafenib and 27% of cases with dabrafenib. Such manifestations can be treated in a similar way to those that appear due to the use of EGFR inhibitors.[28]

Keratic lesions occur in 12% patients treated with vemurafenib and in 8% treated with dabrafenib. In these cases, patients may develop SCC and keratoacanthomas. Treatment is by excision (on suspected SCC) and treatment of nonsuspected injuries with cryotherapy, topical 5-*fluorouracil* (5-FU), imiquimod and photodynamic therapy.[29]

In an attempt to avoid melanoma and alterations in pre-existing nevi, it is recommended that patients undergo a dermatological examination, with mapping and dermoscopy of the lesions, before they start the treatment regimen.

Photosensitivity occurs in 7–12% of patients, who report a burning sensation after 10 minutes of exposure to ultraviolet (UV) light. The use of photoprotectors and photoprotection measures should be advised.[30]

Other events include alopecia, palmoplantar hyperkeratosis and erythema nodosum. In the case of the last event, a biopsy may be considered to exclude a diagnosis of cutaneous metastasis, to prescribe analgesia, anti-inflammatory drugs or prednisone, 0.5 mg/kg, for 7 days and to gradually decrease the dose, until suspension of the target drug is considered.[28–31]

MEK inhibitors: cobimetinib and trametinib

The use of these inhibitors may cause papulopustular or acneiform eruption, maculopapular or exfoliative rash, folliculitis and erysipelas, usually within the first month of treatment. Cutaneous xerosis, fissures and paronychia are reactions that are typically observed later (3 months after the initiation of treatment). The management of these reactions is similar to the treatment of adverse effects that are observed with the use of anti-EGFR agents.[23]

Studies have combined MEK inhibitors with BRAF inhibitors in phase I/II clinical trials for melanoma and have shown a reduced resistance to BRAF inhibitors and a lower incidence of side effects. Another study that involved 43 patients with melanoma showed 20% with cutaneous toxicity, 6% with exanthems and no patients who reported SCC or other hyperproliferative cutaneous lesions.[28–31]

MTOR inhibitors: everolimus and temsirolimus

These drugs can cause papular eruption, acneiform eruption, nail changes (onycholysis), acne vulgaris, pruritus, xeroderma and contact dermatitis.[4] The management of these adverse reactions is similar to that described for adverse reactions associated with EGFR/HER inhibitors.

VEGF inhibitors: sunitinib, sorafenib, pazopanib, axitinib and cabozantinib

Vascular endothelial growth factor (VEGF) inhibitors were developed for antiangiogenic effect in cancer subtypes with high levels of angiogenesis. Despite targeting VEGF pathway, some components of this group (specially, first generation TK inhibitors such as sunitinib and sorafenib) interfere in other pathways, blocking platelet-derived growth factor receptors TK and some other tyrosine kinases.[32]

Several skin toxicities have been observed with extended use of VEGF inhibitors. Hand-foot syndrome, also known by a variety of terms, including acral erythema, palmar-plantar erythrodysesthesia, toxic erythema of the palms and soles, and Burgdorf reaction, is one of the most common. In this syndrome, erythema occurs in the areas of pressure with evolution to hyperkeratosis. In these cases, one should be oriented on the use of specific footwear, how to treat the area with urea-based creams and how to treat calluses.[33,34]

Skin and hair discoloration is a common side effect in VEGF inhibitors. Pazopanib, for instance, can lead to a change in hair color in up to 39% of cases.

Other complications that have been observed are dehiscence, xerosis, exanthems, scaling, and delayed wound healing. The cause of these reactions is unknown, but it has been postulated to be the result of vessel damage by either VEGFR and platelet-derived growth factor (PDGFR) inhibition or the extravasated drug itself. These cutaneous side effects can be dose-dependent and can be reversed by a reduction in dosage or discontinuation for a certain period.[35,36]

Prevention and control

Acneiform rash

Topical antibiotics with anti-inflammatory rather than direct antibacterial effect such as erythromycin, clindamycin, and topical metronidazole are used for the low grades of acneiforme eruption and oral tetracyclines for the more severe grades (doxycycline, 100 mg/day, or lymecycline, 300 mg/day).[37] On the other hand, topical or oral retinoids are in principle not indicated.

Topical corticosteroids can also be very useful for limiting erythema and burning. Mild to moderate topical corticosteroids applied once or twice daily are used preferentially on the face.[28]

All these treatments can be prescribed either in a preventive or reactive setting. A dose adjustment of the cancer treatment is sometimes required, in order to limit the negative impact on the patient's daily activities.[38]

Drug eruptions

The majority of eruptions are stabilized by local treatments comprising emollients and topical corticosteroids and do not require treatment discontinuation. However, in the case of persistent manifestations insufficiently stabilized by local treatments, a dose reduction or even combining it with short-lasting systemic corticosteroid therapy may be attempted. Lastly, in severe and potentially life-threatening drug eruptions, it appears appropriate not to reintroduce the compound and to propose alternative treatment.[38]

Hand-foot syndrome

The first step for management is measuring the impact on the patient, regarding quality of life and clinical severity.[39] Patients must be informed to limit repeated traumas or friction and use of emollient, and if necessary, topical exfoliating products can be used for hyperkeratosis.[40] When clinically severe, temporary discontinuation of treatment to allow clearing of the lesions and reintroduction of treatment at a reduced dose is recommended.[41]

Hypersensitivity

An immediate hypersensitivity reaction constitutes a contraindication to the reintroduction of the causal treatment. However, this approach is much less systematically adopted in oncology because of the frequent lack of therapeutic alternatives and the 'loss of opportunity' that permanent discontinuation of the suspected antineoplastic agent may potentially represent for the patient. The medical staff must choose between the risk of recurrence of a potentially serious reaction and the discontinuation of effective treatment and thus between a life-threatening and life-saving therapy.[42]

If a severe drug-induced skin eruption is suspected, the suspicious drug should be immediately withdrawn. The patient should be transferred to an intensive care unit, and supportive measures may be necessary. The benefit of more specific treatments, such as systemic corticosteroids or intravenous immunoglobulins, will be determined by specialist teams.[43]

Table 4. Classification according to the CTCAE and management of adverse effects of immune checkpoint inhibitors.[13]

Grade	Presentation	Management
1	Macules and papules on <10% surface of the body surface; may be associated with symptoms	Continue treatment, treat with topical corticosteroids and associated antihistamine for pruritus if necessary
2	Macules and papules on 10–30% of the body surface area; may be associated with symptoms, with limitation of daily care and instrumental activities	Stop immunotherapy, treat with prednisone, 1 mg/kg, and treat pruritus with antihistamine if necessary If there is improvement or reduction to Grade 1, progressively withdraw oral corticosteroid in approximately 1 month. If rash does not improve 12 weeks after the last dose of immunotherapy, discontinue the drug
3	Severe rash that affects >30% of the body surface that may be associated with symptoms	Stop immunotherapy, treat with prednisone, 1 mg/kg, and treat pruritus with antihistamine if necessary If there is improvement or reduction to Grade 1, progressively withdraw oral corticosteroid in approximately 1 month If patient becomes worse after 48 hours, consider use of another immunosuppressant such as infliximab If rash does not improve 12 weeks after the last dose of immunotherapy, discontinue the drug
4	Severe cutaneous rash with risk of death, Stevens–Johnson syndrome, TEN, or rash with ulceration, necrosis, and hemorrhagic blisters	Treatment in an intensive care unit. Discontinue immunotherapy, systemic intravenous treatment (methylprednisolone 2 mg/kg/day or equivalent), and if condition worsens after 48 hours, consider using another drug or another immunosuppressant in combination such as infliximab, cyclosporine, or mycophenolate mofetil; use in combination with support measures; discontinue the drug

TEN, toxic epidermal necrolysis.

General

All patients should receive an appropriate education on preventive skin care. Simple and comprehensible cosmetic advice can be offered systematically: daily application of a topical emollient; avoid UV-light exposure and, where applicable, recommend a broad spectrum high-factor sunscreen (sun protection factor: SPF 30+ to 50+), because of the increased risk of spontaneous residual hyperpigmentation or following cutaneous inflammation; gentle, soap-free hygiene product. Lastly, appropriate nonocclusive make-ups with medical camouflage can also be useful, using dermocosmetic products that are suitable for sensitive and irritated skin.

The burden of adverse events should always be assessed and psychological support offered, if required.

Immune checkpoint inhibitors: ipilimumab, nivolumab, pembrolizumab and atezolizumab

Side effects of this class of drugs are caused by exacerbated immune responses against the individual's own tissues. They occur in 64.2% of patients, and approximately 10–15% present with more severe conditions. Skin reactions may be accompanied by other systemic reactions such as enterocolitis and hepatitis.[44]

Maculopapular rash with or without pruritus occurs in the arms and trunk. In addition, desquamation, lichenoid eruption on the skin and mucous membranes, exacerbation of pre-existing psoriasis, psoriasiform reaction, Sweet syndrome, bullous pemphigoid, toxic epidermal necrolysis (TEN) and vitiligoid

Table 5. Main adverse cutaneous side effects related to the use of drugs targeting specific molecular pathways.

Molecular target pathway	Cutaneous side effect
EGFR/HER inhibitor	Papulopustular eruption Xerosis/Pruritus Hair/nail changes
BRAF inhibitor	Keratic lesions Photosensitivity Alopecia Palmoplantar hyperkeratosis Erythema nodosum
MEK inhibitor	Papulopustular/acneiform eruption Maculopapular/exfoliative rash Foliculitis Erysipelas
MTOR inhibitor	Papular/acneiform eruption Onycholysis Acne vulgaris Pruritus/xeroderma
TK inhibitor	Periorbital and lower limb edema Pigmentary changes Hand-foot reaction Maculopapular reaction
Anti-VEGF	Hand-foot syndrome Xerosis Exanthema Delayed wound healing
Immune checkpoint inhibitor	Maculopapular rash Desquamation Psoriasiform reaction Toxic epidermal necrolysis Vitiligoid reaction

EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; HER, human epidermal growth factor; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; TK inhibitor, tyrosine-kinase inhibitor; VEGF, vascular endothelial growth factor.

reaction may also be present. More severe reactions such as TEN occur more frequently when BRAF inhibitor therapy is used soon after the use of an immune checkpoint inhibitor.[45,46]

The treatment depends on the grade of involvement according to the CTCAE and is described in detail in Table 4. Typically, the use of topical corticosteroid creams resolves the condition without the need to reduce or interrupt the use of the immune checkpoint inhibitor.

Anti-PD1/ PD-L1: pembrolizumab, nivolumab and atezolizumab

Vitiligo-like lesions that occur during treatment with selective PD-1 inhibitors, such as pembrolizumab and nivolumab, have been reported in up to 25% of patients and may be associated with a clinical benefit.[47]

Anti-PD1 blockage induces the overexpression of CD8 T-cell-skewed immune response in patients with vitiligo-like lesions characterized by the presence of a CXCR31 CD8 T cell infiltrate together with increased serum levels of CXCL10 and the expression of interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) by skin-infiltrating CD8 T cells, these cells infiltrate and act against normal and pathological melanocytes, producing residual hypopigmentation.[47]

Anti-CTL4: ipilimumab

Ipilimumab pigmentary changes (vitiligo-like lesions) appear to be a direct result of cytotoxic T-lymphocyte antigen-4 inhibition and consequent immune system activation, including against the melanocytes. Clinical depigmentation may serve as a surrogate marker for responsiveness to anticancer treatment.[48]

Conclusions

Cutaneous reactions comprise a portion of the adverse effects that are associated with many molecularly targeted therapies (Table 5). They may occur at different intensities, and a lack of adequate treatment may lead to the need for discontinuation of the antineoplastic drug, which would significantly worsen the quality of life of patients.

On the contrary, the easy identification of these reactions through a simple physical examination can allow effective measures to be taken and the condition to be controlled. In general, the early treatment of cutaneous adverse reactions results in good outcomes.

It is worth emphasizing that, in addition to the therapeutic measures, several preventive actions can and should be administered. Among them, the maintenance of adequate skin hygiene, hydration, and the use of sunscreen are of great value and scope.

Disclosure and potential conflicts of interest: The authors declare no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2018/06/dic.212516-COI.pdf

Funding declaration: There was no funding for this manuscript.

Article URL: https://www.drugsincontext.com/cutaneous-side-effects-of-molecularly-targeted-therapies-for-the-treatment-of-solid-tumors

Correspondence: Daniel I G Cubero, Department of Oncology and Hematology, ABC Foundation School of Medicine. Av Principe de Gales, 821, Anexo 3 – segundo andar, Santo André/SP – Brazil, ZIP 09060-650. danielcubero@uol.com.br

Provenance: invited; externally peer reviewed.

Submitted: 15 November 2017; **Peer review comments to author:** 6 February 2018; **Revised manuscript received:** 14 May 2018; **Accepted:** 15 May 2018; **Publication date:** 17 July 2018.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

For all manuscript and submissions enquiries, contact the Editorial office dic.editorial@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Ma WW, Adjei AA. Novel agents on the horizon for cancer therapy. *CA Cancer J Clin*. 2009;59(2):111–137. https://doi.org/10.3322/caac.20003
2. Lacouture ME. *Dermatologic Principles and Practice in Oncology: Conditions of the Skin, Hair, and Nails in Cancer Patients*. Hoboken, NJ: Wiley-Blackwell; January 2014. ISBN: 978-0-470-62188-2
3. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapy for cancer: part II. Targeted therapy. *J Am Acad Dermatol*. 2014;71(2):217.e1–217.e11; quiz 227–228. https://doi.org/10.1016/j.jaad.2014.04.013
4. Payne AS, Savarese DM. Cutaneous side effects of molecularly targeted therapy and other biologic agents used for cancer therapy. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed October 7, 2017.
5. Tan EH, Chan A. Evidence-based treatment options for the management of skin toxicities associated with epidermal growth factor receptor inhibitors. *Ann Pharmacother*. 2009;43(10):1658–1666. https://doi.org/10.1345/aph.1M241
6. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al.; MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011;19(8):1079–1095. https://doi.org/10.1007/s00520-011-1197-6
7. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer*. 2006;6(10):803–812. https://doi.org/10.1038/nrc1970
8. Fischer A, Rosen AC, Ensslin CJ, Wu S, Lacouture ME. Pruritus to anticancer agents targeting the EGFR, BRAF, and CTLA-4. *Dermatol Ther*. 2013;26(2):135–148. https://doi.org/10.1111/dth.12027
9. Hu JC, Sadeghi P, Pinter-Brown LC, et al. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. *J Am Acad Dermatol*. 2007;56:317–326. https://doi.org/10.1016/j.jaad.2006.09.005
10. Micantonio T, Fargnoli MC, Ricevuto E, Ficorella C, Marchetti P, Peris K. Efficacy of treatment with tetracyclines to prevent acneiform eruption secondary to cetuximab therapy. *Arch Dermatol*. 2005;141(9):1173–1174. https://doi.org/10.1001/archderm.141.9.1173
11. Amitay-Laish I, David M, Stemmer SM. Staphylococcus coagulase-positive skin inflammation associated with epidermal growth factor receptor-targeted therapy: an early and a late phase of papulopustular eruptions. *Oncologist*. 2010;15(9):1002–1008. https://doi.org/10.1634/theoncologist.2010-0063
12. Pinto C, Barone CA, Girolomoni G, et al. Management of skin toxicity associated with cetuximab treatment in combination with chemotherapy or radiotherapy. *Oncologist*. 2011;16(2):228–238. https://doi.org/10.1634/theoncologist.2010-0298
13. Madke B, Gole P, Kumar P, Khopkar U. Dermatological side effects of epidermal growth factor receptor inhibitors: 'PRIDE' complex. *Indian J Dermatol*. 2014;59(3):271–274. https://doi.org/10.4103/0019-5154.131398
14. Eder J, Simonitsch-Klupp I, Trautinger F. Treatment of unresectable squamous cell carcinoma of the skin with epidermal growth factor receptor antibodies—a case series. *Eur J Dermatol*. 2013;23(5):658–662. https://doi.org/10.1684/ejd.2013.2153
15. Lynch TJ Jr, Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007;12(5):610–621. https://doi.org/10.1634/theoncologist.12-5-610
16. Perez-Soler R, Van Cutsem E. Clinical research of EGFR inhibitors and related dermatologic toxicities. *Oncology (Williston Park)*. 2007;21(11 Suppl 5):10–16. PubMed PMID: 18154213
17. Ricciardi S, Tomao S, de Marinis F. Toxicity of targeted therapy in non-small-cell lung cancer management. *Clin Lung Cancer*. 2009;10(1):28–35. https://doi.org/10.3816/CLC.2009.n.004
18. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed September 22, 2017.
19. Burtness B, Anadkat M, Basti S, et al. NCCN Task Force Report: management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer. *J Natl Compr Canc Netw*. 2009;7 Suppl 1:S5–21; quiz S22–24. PubMed PMID: 19470276
20. Hofheinz R-D, Deplanque G, Komatsu Y, et al. Recommendations for the prophylactic management of skin reactions induced by epidermal growth factor receptor inhibitors in patients with solid tumors. *Oncologist*. 2016;21(12):1483–1491. https://doi.org/10.1634/theoncologist.2016-0051
21. Lacouture ME, Laabs SM, Koehler M, et al. Analysis of dermatologic events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat*. 2009;114:485–493. https://doi.org/10.1007/s10549-008-0020-7
22. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol*. 2005;16(9):1425–1433. https://doi.org/10.1093/annonc/mdi279
23. Gutzmer R, Becker JC, Enk A, et al. Management of cutaneous side effects of EGFR inhibitors: recommendations from a German expert panel for the primary treating physician. *J Dtsch Dermatol Ges*. 2011;9:195–203. https://doi.org/10.1111/j.1610-0387.2010.07561.x
24. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. 2010;8:149–161. PubMed PMID: 20822032

25. Deng M, Chen WL, Takatori A, et al. A role for the mitogen-activated protein kinase kinase kinase 1 in epithelial wound healing. *Mol Biol Cell*. 2006;17:3446-3455. https://doi.org/10.1091/bc.E06-02-0102
26. Oberholzer PA, Kee D, Dziunycz P, et al. RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. *J Clin Oncol*. 2012;30:316-321. https://doi.org/10.1200/CO.2011.36.7680
27. Lemech C, Arkenau HT. Novel treatments for metastatic cutaneous melanoma and the management of emergent toxicities. *Clin Med Insights Oncol*. 2012;6:53-66. https://doi.org/10.4137/CMO.S5855
28. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol*. 2005;6(7):491–500. https://doi.org/10.1016/S1470-2045(05)70243-6
29. Manousaridis I, Mavridou S, Goerdt S, Leverkus M, Utikal J. Cutaneous side effects of inhibitors of the RAS/RAF/MEK/ERK signalling pathway and their management. *J Eur Acad Dermatol Venereol*. 2013;27(1):11–18. https://doi.org/10.1111/j.1468-3083.2012.04546.x
30. Chapman PB, Hauschild A, Robert C, et al; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011 30;364(26):2507–2516. https://doi.org/10.1056/NEJMoa1103782
31. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010;363(9):809–819. https://doi.org/10.1056/NEJMoa1002011
32. Wozel G, Sticherling M, Schon MP. Cutaneous side effects of inhibition of VEGF signal transduction. *J Dtsch Dermatol Ges*. 2010;8:243. https://doi.org/10.1111/j.1610-0387.2009.07268.x
33. Lacouture ME, Wu S, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist*. 2008;13(9):1001–1011. https://doi.org/10.1634/theoncologist.2008-0131
34. Gomez P, Lacouture ME. Clinical presentation and management of hand–foot skin reaction associated with sorafenib in combination with cytotoxic chemotherapy: experience in breast cancer. *Oncologist*. 2011;16(11):1508–1519. https://doi.org/10.1634/theoncologist.2011-0115
35. McLellan B, Kerr H. Cutaneous toxicities of the multikinase inhibitors sorafenib and sunitinib. *Dermatol Ther*. 2011;24:396–400. https://doi.org/10.1111/j.1529-8019.2011.01435.x
36. Verheul HM, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. *Nat Rev Cancer*. 2007;7:475. https://doi.org/10.1038/nrc2152
37. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. *Semin Oncol*. 2012;39:227–240. https://doi.org/10.1053/j.seminoncol.2012.01.009
38. Bryce J, Chan A, Epstein JB, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011;19:1079–1095. https://doi.org/10.1007/s00520-011-1197-6
39. Janusch M, Fischer M, Marsch W, Holzhausen HJ, Kegel T, Helmbold P. The hand-foot syndrome – a frequent secondary manifestation in antineoplastic chemotherapy. *Eur J Dermatol*. 2006;16:494–499. PubMed PMID: 17101468
40. Macedo LT , Nogueira JP, Viera dos Santos L, Deeke Sasse A. Prevention strategies for chemotherapy-induced hand foot syndrome: a systematic review and meta-analysis of prospective randomised trials. *Support Care Cancer*. 2014;22(6):1585–1593. https://doi.org/10.1007/s00520-014-2129-z
41. Saif MW. Capecitabine and hand-foot syndrome. *Expert Opin Drug Saf*. 2011;10:159-169. https://doi.org/10.1517/14740338.2011.546342
42. Sanborn RE, Sauer DA. Cutaneous reactions to chemotherapy: commonly seen, less described, little understood. *Dermatol Clin*. 2008;26:103–119. https://doi.org/10.1016/j.det.2007.08.006
43. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol*. 2013;69:187. https://doi.org/10.1016/j.jaad.2013.05.002
44. Goldinger SM, Stieger P, Meier B, et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res*. 2016;22(16):4023–4029. https://doi.org/10.1158/1078-0432.CCR-15-2872
45. Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. *Dermatol Ther*. 2011;24(4):386-395. https://doi.org/10.1111/.1529-8019.2011.01431.x
46. Jaber SH, Cowen EW, Haworth LR, et al. Skin reactions in a subset of patients with stage IV melanoma treated with anti-cytotoxic T-lymphocyte antigen 4 monoclonal antibody as a single agent. *Arch Dermatol*. 2006;142(2):166–172. https://doi.org/10.1001/archderm.142.2.166
47. Larsabal M, Marti A, Jacquemin C, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol*. 2017;76:863–870. https://doi.org/10.1016/j.jaad.2016.10.044
48. Pavlick AC, Ott PA, Kannan K, et al. Hair depigmentation as an indicator of a durable response to CTLA-4 therapy [abstract]. *J Clin Oncol*. 2010;28(suppl 15):8571. https://doi.org/10.1200/jco.2010.28.15_suppl.8571