Adverse mucocutaneous reactions related to chemotherapeutic agents – Part II

Reações tegumentares adversas relacionadas aos agentes antineoplásicos – Parte II

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Abstract: Events and reactions involving chemotherapy are common in clinical oncology. Chemotherapeutic agents are widely used in therapy. Side effects range from the common to the rare and may be confused with other mucocutaneous manifestations resulting from the oncological treatment. The objective of this paper was to present data on skin reactions to chemotherapy, particularly those cases in which the dermatologist is requested to issue a report and asked to comment on the safety and viability of readministration of a specific drug. The authors describe aspects associated with these events, presenting a detailed analysis of each one of them.
Keywords: Chemotherapy, adjuvant ; Drug therapy; Drug therapy, combination; Skin; Skin abnormalities; Skin pigmentation

Resumo: Os eventos e reações envolvendo quimioterapia são frequentes na prática oncológica. Agentes quimioterápicos são uma modalidade de tratamento amplamente utilizada. Efeitos colaterais podem variar de frequência e também ser confundidos com outras manifestações tegumentares do tratamento oncológico. Este artigo objetiva expor as informações sobre reações cutâneas à quimioterapia, em especial, aqueles para os quais o dermatologista é requisitado a emitir parecer e a comentar sobre a segurança e a viabilidade da readministração de uma droga específica. Os autores descrevem os aspectos associados a esses eventos, fazendo uma análise detalhada de cada um deles.
Palavras-chave: Anormalidades da pele; Quimioterapia; Quimioterapia adjuvante; Quimioterapia combinada; Pele

INTRODUCTION

Evaluation of the oncology patient requires knowledge of the primary disease as well as the expected effects and side effects of the medication used. The variety of drugs in general, including immunosuppressive and chemotherapeutic drugs, and the general health of the patient, who is often debilitated, must be taken into account in the routine evaluation of this group of patients. These drugs interact with the skin in various ways and many of the chemotherapeutic agents have been associated with particular clinical presentations. Familiarization with these manifestations is essential in order to assure that the patient using these drugs is correctly evaluated. An accurate diagnosis is important in guarantee-

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ing that the patient receives the most appropriate treatment and to evaluate whether the drug in question should be discontinued or switched. This paper presents the second part of a review of the mucocutaneous adverse reactions associated with the use of antineoplastic agents (Table 1).

EPIDERMAL, DERMAL AND COLLAGEN-RELATED ABNORMALITIES

Intertrigo-like eruption

Also referred to as epidermal dysmaturation, this condition is characterized by erythema and maceration of intertriginous areas (Figure 1), often complicated by candidiasis or bacterial infection. It may appear as a side effect of the use of liposomal doxorubicin (8%) or dactinomycin. [1] The lesions may be treated with astringent compresses and topical corticosteroids associated with antibiotics and antifungal medication. [2]

Hyperpigmentation

This is a common adverse effect of chemotherapeutic agents and may affect the skin, hair, nails and mucous membranes. [3] The area affected may be localized or diffuse. [4] Pigmentation may follow a specific pattern that correlates with anatomical distribution or the type of drug or may correspond to a site of contact with external material such as occlusive dressings. Hyperpigmentation of the skin may be secondary to an increase in the quantity of melanin, carotene or hemoglobin. [5] In the case of hyperpigmentation induced by chemotherapeutic drugs, the mechanisms still remain to be clarified. The exact physiopathology probably varies depending on the drug in question. Tables 2 and 3 show the drugs involved and the course of the adverse reaction. [6] There is no specific treatment for hyperpigmentation. The condition usually disappears some months or years after discontinuation of the drug that triggered the effect. [7]

Autoimmune reactions

Clinical conditions such as subacute cutaneous lupus erythematosus and scleroderma-like reactions may be associated with the use of 5-fluorouracil (5-

QUADRO 1: Cutaneous adverse reactions related to antineoplastic agents

1. Abnormalities in the skin, hair and nails.	1.1. Alopecia 1.2. Trichomegaly and hair coiling 1.3. Ungual, subungual and periungual abnormalities 1.4. Neutrophilic eccrine hidradenitis 1.5. Eccrine squamous syringometaplasia 1.6. Acral erythema or palmar-plantar erythrodysesthesia 1.7. Acneiform eruption
2. Abnormalities in the mucosa	2.1. Stomatitis
3. Abnormalities in the epidermis, dermis and collagen	3.1. Intertrigo 3.2. Hyperpigmentation 3.3. Autoimmune reactions 3.4. Inflammation of preexisting keratoses 3.5. Leg ulceration
4. Vascular abnormalities	4.1. Vasomotor abnormalities 4.2. Flushing
5. Interactions with radiation	5.1. Interaction with UV light 5.2. Radiation recall 5.3. Exacerbated radiation
6. Hypersensitivity reactions	6.1. Hypersensitivity reactions
7. Local reactions	7.1. Local toxicity 7.2. Drug extravasation
8. Diverse reactions	8.1. Periorbital edema 8.2. Cutaneous eruption of lymphocyte recovery 8.3. Skin toxicities associated with anti EGFR/TKI 8.4. Other adverse skin reactions observed with chemotherapeutic agents.

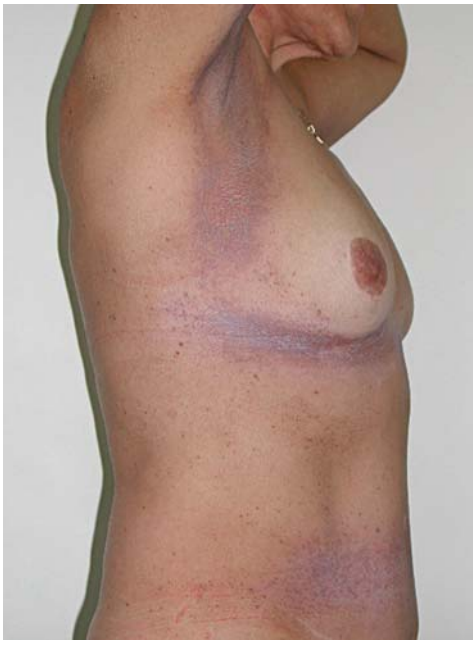

Figure 1: : Erythema and maceration in the flexural areas following use of doxorubicin. Intertrigo-like eruption

FU), bleomycin, hydroxyurea and taxanes, as well as dermatomyositis-like lesions due to hydroxyurea. [8-10]

Inflammation of preexisting keratoses

Selective inflammation of actinic and seborrheic keratoses, even if subclinical or nonapparent, may occur with the use of certain chemotherapeutic agents. [11] The drug most commonly associated with inflammation of actinic keratoses is 5-FU when used systemically. The physiopathogenesis of the condition is unknown; however, it is speculated that dysplastic keratinocytes may become more sensitive to cytotoxic agents because of an increase in the quantity of DNA damaged by ultraviolet radiation (inside and around the actinic keratosis). Another possibility is radiation recall dermatitis. The inflammation in seborrheic keratoses may occur following administration of cytarabine and may trigger the appearance of a squamous cell carcinoma following the use of fludarabine. Capecitabine is another agent responsible for inflammation of actinic keratoses. [11]

Clinically, actinic keratosis and seborrheic lesions become inflamed, erythematous and pruriginous (Figure 2). The reaction always occurs in areas of the skin exposed to the sun, generally in the first week following chemotherapy. Regression of the inflammation occurs 1-4 weeks after discontinuation of the drug. Relief of the symptoms may be obtained with the use of topical corticosteroids of low to moderate potency. Discontinuation of chemotherapy is not indicated, since the reaction may be self-limiting and may even have a beneficial therapeutic effect. The drugs associated with inflammation of lesions of actinic keratoses are: docetaxel, doxorubicin, 5-FU, pentostatin, dactinomycin, vincristine, dacarbazine, cytarabine, 6-thioguanine, sorafenib and cisplatin. Cytarabine and gemcitabine are associated with seborrheic keratoses. [12,13]

Leg ulceration

Ulcerated lesions of the lower limbs may develop with the use of hydroxyurea, methotrexate, cisplatin, gemcitabine and rituximab. [14,15]

VASCULAR CHANGES

Vasomotor changes

Various vascular alterations have been described, probably as a result of a direct effect on arterial smooth muscle fibers or by acting on the autonomic nervous system. [3] Manifestations may include blood vessel spasms with livedo, Raynaud's phenomenon and distal necroses, which may be triggered by bleomycin and cisplatin. [16] Vasodilatation with erythema and flushing may result from the use of bleomycin, cisplatin, asparaginase, dacarbazine, taxanes, 5-FU, doxorubicin, cyclophosphamide, gefitinib and carmustine. [17,18]

Flushing

Flushing consists of a temporary erythema of the face, neck, upper chest, ears or upper abdomen. The mechanism responsible for flushing is a transitory vasodilation mediated by the autonomic nervous system or by the direct effect of circulating substances that act on the musculature of the vessel walls. The nerves of the autonomic nervous system also control the sweat glands so that flushing mediated by these nerves is known as "wet flushing", whereas when the substance acts directly on the vascular wall muscles it is known as "dry flushing". [19] Derivatives of biological agents such as L-asparaginase and bleomycin are notorious for causing flushing, which occurs soon after infusion. [20] Irinotecan, a topoisomerase I inhibitor, causes dysautonomia, the symptoms of which include diarrhea, bradycardia and flushing. [21] Hormonal agents such as antiestrogens (tamoxifen, anastrozole), LHRH analogs (leuprolide) and antiandrogens (flutamide and diethylstilbestrol) may result in flushing. Other agents that also deserve mention include: 5-FU, carboplatin, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, etoposide and methotrexate. [22,23]

INTERACTIONS WITH RADIATION

Interaction with ultraviolet (UV) light

Eruptions due to photosensitivity are caused by various agents, principally following exposure to ultraviolet radiation (UVR) (Table 4). Phototoxicity caused by dacarbazine, fluoropyrimidines (systemic 5-

Table 2: Chemotherapeutic agents and skin hyperpigmentation

Class of Drug	Drug	Description / localization	Characteristics
Alkylating agents	Busulfan	Diffuse brown pigmentation, tanned or powdered on the face, neck, chest, forearms, palmar folds and abdomen.	May persist or regress with discontinuation of the drug.
	Topical mechlorethamine (topical nitrogen mustard)	Generally located on the treated areas.	Pigmentation decreases after 6-8 weeks, even if treatment is continued.
	Cyclophosphamide	Regional involvement of the palmar and plantar areas, nails or teeth or generalized pigmentation.	Appears after 4 or more weeks of treatment and disappears within 6-12 months after discontinuation of the drug.
	Iphosphamide	Flexural areas, dorsal and ventral surfaces of the feet and hands, extensor surface of the fingers, scrotum and trunk.	Varied onset. Early or even 10 months after initiation of treatment.
	Topical carmustine (BCNU)	Skin hyperpigmentation under occlusive dressings.	After 8 days of treatment. Lightens gradually.
	Cisplatin	In around 70% of patients, localized pigmentation or as stains on the dorsal surface of the limbs, nails, elbows, knees and at sites of trauma and pressure.	Occurs after the 2nd or 3rd course of treatment.
	Thiotepa	Circumscribed hyperpigmentation in the exact shape of contact with dressings. Leukodermia may be present.	It is not preceded by erythema and appears around the 4th day of treatment.
Antimetabolic agents	Fluorouracil	Varying patterns: (a) diffused tan in areas exposed to the sun; (b) The linear pattern, serpentine supravenous hyperpigmentation from the hand to the shoulder; (c) generalized reticular pigmentation; (d) Brownish, serpiginous linear macules on the back and buttocks; (e) localized patterns: transversal bands over small articulations, diffuse palmar hyperchromia, pigmented macules on palms of the hands, soles of the feet and trunk.	Varying reactions: (a) Immediate reaction 30 minutes following sun exposure or later, after weeks or months; (b) around the 18th week of treatment; (c) one day after treatment; (d) after 48 hours of treatment.
	Intralesional fluorouracil	Hyperpigmentation at the injection site.	Occurs after 1 or 2 doses

Continue

Class of Drug	Drug	Description / localization	Characteristics
	Tegafur/Capecitabine	In around one-third of patients: Limited to the palmar and plantar regions, nails and glans penis, in the form of nonconfluent macules of 2-5 mm.	Between the 2nd and 6th months of treatment
	Methotrexate	(a) On the body: brownish pigmentation. (b) In the hair: horizontal hyperpigmented lines alternating with the normal color of the hair, eyebrows and eyelashes of the patient, known as the "flag sign" of chemotherapy.	(a) This condition is rare; (b) Corresponds to the weekly cycles of methotrexate use.
Antibiotic agents	Bleomycin	(a) Pigmentation in macules in areas of pressure; (b) Linear pigmentation in bands, known as flagellate dermatitis, located in sites of trauma on the trunk and the portion close to the extremities; (c) situated at or close to striations.	(a) Reversible with discontinuation of the drug; (b) Occurs in around 8-20% of patients who receive cumulative doses of 100 mg or even less. Onset around one month after beginning treatment.
	Dactinomycin	Diffuse melanosis.	
	Doxorubicin	(a) Generalized hyperpigmentation, including the palmar and plantar ridges; (b) bluish-gray pigmentation on the face, neck and shoulders.	Regresses spontaneously following discontinuation of the drug.
	Daunorubicin	(a) Generalized pigmentation in areas exposed to the sunlight; (b) Polycyclic pigmentation on the scalp.	
	Mitoxantrone	Pigmentation on the face, back of the hands and nails.	Onset after one month of treatment.
Others	Hydroxyurea	Generalized hyperpigmentation of the face, neck and arms, accentuated in areas of pressure.	After prolonged therapy.
	Docetaxel	Erythema and later pigmentation in the area of application of the pacemaker adhesive.	

FU, topical 5-FU, tegafur and capecitabine) and vinblastine has been well-documented. [24] Phototoxicity caused by dactinomycin, doxorubicin, hydroxyurea, procarbazine, brequinar sodium, mitomycin, 6-thioguanine and flutamide, as well as by the porphyrin compounds that are used in photodynamic therapy, is uncommon. [25,26]

Reactivation of sunburn is a well-documented adverse effect following the use of methotrexate (MTX). It occurs when the drug is administered 1-3

Table 3: Chemotherapeutic agents involved in mucosal pigmentation

Drug	Description
Busulfan	Linear deposit of pigment in the gum.
Fluorouracil	Affects the conjunctive and tongue with brownish marks.
Tegafur	Pigmented macules on the lower lip and glans penis.
Doxorubicin	Blackened pigmentation on the tongue and pigmented macules in the oral mucosa.
Hydroxyurea	Pigmented macules on the tongue and oral mucosa.
Cisplatin	Oral hyperpigmentation.
Cyclophosphamide	Pigmented bands around the rim of the gum.

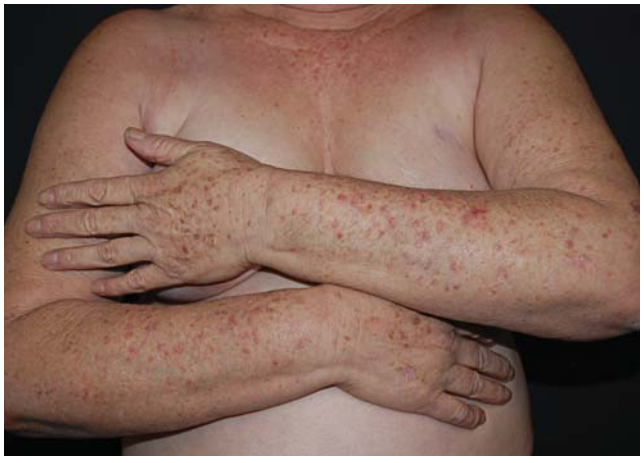

Figure 2: Multiple inflamed actinic keratoses in photo-exposed areas following use of 5-Fluorouracil. Inflammation of preexisting actinic keratoses

days after exposure to UV radiation, when the erythema from the previous exposure has been in the process of disappearing. [27] Leucovorin does not prevent this reaction. Phototoxic reactions resemble intense sunburn in areas of the skin that are exposed to light, with erythema, edema, pain or pruritus. Blisters may be present and desquamation may occur in severe cases. Residual hyperpigmentation may persist for months. Diagnosis is made according to the distribution of the lesions and by the temporal relationship between chemotherapy and light exposure. Treatment includes discontinuation of the agent and protection from the sun for at least two weeks. Physical sunscreens are recommended. Cold compresses, systemic antihistamines and topical or oral corticosteroids are used as associated symptomatic treatment. [28]

Radiation recall

This is a phenomenon in which the chemotherapeutic agent induces an inflammatory reaction in an area previously exposed to radiation. These reactions are predominantly cutaneous; however, they may affect internal organs such as the lungs, heart, bladder mucosa, esophagus, oral or bowel mucosa and supraglottic larynx. It occurs more often with the use of doxorubicin, dactinomycin and gemcitabine and is less common with bleomycin, etoposide, hydroxyurea, methotrexate, trimetrexate, vinblastine, 5-fluorouracil, lomustine, daunorubicin, melphalan, cyclophosphamide, cytarabine, docetaxel, edatrexate, idarubicin, paclitaxel, tamoxifen and vinblastine. [29-31]

The mechanism of radiation recall is unknown but it is probably related to DNA repair. Relapsing dermatitis or radiation recall may occur between 8 and 15 days following radiotherapy and generally appears hours to days after administration of the chemotherapeutic agent. Clinically, the patient may or may not experience a painful erythema with or without vesiculation, edema, desquamation and pruritus. The borders of the lesion are well defined and correspond to the exact site at which the radiation was applied. In severe cases, necrosis and ulceration may occur. The severity appears to directly reflect the brevity between radiation and chemotherapy as well as the doses of both radiation and chemotherapy. The reaction improves spontaneously within hours or weeks following cessation of chemotherapy, treatment being symptomatic. The use of systemic corticosteroids associated with the discontinuation of chemotherapy generally results in a marked improvement and may permit reintroduction of the treatment. [32]

Table 4: Interaction between chemotherapeutic agents and ultraviolet radiation

Side Effect	Drug used
Phototoxicity	Dacarbazine Dactinomycin Doxorubicin Fluorouracil Hydroxyurea Methotrexate Mitomycin C Porphyrins Procarbazine Tegafur Thioguanine Vinblastine
Photoallergy	Flutamide Tegafur
Photo-onycholysis	Mercaptopurine
Ultraviolet recall	Etoposide / cyclophosphamide Methotrexate Methotrexate / cyclophosphamide / Fluorouracil

Exacerbation of radiation

This occurs when a chemotherapeutic agent increases the toxicity of radiotherapy. This phenomenon may occur in virtually all the organs of the body including the skin, mucosa, esophagus, lungs, heart, digestive tract, kidneys, liver, brain, bladder and eyes. The agents most associated with exacerbation of radiation are bleomycin, gemcitabine, dactinomycin, doxorubicin, fluorouracil, hydroxyurea, 6-mercaptopurine, oxyplatin and methotrexate. [33,34] Clinically, the reaction resembles residual dermatitis secondary to acute dermatitis from radiation, with erythema, edema, vesiculation, blisters or erosions. The reaction generally appears at the site of radiation; however, the area affected may be more extensive. Severe mucositis may occur. The reaction is associated with the dose, the type of drug used and the sequence of time between radiation and the use of chemotherapy. [35] Toxicity may be additive or supra-additive (synergic). In supra-additive toxicity, the reaction is greater than that of the sum of each one of the types of treatment alone. Treatment is symptomatic: applying cold compresses, taking precautions at the site to prevent infection and avoiding trauma, heat and UV light. Sequelae such as fibrosis, skin atrophy and telangiectasia-related disorders may occur. [36]

Hypersensitivity reactions

In theory, all chemotherapeutic agents may trigger hypersensitivity eruptions. With certain drugs derived from biological agents such as L-asparaginase, mitomycin-C and bleomycin in addition to paclitaxel the incidence of hypersensitivity reactions is high. In the case of paclitaxel, this is due to the fact that it is dissolved in Cremophor EL castor oil. [37] According to the classification system defined by Gell and Coombs, the majority of hypersensitivity reactions are type I, i.e. IgE-mediated. They present as urticaria, pruritus, angioedema and anaphylaxis. They generally occur within the first hour after use of the drug, but onset may be delayed until up to 24 hours after using the medication. [38] Type III reactions occur due to the formation of circulating immunocomplexes and cause eruptions such as polymorphous erythema and vasculitis. Nonetheless, L-asparaginase and procarbazine cause urticarial reactions via type III reactions. Allergic contact dermatitis, a type IV reaction, may occur, principally as a consequence of the topical use of nitrogen mustard (mechlorethamine).[39]

Other severe reactions may occur such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), as well as exanthematous eruptions, all currently classified as type IV reactions according to the extended Gell and Coombs classification, i.e. SJS and TEN, respectively (type IVc, mediated by Fas, granzymes and perforin) and exanthematous eruptions (type IVb, mediated by T-cells with IL-5 production, with chemotaxis of eosinophils). [40,41] The different hypersensitivity eruptions, their immunopathogenesis and the agents most commonly involved are shown in Table 5.

LOCAL REACTIONS

Local toxicity

Antineoplastic drugs may be classified according to their potential aggressiveness towards blood vessels and adjacent tissues. They may be *non-irritating, irritating* or *vesicant*, causing effects that range from mere local discomfort to tissue necrosis. *Non-irritating* drugs (thioguanine, asparaginase, bleomycin, cyclophosphamide, chlorambucil, methotrexate, hydroxyurea) provoke an edema that is indicative of a site of extravasation; however, they do not cause necrosis or tissue irritation. *Irritating* drugs (fluorouracil, carmustine, docetaxel and etoposide) cause tissue damage that does not progress to necrosis. They trigger erythema, pain, inflammation at the puncture site and along the venous pathway, burning and local

TABLE 5: Hypersensitivity reactions to chemotherapeutic agents

Morphology	Type of Gell and Coombs reaction and immunopathogenic mechanism	Drugs
Urticaria, angioedema pruritus, bronchospasm and anaphylaxis	Type I (IgE-mediated) Grade according to the National Cancer Institute criteria Grade I Transitory flushing or erythematous eruption; fever ≥ 38oC Grade II Extensive erythema; flushing; urticaria, dyspnea, fever ≥ 38oC Grade III Symptomatic bronchospasm with and without urticaria; parenteral medication indicated for treatment; angioedema or edema; hypotension. Grade IV Anaphylaxis Grade V Death	L-asparaginase, bleomycin, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, etoposide, 5-fluorouracil, mechlorethamine, melphalan, methotrexate, mitomycin C, mitotane, mitoxantrone, paclitaxel, pentostatin, procarbazine, teniposide, thiotepa, trimetrexate, vincristine
Localized urticaria (exacerbated reactions)	Remains to be fully clarified: Type I (IgE-mediated) or anaphylactoid or direct release from mastocyte mediators	Doxorubicin, epirubicin, idarubicin
Hemolytic anemia	Type II (IgM antibodies or IgG cytolytics)	Oxaliplatin
Vasculitis	Type III (antigen-antibody complex)	Busulfan, cyclophosphamide, cytarabine, hexamethylene, hydroxyurea, levamisole, 6-mercaptopurine, methotrexate, mitoxantrone, tamoxifen
Allergic contact dermatitis	Type IVa (sensitized T-lymphocytes)	Topical mechlorethamine, topical cisplatin, topical daunorubicin, topical doxorubicin, topical 5-fluorouracil, intravenous 5-fluorouracil, intravesical mitomycin C
Exanthema	Type IVb (sensitized T-lymphocytes)	Bleomycin, carboplatin, cis- dichlorobisisopropylamine trans-dihydroxy platinum, chlorambucil, high-dose cytarabine, docetaxel, diethylstilbestrol, intravesical doxorubicin, etoposide, 5-fluorouracil, high-dose hydroxyurea, methotrexate, mitomycin C, mitotane, mitoxantrone, paclitaxel, pentostatin, procarbazine
Toxic epidermal necrolysis / Stevens-Johnson Syndrome	Type IVc (CD8+ T-lymphocyte, granzymes, porphyrins, Fas)	Asparaginase, bleomycin, chlorambucil, cladribine, cytarabine, doxorubicin, 5-fluorouracil, methotrexate, procarbazine
Acute generalized exanthematous pustulosis	Type IVd (T-lymphocyte and monocyte producers of Il-8, GM-CSF)	Pemetrexed (antifolate drug), imatinib and azathioprine

edema, without blistering. The vesicant drugs (dactinomycin, doxorubicin, melphalan, vincristine, vinblastine and dacarbazine) cause severe skin irritation with pain, erythema, edema, blistering and necrosis with functional and esthetic damage. [42-44]

Drug extravasation

This is defined as the leakage of a chemotherapeutic drug from the vessel bed to the surrounding tissues, either as a result of vascular rupture or by direct infiltration. The frequency of this event in adults is estimated at 0.1% to 6% and it is more common among children. Severe sequelae are rare. The severity of tissue damage is related to the type of chemotherapeutic agent used and the quantity and concentration of the drug administered. Cytotoxic agents are classified as *irritants* or *vesicants* as a function of their potential for local toxicity. An *irritant* is defined as an agent that causes an inflammatory reaction, paresthesia, pain or phlebitis at the puncture site or along the venous pathway. Clinical signs include sclerosis and hyperchromia along the passage, as well as burning, increased temperature at the site, discomfort, erythema and pain at the area of extravasation. Necrosis does not occur with this condition. The symptoms are generally short-lived and leave no sequelae. The drugs most associated with this complication are: 5-FU, carboplatin, cisplatin, bleomycin, mitomycin, dactinomycin, idarubicin, daunorubicin, dacarbazine, iphosphamide, cyclophosphamide, mechlorethamine, carmustine, mitoxantrone, paclitaxel, docetaxel, streptozocin, vinblastine, vinorelbine and etoposide. [45,46]

The *vesicant* agents (melphalan, bleomycin, mechlorethamine, carmustine, mitomycin, mitoxantrone, cisplatin, paclitaxel, dacarbazine, dactinomycin, daunorubicin, streptozocin, doxorubicin, epirubicin, vinblastine, vincristine, etoposide, vindesine and vinorelbine) have the potential to cause more severe and long-lasting tissue damage, including necrosis of the affected area. The initial manifestations are often subclinical and may appear immediately following extravasation or after several days or weeks. The initial signs include local burning or paresthesia at the site of infusion, mild erythema, pruritus and edema. A change in the infusion rate or the absence of venous return in the aspirate may indicate the occurrence of extravasation. After 2-3 days, erythema increases and there is pain, a brownish discoloration, induration, dry desquamation or the appearance of blisters. If the amount extravasated was small, the signs and symptoms may disappear in the following weeks. If a significant amount was extravasated, the following symptoms may appear in the coming weeks: necrosis, formation of eschar and painful, necrotic ulceration with raised, erythematous borders and a yellowish base. There is generally no granulation tissue with these ulcerations. They may resolve slowly or persist, increasing gradually in area. Involvement of the tendons, nerves and vessels may occur if appropriate treatment is not given, leading to severe sequelae such as nerve compression syndrome, a reduction in joint mobility, contractures, neural deficits and reflex sympathetic dystrophy. Cellulitis and the formation of abscesses are rare events. [47,48]

The interval between detecting the condition and adopting the appropriate measures should be as short as possible. The nursing team should be trained in this respect. Preventive measures should be adopted such as avoiding puncturing emaciated limbs, lower limbs, limbs with multiple punctures, limbs with phlebitis or those that have been subjected to radiation, the ipsilateral limb to a mastectomy, in vena cava syndrome and in veins that protect articulations, nerves and tendons. It is important to evaluate the venous conditions of the patient and, if necessary, to use an indwelling catheter. The use of common needles for venous access should be avoided. Adequate fixation should be performed and blood reflux should be tested, with an infusion of 0.9% saline solution or 5% glucose-saline solution used for every 2 ml of the chemotherapeutic agent. After administration of all the drugs, 20 ml of saline or glucose-saline solution should be infused in order to reduce any possibly toxic residues. Vesicant drugs should always be given first. In prolonged sessions of chemotherapy (those lasting over an hour) with vesicant drugs, central venous access should be used. Always listen to the patient's complaints. If extravasation occurs, stop the infusion immediately. Remove the puncture device and elevate the affected limb. In the case of extravasation of drugs such as etoposide, paclitaxel, vinblastine, vincristine and vinorelbine, apply local heat (leading to vasodilation and dilution of the drug) for 30 minutes and ice (venous constriction and greater degradation of the toxic metabolites in addition to alleviating pain and inflammation) every 30 minutes, 6 times a day in the first 48 hours. For the other drugs, apply ice every 30 minutes, 6 times a day. When indicated, the specific antidote for the drug in question should be used. [49,50]

The use of intralesional corticosteroid and sodium bicarbonate should be avoided. Ulcers that fail to heal may require debridement and grafting. In case of persistent edema and erythema and pain without ulceration that persists despite conservative therapy or in the presence of extensive areas of necrotic tissue or skin ulceration, surgery may be indicated. [51]

OTHER REACTIONS

Periorbital edema

Edema of the eyelids has been described with the use of gemcitabine. [52]

Cutaneous eruption of lymphocyte recovery

Cutaneous eruption of lymphocyte recovery (ELR) is observed in leukemia patients who receive bone marrow ablation. In general, it appears between the 6th and the 21st days after chemotherapy. This point corresponds to the beginning of the recovery of peripheral lymphocytes following the nadir of leukocyte count induced by chemotherapy. Although the exact mechanism has yet to be clarified, it is believed that the eruption is caused by the return of immunocompetent lymphocytes to peripheral circulation with cutaneous cytotoxicity. T-lymphocytes and Langerhans cells are found at histopathological evaluation of these reaction sites. [53,54]

Clinically, the condition consists of pruriginous, erythematous macules, papules or papulous plaques that become confluent. Erythrodermia may occur. In addition, this condition is associated with an elevation in body temperature that occurs together with the appearance of the eruption. The temperature falls in the following 2-3 days and the skin eruption tends to diminish after several days, progressing with desquamation and mild residual hyperchromia. The drugs most associated with these reactions are: cytarabine, daunorubicin, amsacrine, etoposide, cyclophosphamide and vincristine. Differential diagnosis should be made with sepsis, viral exanthems, graft-versus-host disease, leukemia or lymphoma cutis and drug hypersensitivity or toxicity. [55]

Histopathology is nonspecific. The most characteristic findings are superficial perivascular mononuclear cell infiltrate, mild epidermal alterations such as spongiosis, vacuolar alteration of the basal cell layer and loss of keratinocyte maturation secondary to chemotherapy. Dyskeratotic keratinocytes are rare and eosinophils are absent. On occasions in which the patient was treated with granulocyte-macrophage colony-stimulating factor associated with IL-3, atypical lymphocytes with large pleomorphic and hyperchromatic nuclei were found at histopathology. Differentiation may be difficult between ELR and graft-versus-host disease. [56]

Skin toxicity associated with epidermal growth factor receptor tyrosine kinase inhibitors EGFR/TKI

Anti-epidermal growth factor receptors (anti-EGFR) currently consist of panitumumab, cetuximab, erlotinib and gefitinib. Skin toxicity with anti-EGFRs is actually more of a pharmacological effect than a hypersensitivity reaction, since this is a clinical marker of the efficacy of the inhibiting effect of these drugs on the tumor, with the severity of the eruption corresponding to tumor response. [57] The skin effects observed with the anti-EGFR are alterations in capillary growth and in the texture of the hair, paronychia with or without secondary infection or the formation of pyogenic granuloma, generalized asteatosis, skin desquamation and blepharitis. The most characteristic and intense manifestation is a papular-pustular, follicular, comedone or non-comedo (acneiform eruption) that occurs on the head, neck and the central portion of the chest and back, which later disseminates (Figure 3A). There may be pruritus, which differentiates this reaction from the acneiform eruptions caused by corticosteroids, antiepileptic drugs and vitamins B6 and B12. Acneiform eruptions occur in more than 50% of patients in use of cetuximab and this percentage may reach as high as 75% to 100%. The manifestations generally occur in the first weeks (2 days to 6 weeks) after the beginning of treatment (cetuximab and panitumumab). The eruption is dose-dependent; however the duration of the condition does not correlate with the duration of treatment. The acneiform eruptions induced by monoclonal antibodies are more severe and extensive than those resulting from the use of tyrosine kinase inhibitors. Blepharitis caused by anti-EGFR may range from mild to intense (Figure 3B). Table 6 shows the National Cancer Institute's classification of these eruptions. [57,58]

Histopathology of the papular-pustular lesions

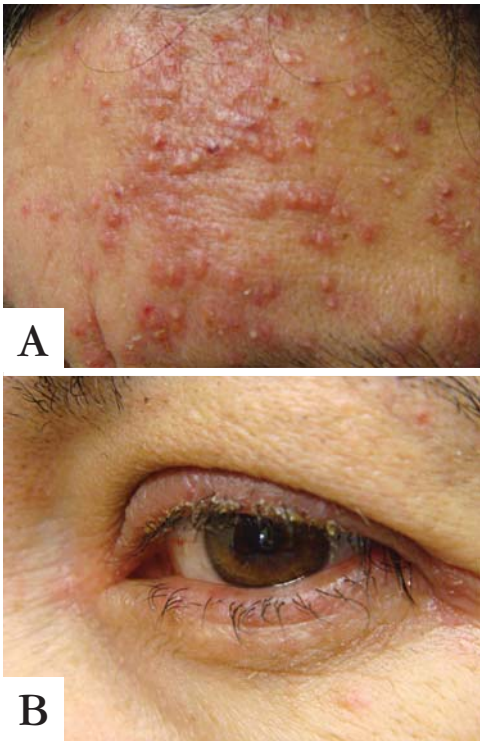

Figure 3: **A.** Papules and pustules on the forehead. **B.** Erythema and scabs on the eyelid rims. Acneiform eruption (A) and blepharitis (B) due to erlotinib, an anti- epidermal growth factor receptor agent (anti-EGFR)

Table 6: Agentes antirreceptores do fator de crescimento epidérmico, classificação das reações e tratamento

Skin toxicity		NCI CTC v 4.0	Tratamento
Desquamation	Grade 1	<10% of total body area affected. No association with erythema or pruritus.	No recommended intervention.
	Grade 2	10-30% of total body area affected. Association with erythema or pruritus.	No recommended intervention.
	Grade 3	>30% of total body area affected. Association with pruritus.	No recommended intervention.
	Grade 4	-	No recommended intervention.
Acneiform eruption	Grade 1	Papules and/or pustules affecting < 10% of total body area. May or may not be associated with symptoms of pruritus or pain.	Intervention not indicated.
	Grade 2	Papules and/or pustules affecting 10-30% of total body area. May or may not be associated with symptoms of pruritus or pain. Associated psychosocial problems.	Topical: benzoyl peroxide, metronidazole, erythromycin, clindamycin ± topical retinoids. Oral tetracycline ± topical retinoids. Oral tetracycline should not be used if paronychia is present, since this may exacerbate the condition. Oral antihistamines if pruritus is present. Modify the dose or therapeutic regimen of anti-EGFR.
	Grade 3	Papules and/or pustules affecting >30% of total body area. May or may not be associated with symptoms of pruritus or pain. Associated psychosocial problems. Local super-infection associated with indication for oral antibiotic therapy.	High-dose of oral tetracycline to reduce the acute inflammation. Oral isotretinoin (may aggravate the paronychia. Do not use concomitantly with tetracycline). Space out the anti-EGFR treatment.
	Grade 4	Papules and/or pustules affecting any percentage of total body area. May or may not be associated with symptoms of pruritus or pain. Extensive super-infection associated with indication for intravenous antibiotic therapy. Risk of death.	Discontinue treatment with anti-EGFR. Possible management in intensive care unit.

shows no increase in sebaceous gland activity, comedones or follicular rupture that would explain the inflammation, differentiating it from acne vulgaris. The follicles are rather wide and at times obstructed by an excess of keratinocytes. In the dermis, neutrophilic infiltrate may be found, particularly involving the follicular infundibulum. Intraepidermal acantholysis may be present in association with the eccrine gland ducts. In the lesions of patients in use of gefitinib, there is an expressive thinning of the stratum corneum layer, with loss of the normal basket-weave pattern. [59] Paronychia occurs in around 10-15% of patients in use of cetuximab and gefitinib, appearing at 6 to 8 weeks of treatment or sometimes after 6 months. It affects various fingers and the first toes. Treatment consists of potent topical corticosteroids. In case of onychocryptosis, anti-EGFR may be temporarily interrupted and canthotomy may be performed. Asteatosis occurs in around 35% of patients, particularly with the use of gefitinib. There is a

predilection for the areas previously or simultaneously affected by acneiform eruption. Some patients have xerosis of the vaginal mucosa, with micturition discomfort. Xerosis may progress to chronic asteatotic eczema, with a greater susceptibility to *Staphylococcus aureus* infection or human herpes virus type 1. Emollients and topical corticosteroids should be used for the eczema. Fissures can be treated with a solution of 50% propylene glycol under plastic occlusion or a hydrocolloid dressing. [57,58]

Other adverse skin reactions found with chemotherapeutic drugs

Various patterns of skin lesions have been reported, the most important of which are described in Table 7.

Table 7: Other adverse skin reactions to chemotherapeutic agents

Adverse reaction	Associated drugs
Acne	Anti-epidermal growth factor receptor agents, dactinomycin, fluoxymesterone, medroxyprogesterone, vinblastine
Acanthosis nigricans	Diethylstilbestrol
Erythrodermia	Chlorambucil / busulfan, cisplatin, methotrexate, intravesical mitomycin C
Fixed drug eruption	Dacarbazine, hydroxyurea, paclitaxel, procarbazine
Lichen planus-like drug eruption	Hydroxyurea
Lichenoid eruption	Hydroxyurea, tegafur
Dermatomyositis-like eruption	Hydroxyurea, tamoxifen, tegafur
Erythema nodosum	Busulfan, diethylstilbestrol
Exacerbation of herpetiform dermatitis	Cyclophosphamide/doxorubicin/vincristine
Folliculitis	Dactinomycin, liposomal daunorubicin, fluorouracil, methotrexate
Raynaud's phenomenon	Bleomycin, bleomycin / vinblastine, bleomycin / vinblastine / cisplatin, bleomycin / etoposide / cisplatin, bleomycin / cisplatin / Velban, bleomycin / vincristine, bleomycin / vincristine / cisplatin, bleomycin / vincristine / doxorubicin, bleomycin / doxorubicin / dacarbazine / vinblastine, nitrogen mustard / vincristine / procarbazine / prednisone, vincristine
Drug-induced lupus	Aminoglutethimide, diethylstilbestrol, hydroxyurea, leuprolide, tegafur
Hirsutism	Diethylstilbestrol, fluoxymesterone, tamoxifen
Bullous pemphigoid	Dactinomycin / methotrexate
Late cutaneous porphyria	Busulfan, cyclophosphamide, diethylstilbestrol, methotrexate
Cutaneous pseudolymphoma	Tamoxifen
Pustulous psoriasis	Aminoglutethimide
Scleroderma-like reaction	Bleomycin, docetaxel
Telangiectasia	Carmustine, hydroxyurea
Leg ulceration	Hydroxyurea, methotrexate

Final considerations

All antineoplastic agents may cause some degree of adverse skin reaction. These agents differ from other drugs used in medicine in two basic points: 1) their objective is to destroy neoplastic cells, and 2) their therapeutic/toxic index is generally very narrow or non-existent, resulting in frequent cutaneous adverse reactions. Therefore, the dermatologist must be capable of recognizing the wide spectrum of adverse reactions to antineoplastic drugs, which often can be mimicked by other drugs used within this clinical scenario such as antibiotics, antiemetics and analgesics. Furthermore, immunosuppressed patients often present with a variety of infectious, neoplastic and paraneoplastic cutaneous events. Unfortunately, only a few antineoplastic agents have mucocutaneous reaction features that are "characteristic" of that group of agents. The dermatologist may be requested to identify these adverse reactions and give an opinion on the decision to be made with respect to whether or not to discontinue use of the drug in question. Table 8 provides guidelines in this respect. Knowledge on morphology and physiopathogenesis therefore become crucial for the diagnosis and management of these adverse reactions. ❑

Table 8: Procedures to be adopted in the case of severe adverse reactions to chemotherapeutic agents

Medicamento	**Manejo após reações adversas graves**
Anthracyclines (doxorubicin, daunorubicin, epirubicin and idarubicin)	Reduce infusion rate, desensitization.
Cyclophosphamide and Iphosphamide	Discontinue
Cytarabine	Discontinue
Platinum compounds [(Platinun): oxaliplatin, carboplatin, cisplatin]	Desensitization
Epipodophyllotoxins (teniposide, etoposide)	Pre-medication with antihistamines and reduce the infusion rate.
L-Asparaginase	Substitute with different preparations; pre-medication with corticosteroids or antihistamines; desensitization.
6-Mercaptopurine e Azathioprine	Desensitization
Methotrexate (MTX)	Premedication with corticosteroids or antihistamines or desensitization.
Procarbazine	Discontinue
Taxanes (paclitaxel and docetaxel)	Premedication with corticosteroids and antihistamines

Adapted from: Pagani M[60]

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