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Cutaneous side effects of oncology treatments Part I. Chemotherapy

There are two therapeutic options for patients with cancer: radiotherapy and chemotherapy. The latter is subdivided into conventional chemotherapy and targeted chemotherapy.

Both categories of chemotherapy treatment induce side effects, although these are more frequent with conventional chemotherapy than with targeted chemotherapy. These side effects are frequently affecting the skin, hair and nails. In this review, all categories of chemotherapeutical drugs are considered and the adverse events related with each drug are described. The most severe events are hypersensitivity reactions, which can endanger the patient's life. Besides, the most common cutaneous reactions will be maculopustular or papulopustular rashes, hand and foot skin syndrome, edema, erythema, hyperpigmentation disorders or photosensitivity reactions. Stomatitis is also frequent on oral mucosa. Regarding hair, anagen effluvium and alopecia are frequently observed, whilst the nails are also affected by many of these treatments. This review describes these side effects and their symptoms and diagnosis, giving tips for prevention and treatment of the same.

Key words

Chemotherapy, side effects, rash, hand foot skin syndrome, stomatitis, alopecia, prevention, treatment.

Introduction

Radiation therapy and chemotherapy, separately or combined, are used worldwide to treat various types of cancers. Despite advances in medical technology, cancer patients experience various treatment-related ailments. Although these side effects are generally not life-threatening, they may have a severe impact on the quality of life of these patients, in particular considering that these latter are psychologically more fragilized by the course of their disease. For this reason, the dermatologists must be able to correctly identify those side effects and bring adequate response to their patients as well in terms of prevention as treatment.

Chemotherapy encompasses the use of conventional chemotherapeutic drugs and the use of targeted therapies.

Traditionally, chemotherapy treatments were using conventional therapeutic drugs which work by disrupting specific phases of the cell cycle in actively dividing cancer cells. Targeted therapies were introduced later (Tamoxifen was the first molecule in this category, dating from the seventies) and block the growth and spread of cancer by inhibiting specific molecules involved in tumour pathogenesis.

Cutaneous side effects of conventional chemotherapy

Conventional chemotherapeutic drugs

These agents are listed in Tabl. 1.

ALKYLATING AGENTS: Cyclophosphamide, ifosfamide and thiotepa

Cyclophosphamide can cause hyperpigmented patches after 4 weeks of therapy that fade within 6 to 12 months after discontinuation [1]. Affected areas are generally palms, soles, nails and teeth, but general skin hyperpigmentation may be observed [2]. On the nails, longitudinal bands, or transverse streaks, onychodystrophy, onycholysis, Beau's lines, Muehrke's lines or onychodermal bands may appear [2].

A similar hyperpigmentation occurs with **ifosfamide,** more likely on the flexural areas, hands, feet, and scrotum, and under occlusive dressings, but also as large pigmented areas on the trunk [1]. It can occur after a single course or many months of therapy, and its course is more capricious that that of cyclophosphamide.

Thiotepa can also provoke hyperpigmentation under occluded areas.

Table 1. **Mechanism of action of conventional chemotherapeutic drugs** (1)

Categories	Products	Mechanism of action
Alkylating agents		
Classical alkylating agents	Cyclophosphamide, ifosfamide, and thiotepa.	Crosslink with DNA molecules and damage cells in all phases of the cell cycle
Platinum agents	Cisplatin, carboplatin and oxaliplatin	
Antimetabolites		
Analogs	Fludarabine, cladribine, gemcitabine, and pemetrexed	Substitute building blocks of DNA and RNA and damage cells in the S phase
Fluorouracil	5-fluorouracil, capecitabine and tegafur	
Antitumour antibiotics		
Anthracyclins	Doxorubicin and daunorubicin	Intercalate with DNA base pairs and interfere with topoisomerase II in all cell cycle phases. Induces DNA strand breaks at G2 phase
Bleomycin		
Mitotic inhibitors		
Taxanes	Docetaxel and paclitaxel.	Prevent the formation of spindles or microtubules during the M phase
Vinca alkaloids	Vincristine, vinblastine and vinorelbine	
Topoisomerase inhibitors		
Topoisomerase I	Topotecan and irinotecan.	Interfere with topoisomerase I or II during DNA replication in all cells in the S or G2 phase
Topoisomerase II	Etoposide, teniposide and amsacrine	

In general, **alkylating agents** may also induce erythema, desquamation and pruritus [3] but also pain and phlebitis at the infusion site [1]. Anagen effluvium, i.e. hair loss induced by an abrupt cessation of mitotic activity in the rapidly dividing hair matrix cells so that either no hair is produced, or a narrowed and defective hair shaft is produced, commonly occurs within 7 to 10 days of initiation of treatment and usually reverts at the end of treatment [2].

Urticarial hypersensitivity reactions were also reported upon administration [2].

ALKYLATING AGENTS:
Cisplatin, carboplatin and oxaliplatin

Cisplatin is the oldest drug in this category and brings many side effects, whilst carboplatin and oxaliplatin are newer and present less side effects [1]. Their extensive use over the decade 2000—2010 has led to a significant increase in the incidence of hypersensitivity reactions [4]. Skin rash, fiushing, abdominal cramping and itchy palms, are common symptoms. Cardiovascular and respiratory complications can prove fatal. Hypersensitivity usually appears after multiple infusions, suggesting type I allergic reactions; however, other types of hypersensitivity also seem to be implicated [4]. Allergic patients can be managed with a slower infusion rate and premedication with antihistamines and corticosteroids and desensitization can also be performed [1]. Cisplatin produces hyperpigmentation in around 70 % of patients, which can be localized or patchy and can affect the hair, nails, and oral mucosa. This risk increases with subsequent courses [1]. Anagen effluvium and permanent alopecia may also be consequences of treatments with cisplatin [5].

ANTIMETABOLITES:
Fludarabine, cladribine, gemcitabine and pemetrexed

Paraneoplastic pemphigus, a severe mucocutaneous disease associated with B-cell lymphoproliferative disorders, was reported in patients under treatment with **Fludarabine** [6]. The bullous lesions appeared after 1 to 9 pulses of fludarabine and after 2 to 14 days from its administration. Lesions improved after the administration of immunosuppressive drugs and the withdrawal of fludarabine. Hypothesized possible mechanisms are the induction of particular autoantibodies to the skin by fludarabine or the induction of drug-induced antitumor antibodies that cross react with epidermal proteins [6]. Less severe reactions such as rash, stomatitis, and acral erythema may also occur upon administration of fludarabine [1].

With **cladribine,** 21 % of patients developed a disseminated eruption during the month following the initiation of treatment [7], with toxic epidermal necrolysis in few of them.

A high frequency of skin rash (51 %) was also reported in a group of patients with hairy cell leukemia treated with cladribine. An increased rate of drug hypersensitivity, possibly due to T-cell imbalance induced by cladribine was found among these patients and a desensitization protocol was considered in their case [8].

Skin reactions occur in 25 to 39 % of patients treated with **gemcitabine**, including alopecia and maculopapular rash [1]. One case of induced acute lipodermatosclerosis-like reaction was reported in a patient under treatment with this drug [9], but also cases of bullous reactions [10] or Stevens-Johnson syndrome [11].

In a phase II study with **pemetrexed,** 79 % of patients developed a pruritic generalized rash, 39 % with a grade 3 [12]. In another report, cutaneous reactions occurred in 35 % of patients, followed by periorbital and leg edema [13]. In fewer cases, asteatotic eczema, hyperpigmentation of the palms and soles, urticarial vasculitis, melanonychia with onycholysis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and radiation recall dermatitis were observed [1].

ANTIMETABOLITES:
5-Fluorouracil, capecitabine and tegafur

Treatments with these drugs are the most common cause of Hand-Foot Syndrome (HFS). HFS, also named palmoplantar erythrodysesthesia or acral erythema, features well demarcated reddening, swelling, numbness and desquamation on palms of the hands and soles of the feet (and, occasionally, on the knees, elbows, and elsewhere). HFS grading and management include: grade 1 (i. e., mild erythema and slight or no dysesthesia) managed with supportive care, topical steroids, and urea; grade 2 (i. e., skin redness, dysesthesias, and pain) managed with topical steroids, keratolytics, and nonsteroidal anti-inflammatory drugs; and grade 3 (i. e., severe blistering, desquamation, pain, and impaired function) managed with drug discontinuation [14].

Premedication with pyridoxine and/or oral dexamethasone are advised by some authors [15]. There is higher incidence of HFS with capecitabine (53 %) than with 5-FU (6 %) than with tegafur (2 %) [1]. Hyperpigmentation from 5-FU is quite common and can have a varied appearance, including the following: (1) photodistributed, (2) serpentine supravenous hyperpigmentation from hand to shoulder, (3) widespread reticulate hyperpigmentation, (4) serpentine streaks in the back and buttocks and (5) acral pigmentation [1]. This pigmentation can occur after several sessions of therapy and may fade gradually over time and may not recur in subsequent infusions [1].

The cutaneous adverse effects of capecitabine and tegafur also include mucositis, photosensitivity, diffuse or nail-restricted hyperpigmentation, palmoplantar keratoderma, sclerodactyly and Raynaud phenomenon [16]. Alopecia and stomatitis occur in 5-FU patients (21 and 62 %, respectively) and less commonly in patients who are taking capecitabine (6 and 24 %, respectively) [17]. Inflammation of actinic keratosis and radiation recall have also been well documented from use of 5-FU and capecitabine [1]. Radiation recall is a severe skin reaction occurring with certain chemotherapy drugs where the rash appears like a severe sun burn. Cases of subacute and discoid cutaneous lupus have also been reported [1].

ANTITUMOR ANTIBIOTICS:
doxorubicin and daunorubicin

HFS from both anthracyclines presents similarly as HFS caused by antimetabolites. HFS occurs in 29 to 49 % of doxorubicin patients, and less commonly with daunorubicin [18].

Its onset is within the first 2 to 3 cycles of treatment, and it is usually self-limiting, with resolution reported within 1 to 5 weeks of medication discontinuation [19]. Alopecia may occur in 7 % of patients, and mucositis in 37 % of patients treated with liposomal doxorubicin [20]. Other uncommon skin reactions may include diffuse follicular rash, intertrigo-like eruption in the axilla, groin, and waist, melanotic macules on the trunk and extremities, and radiation recall [21].

ANTITUMOR ANTIBIOTICS: bleomycin

A common side effect in bleomycin treatments is flagellate dermatitis, which shows very characteristic lesions: linear erythema or hyperpigmentation in various areas of the skin. It occurs in 20 to 30 % of patients who are taking bleomycin and can appear 12 to 24 hours up to 6 months after drug induction [22]. The lesions are self-limiting with the cessation of the drug and recur upon reexposure; recurrence is often more severe and widespread [1]. Several cases of Raynaud's phenomenon have been reported during combination chemotherapy involving bleomycin and also following local intralesional injections of bleomycin for recalcitrant warts [23]. Raynaud's phenomenon can be induced independently of the method of administration or dosage of bleomycin, may be persistent or temporary, and is limited to the fingers that have been injected. It has been suggested that bleomycin causes vascular endothelial cell injury, especially in small blood vessels, which may account for the development of Raynaud's phenomenon [23]. Systemic scleroderma changes have been reported to occur in patients during or following systemic chemotherapy involving bleomycin [23]. On the other hand, bleomycin is one of the chemotherapeutic agents known to cause alopecia and has also been associated with nail pigmentation. The pigment is deposited in horizontal or vertical bands, which may be brown or blue, and generally grow out with the nail [23].

MITOTIC INHIBITORS: paclitaxel and docetaxel

A distinct subtype of HFS, in which erythematous plaques develop on the dorsal surfaces of the hands, Achilles tendon, and malleoli, has been reported with paclitaxel and docetaxel in 10 and 5 % of patients, respectively [1]. A review about nail toxicity of paclitaxel and docetaxel includes onycholysis, Beau lines, onychomelanosis, and subun-

Table 2. **Targeted therapy drugs** (25)

Categories	Products	Mechanism of action
Signal transduction inhibitor	Imatinib	bcr-abl, c-kit, and PDGFRs
Multikinase inhibitor	Dasatinib	bcr-abl, c-kit, PDGFRs, Src, and ephrin receptor kinase
	Nilotinib	bcr-abl, c-kit, and PDGFRs
EGFR inhibitor	Gefitinib and erlotinib	Intracellular domain of the EGFR
	Cetuximab and panitimumab	Extracellular domain of the EGFR
Vismodegib		Inhibits smoothened (SMO) receptor
Apoptosis-inducing inhibitor	Bortezomib	Inhibits degradation of κB-protein and prevents NF-κB activation
Angiogenesis-inducing inhibitor	Sorafenib	Raf, c-kit, PDGFR-b, VEGFRs 2 and 3, FMS-like tyrosine kinase 3 (Flt-3), and RET receptor tyrosine kinase
	Sunitinib	VEGFR 1-3, PDGF-a, c-kit, Flt-3, colony stimulating factor-1, and the glial cell line-derived neurotrophic factor receptor
Immunomodulator	Ipilimumab	CTLA-4
Gene therapy	Vermurafenib	BRAF V600E
	Dabrafenib	BRAF V600E
	Trametinib	MEK1 and MEK2

gual haemorrhage associated with paronychia [24]. Hypersensitivity reactions, radiation recall, photosensitivity, subacute cutaneous lupus erythematosus and scleroderma may also occur [1].

MITOTIC INHIBITORS:
vincristine, vinblastine and vinorelbine

Alopecia, maculopapular rash, erythema multiforme-like lesions and HFS have been reported when treatment with these drugs [1].

TOPOISOMERASE INHIBITORS:
topotecan and irinotecan

These drugs were reported as susceptible of causing hair loss [1].

TOPOISOMERASE INHIBITORS:
etoposide, teniposide and amsacrine

Alopecia and allergic reactions are the major side effects suffered by treatments with these molecules [1].

Cutaneous side effects of targeted therapies

The drugs part of this category are normally more effective and less harmful than conventional chemotherapeutic drugs.

They are listed in Tabl. 2.

SIGNAL TRANSDUCTION INHIBITORS:
imatinib, dasatinib, and nilotinib

Cutaneous reactions are one of the most common nonhematological side effects of imatinib and are reported in 7 to 88.9 % of patients in different series [26]. Their occurrence and severity are dose dependent: studies noted a 7 % incidence of skin rash in patients treated with an almost noneffective dose of 25—140 mg/day of imatinib compared to a rate of 21—88 % in patients treated with 400—800 mg/day [26]. On the contrary, fewer side effects are noted with the newer drugs dasatinib and nilotinib (respectively 13—24 % and 35 %) [26].

Superficial edema of mild to moderate severity, mainly localized to the face and particularly the eyelids, occurred in 48—65 % of patients treated with imatinib [27, 28].

Erythematous maculopapular rash is another cutaneous side effect of imatinib, usually involving forearms, trunk and less frequently the face, tending to be mild and self-limiting [26]. Its incidence was reported as 66.7 % of patients in a published study [27]. In other studies with patients under treatment with dasatinib [29] the incidence was only 28 % and 11—27 % in treatments with nilotinib [30]. This rash is often accompanied by **pruritus**, which is also a side effect of treatments with nilotinib (reported incidence of 24 % [30]).

Pigmentary changes, under the form of localized patchy or diffuse hypopigmentation and depigmentation are often reported in treatments with imatinib [26]. Incidence of this ailment may reach 41 % of treated patients [28], affect more likely patients with high phototypes and are usually reversible after discontinuation of therapy. Patchy hyperpigmentation may also occur secondary to imatinib treatment, but with a lesser incidence (3.6 %) [28]. These side effects, to the best of our knowledge, were not described with dasatinib and nilotimib.

Skin dryness is quite common during imatinib treatments; its incidence was rated as 31.5 % in a study [27]. This incidence appears to be lower with nilotinib (13—17 %) [29] and was not reported for dasatinib.

A mucosal/cutaneous **lichenoid eruption** was reported in about 15 imatinib-treated patients to date [26]. All these eruptions were considered as dose-related, and lesions developed 1—12 months after drug initiation. Such side effects were not reported with dasatinib and nilotinib.

Psoriasiform rash/psoriasis are sometimes described upon imatinib treatment, affecting predominantly the scalp, arms and trunk [26], and subsided with discontinuation or reduction of imatinib therapy. Its incidence was 7.4 % in an afore mentioned study [27]. No such side effect is usually noted with dasatinib and nilotinib.

Pytiriasis rosea was described at least in three cases of imatinib treated patients, but not in individuals treated with the other two molecules [26].

For **acute generalized exanthematous pustulosis** the situation is quite similar to that of pytiriasis rosacea. Anyhow it's not a frequent side effects with these drugs [26].

Stevens-Johnson syndrome was also reported only with imatinib in a few cases [26].

SIGNAL TRANSDUCTION INHIBITORS: gefitinib, erlotinib, cetuximab and panitumumab

Papulopustular rash appears about a week after initiating EGFRI therapy, and occurs in 24 to 62 % or patients taking gefitinib, 49 to 67 % of patients taking erlotinib, and 75 to 91 % of patients taking cetuximab [31]. An acneiform eruption affects the scalp, face, chest, back and less commonly, the extremities, lower back, and abdomen [31].

Paronychia is the second most common reaction to EGFRIs and occurs in the nails and digits, with the first digit being the most commonly affected. Reactions may present as nail discoloration, pitting, paronychia, periungual pyogenic granuloma, cracked and swollen nail folds and cuticles, ingrowth of nails, and the partial or complete loss of nails [31]. These appear 1 to 2 months after beginning treatment and occur in 10 to 15 % of patients.

Hair changes: Hair may become finer, brittle, curled, or slow in growth, and alopecia may follow several months into therapy [31]. Hypertrichosis, facial hirsutism, and trichomegaly may also occur. These changes are only temporary and normal hair growth reappears only after one month of discontinuation of the medication [31].

Unfortunately, **pruritus** occurs in about half of patients following these treatments [26].

Skin dryness appears over time and is reported in 35 % of patients under these treatments and may in some cases result in asteatotic eczema and acral fissures [32].

Anaphylaxis occurs in 1.2 to 3.5 % of patients taking cetuximab and 1 % of patients taking panitumumab [31].

SIGNAL TRANSDUCTION INHIBITORS: vismodegib

Treatments with this drug are particularly prone to cause alopecia (up to 63 % of patients) [26].

APOPTOSIS-INDUCING INHIBITORS: bortezomib

Cutaneous reactions secondary to bortezomib affect 10 to 24 % of patients and are variable in presentation (rash is the most common presentation, but also erythematous nodules and plaques) [33].

ANGIOGENESIS-INDUCING INHIBITORS: Sorafenib and sunitinib

Cutaneous reactions to this class of drugs are common, and in a prospective study, were found to occur in 74 % of patients taking sorafenib and 81 % of patients taking sunitinib [34].

The most common is **HFS** occurring in 10 to 62 % of patients taking sorafenib and 10 to 28 % of patients taking sunitinib [35]. Different from HFS occurring with conventional drugs, it features painful localized patches developing on friction and trauma-prone areas, such as the heel, lateral aspects of the soles, and web spaces. Lesions appear during the first 2 to 4 weeks of treatment [35].

Stomatitis is the second most common cutaneous reaction from treatment with sorafenib (26 %) and sunitinib (36 %) [34].

Alopecia begins 2 to 28 weeks after the onset of therapy and occurs in 26 % of patients taking sorafenib and 6 % of patients taking sunitinib [34]. Sunitinib may also cause depigmentation of hair in 10 % of patients occurring after 5—6 weeks of treatment and returning to normal 2 to 3 weeks after cessation [34].

Seborrheic dermatitis-like **facial erythema** is reported in 63 % of patients taking sorafenib and, to a lesser extent, with sunitinib [34]. It appears early in the course of treatment and resolves less than 2 months after drug discontinuation.

Fingernail subungual splinter hemorrhages develop in 70 % of patients taking sorafenib and 25 % of patients taking sunitinib. They present during the first 2 months of therapy and resolve spontaneously without treatment [34].

Yellow skin pigmentation occurs in 28 % of patients taking sunitinib since the beginning of treatment and spontaneously resolves upon termination of the same [34].

Development of new **squamous cell carcinomas** was reported in 10 % of patients taking sorafenib

[36]. Inflammation of existing lesions of actinic keratoses was also reported by the same authors.

IMMUNOMODULATORS: ipilimumab

Dermatitis and pruritus are the most common adverse events observed with this drug. Cutaneous reactions usually occur 3—4 weeks after drug initiation in 47 to 68 % of patients, and severe reactions were found to affect 4 % of patients [37]. These reactions are located over the proximal extensors, trunk, and sometimes head.

GENE THERAPY: vemurafenib and dabrafenib

Cutaneous reactions are the most common toxicity with these drugs, affecting 74 % of patients [38].

Exanthematous rash affects 15 to 18 % of patients taking vemurafenib and 27 % of patients taking dabrafenib [39]. This rash features papulopustular lesions, developing on the face, torso, and arms. The lesions appear in the first few months of therapy and clear with dose interruption or reduction.

12 and 8 % of patients treated with vemurafenib and dabrafenib respectively develop **squamous cell carcinoma** and keratoacanthoma between 2—14 weeks from the beginning of treatment [39]. **Acantholytic dermatosis, seborrheic keratosis, verruca vulgaris**, and **hypertrophic actinic keratosis** may also be observed [40].

Photosensitivity occurs in 7 to 12 % of patients under treatment with vemurafenib [39].

Alopecia was reported in 8 to 36 % of patients under these treatments, whilst **plantar hyperkeratosis** occurs in 9 to 10 % of patients taking vemurafenib and 20 % of patients taking dabrafenib [41]. For h**yperkeratosis** the incidence is 8 to 29 % of patients taking vemurafenib and 27 to 49 % of patients under dabrafenib [41].

GENE THERAPY: trametinib

Skin toxicity with this drug is reported in 13—20 % of patients, essentially under the form of **exanthema** [26].

Prevention of cutaneous side effects of oncology treatments

The prevention of cutaneous side effects is essential to improve the quality of life of patients undergoing these treatments, and thus makes easier the good compliance and avoid further reductions in doses that could affect the correct outcome of treatment.

Regarding **hypersensitivity reactions**, which is probably the most critical cutaneous side effect, when the drug to be administered is known as a potential cause of cutaneous hypersensitivity, as this is the case for platinum derivates, previous intradermal testing is probably the best solution [4]. Systematic premedication with corticosteroids and antihistamines can also be a good decision. **Dry skin** is also a common side effect in cancer treatments. Patients should be advised about the risk and to use systematically skin moisturizers in order to prevent as far as possible this side effect. Concerning **cutaneous rash**, which is another frequent ailment in cancer patients, a good prevention consists in preventive administration of antihistamines and also use of topical antioxidants all over the treatment. **Alopecia** is an almost constant side effect of chemotherapeutic treatments and strongly affects the patient's quality of life and self-esteem. Although hair loss caused by chemotherapy is almost always reversible with regrowth, occurring once the administration of the toxic agents has ceased, prevention can be considered in order to minimize this inconvenience. Measures to decrease hair loss have met only limited success. Scalp hypothermia and scalp tourniquets used to decrease the amount of drug reaching the hair follicles may delay or diminish the onset of hair loss but will not prevent it completely [2]. 2 % minoxidil has shown to be ineffective in preventing chemotherapy-induced alopecia [42]. Preventive measures for **stomatitis** include maintaining oral hygiene through brushing, flossing, and rinsing with water, saline, sodium bicarbonate, or hydrogen peroxide [43]. Cooling with ice chips or ice water to prevent mucositis induced by fluorouracil and high-dose melphalan has also been successful [43]. For the prevention of **pigmentation disorders** and **photosensitivity**, the recommendation of a compulsory photoprotection with a sunscreen SPF 30 or more until the end of treatment is necessary. The same recommendation must be done to patients affected by **seborrheic or actinic keratoses** previous to the treatment. Prevention of **acral erythema** may be obtained with the application of ice water to the acral regions during chemotherapy infusion to decrease blood flow to the hands and feet, thereby preventing drug accumulation at these sites [2].

Treatment of cutaneous side effects of oncology treatments

Treatment of **stomatitis** is essentially supportive. This includes meticulous oral care as well as the application of topical coating agents such as attapulgite, magnesium/aluminium hydroxide products and vitamin E [2]. In addition, topical anaesthetic agents such as diphenhydramine elixir, dyclonine hydrochloride, benzocaine, and lidocaine viscous are frequently used [44]. Oral pain medications such as acetaminophen, propoxyphene, or paracetamol/codeine, and intravenous pain medications such as morphine sulphate, may be necessary to

palliate the symptoms of severe mucositis [43]. Because of the high risk of infection, patients with stomatitis must be routinely assessed for the onset of infection and immediately consult a physician in such case. Then systemic antibiotics are the rule.

Pigmentation disorders treatment is well-known by the dermatologist. Hydroquinone 4 % or azelaic acid 15 % are the most common treatments of hyperpigmentation occurring during chemotherapeutic treatments.

Other than cessation of chemotherapeutic treatment, there is no therapy for **acral erythema** that has been proven to be effective in large-scale clinical trials [2]. Small-scale studies and anecdotal evidence point to the usefulness of oral pyridoxine 150mg/day in the treatment of this disorder [45]. Corticosteroids have also been suggested as treatment for AE, but their use has been associated with equivocal success rates [2].

Radiation recall clears spontaneously within hours to weeks of cessation of chemotherapeutic treatment. Its management uses to be symptomatic [2]. Systemic corticosteroids in conjunction with discontinuation of the drug will often produce dramatic improvement and may even allow for continuation of the chemotherapeutic regimen [47].

Treatment of **photosensitivity** includes discontinuation of the offending agent and avoidance of direct sunlight with protective clothing and sunscreens for at least 2 weeks [48]. Cool, wet dressings such as ice-cold compresses of Burow's solution, systemic antihistamines, and topical corticosteroids will provide symptomatic relief; however, in severe cases, systemic corticosteroid therapy may be necessary [48].

In case of **hypersensitivity reaction,** first cessation of the causative agent is needed. Treatment is predicated on the severity of the symptoms, both cutaneous and systemic. Corticosteroids are used for both treatment of symptoms and prevention of progression. For milder cases, systemic corticosteroids dosed at 0.5 to 1 mg/kg/day and tapered over 6 to 8 weeks are recommended [49]. For Stevens-Johnson Syndrome, 1 mg/kg/day of prednisolone or 1 to 2 mg/kg/day of methylprednisolone is recommended [49]. For patients with extensive skin involvement, supportive care in an acute burn or intensive care unit is recommended for life support measures, pain management, and prevention of infection [50].

Edema is managed with low salt diet, diuretics, and topical phenylephrine 0.25 % ophthalmic drops for periorbital edema [26].

In **maculopapular rash,** patients can be managed with topical or oral steroids and antihistamines [26].

Mild cases of **Papulopustular rash** can be treated with medium to high potency topical steroids, topical clindamycin, or erythromycin; oral minocycline and doxycycline are recommended for more advanced cases [32]. Isotretinoin can be useful in cases that are not responsive to antibiotic therapy [51].

Warm compresses, silver nitrate, topical corticosteroids, and systemic tetracyclines may also be used to reduce **periungual inflammation** [32].

In case of **itch**, gentle skin care using cool or lukewarm baths (instead of hot showers), mild soap, fragrance and alcohol-free emollients, sunscreens, and sun avoidance are advised [32]. Systemic antihistamines, doxepin, pregabalin, and gabapentin may also be given for relief of itchiness [32].

Skin dryness will be treated obviously by application of moisturizers and emollients; bathing using tepid water and mild soap are advised. For fissures, protective covering for the feet and hands help prevent additional skin injury and promote healing [32].

The treatment of **Hand-Foot Skin Reaction** depends on its grade. Grade 1 reactions with minimal skin changes require supportive management, such as protective gloves and footwear to minimize friction, and the use of topical keratolytic medications, such as urea or tazarotene [32]. Grade 2 reactions, which include painful skin changes that limit activities of daily living, can be treated with pregabalin or nonsteroidal drugs to help with pain, topical clobetasol, and topical lidocaine [32]. Grade 3 reactions need interruption of at least 1 week or until symptoms become minimal [32].

Conclusions

The drugs used by oncologists for treating their patients are various, and most of them are causing adverse effects, some of them affecting particularly the skin, hair or nails. For this reason, the dermatologist will be frequently asked about such side effects by patients under oncological treatment. He (or she) must know about these side effects, their correct diagnosis and be able to bring them adequate treatment, all the more because these ailments are deeply affecting the patient's quality of life. Radiotherapy is another option for the treatment of cancer which has not be mentioned in this paper. Radiotherapy has also side effects and these and their treatments will be approached in a further article.

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Шкірні побічні ефекти онкологічного лікування Частина І. Хіміотерапія

Існує два терапевтичних шляхи для пацієнтів онкологічного профілю: променева терапія і хіміотерапія. Останню поділяють на традиційну і цільову.

Обидві категорії хіміотерапевтичного лікування дають побічні ефекти, хоча вони частіше бувають у разі традиційної хіміотерапії, ніж цільової. Ці побічні ефекти часто впливають на шкіру, волосся і нігті. У цьому огляді розглянуто всі категорії хіміотерапевтичних препаратів та описано побічні впливи, пов'язані з кожним лікарським засобом. Найтяжчими є реакції гіперчутливості, які можуть загрожувати життю пацієнта. Крім того, найпоширенішими нашкірними реакціями є макулопустулярний або папулопустульозний висип, синдром шкіри долонь і стоп, набряк, еритема, гіперпігментаційні розлади або реакції фоточутливості. Стоматит також часто уражує слизову оболонку порожнини рота. Що стосується волосся, то часто бувають анагенне випадіння волосся і алопеція, крім того, багато з цих процедур також впливають на нігті. У пропонованому огляді описано ці побічні ефекти, їхні симптоми і діагностику, рекомендації щодо профілактики та лікування.

Ключові слова: хіміотерапія, побічні ефекти, висип, синдром шкіри долонь і стоп, стоматит, алопеція, профілактика, лікування.

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Кожные побочные эффекты онкологического лечения Часть I. Химиотерапия

Существует два терапевтических пути для пациентов онкологического профиля: лучевая терапия и химиотерапия. Последняя подразделяется на традиционную и целевую.

Обе категории химиотерапевтического лечения вызывают побочные эффекты, хотя они чаще встречаются при традиционной химиотерапии, чем при целевой. Эти побочные эффекты часто влияют на кожу, волосы и ногти. В этом обзоре рассматривают все категории химиотерапевтических препаратов и описаны побочные проявления, связанные с каждым лекарственным средством. Наиболее тяжелые – реакции гиперчувствительности, которые могут угрожать жизни пациента. Кроме того, к наиболее распространенным кожным реакциям относятся макулопустулярная или папулопустулезная сыпь, синдром кожи ладоней и стоп, отек, эритема, гиперпигментационные расстройства или реакции фоточувствительности. Стоматит также часто встречается на слизистой оболочке полости рта. Что касается волос, то часто отмечаются анагенное выпадение волос и алопеция, многие из этих процедур также влияют на ногти. В предлагаемом обзоре описывают эти побочные эффекты, их симптомы и диагностику, рекомендации по профилактике и лечению.

Ключевые слова: химиотерапия, побочные эффекты, сыпь, синдром кожи ладоней и стоп, стоматит, алопеция, профилактика, лечение.

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