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Dermatologic Adverse Events in Oncologic Therapies

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ABSTRACT During recent decades, the number of patients diagnosed with cancer has been increasing. Conventional treatments, which comprise chemotherapy, radiotherapy, surgery, and hormonal treatment, represent improvements in effectiveness and safety of administration and continue to be the standard model of treating malignancies. Advances in oncology have enabled the development of newer therapies such as immunotherapy and targeted therapy. However, numerous adverse events continue to emerge, including dermatologic adverse events, which significantly impact the course of treatment, treatment outcomes, and patient quality of life. Alopecia occurs most commonly, along with mucositis, xerosis, pruritus, hyperpigmentation, acral erythema, nail changes, and many others. The early detection, monitoring, and adequate treatment of these adverse events could prevent reduction, interruption, or permanent discontinuation of oncologic therapies. Herein we review various dermatologic adverse events that may occur due to the therapy applied, present their possible treatments, and emphasize the need to evaluate their impact on patient quality of life.

KEY WORDS: cancer treatment, dermatologic adverse events, quality of life

INTRODUCTION

Cancer is one of the leading health care challenges in the world. According to the International Agency for Research on Cancer (IARC), an estimated 19.3 million new cases were diagnosed worldwide in 2020. During the same year, 2.7 million new cases occurred in the European Union, according to the European Cancer Information System (ECIS), of which 25 thousand cases occurred in Croatia (1-3).

The overall cancer survival rate has been slowly increasing. For example, survival has increased by up to 5% for liver, pancreas, and lung cancer during 2000-14 in some countries. The 5-year survival rate for women diagnosed with breast cancer from 2010-14 was 85% or higher in 16 European countries (4,5). This confirms that great strides have been made over recent decades in cancer treatment, including chemotherapy, radiotherapy, surgical treatment, and hormonal therapy. In addition, remarkable achievements are being made with newer therapeutic options such as immunotherapy and targeted therapy. However, unexpected adverse events (AEs) continue to emerge, especially numerous dermatologic AEs

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that significantly impact the quality of life (QoL) of patients with cancer, which have become an essential part of the overall care of patients with cancer (6).

The aim of this review was to describe various dermatologic AEs that may occur as a result of the applied therapy, highlight possible treatments, and assess their impact on patient QoL.

CHEMOTHERAPY-RELATED ADVERSE EVENTS

Hypersensitivity reactions

The vast majority of hypersensitivity reactions are IgE-mediated type I reactions, which generally occur within 1 hour of administration of the causing agent and present with urticaria, angioedema, pruritus, and life-threatening anaphylaxis (7). The two most common classes of chemotherapeutic agents that cause hypersensitivity reactions are platinum drugs and taxanes. Risk factors for developing hypersensitivity reactions to platinum drugs include younger age, female gender, atopy, repeated exposure of the same platinum drug, and a longer interval between administration of platinum drugs (8). Clinical manifestations of taxanes are moderate in severity and include urticaria, morbilliform rash, angioedema, and pruritus. However, severe anaphylactoid reactions are also possible. It is believed that solvents for paclitaxel and docetaxel (Cremophor EL and Polysorbate 80), which may activate, complement, and trigger basophil and mast cell activation, respectively, play an essential role in the underlying mechanism of hypersensitivity reactions (9-11). Patients require pretreatment with steroids and antihistamines before each drug administration (12). If platinum drugs or taxanes are first-line therapy, drug desensitization should be considered (13).

Extravasation

The overall incidence of drug extravasation is low and is estimated to be from 0.01% to 7.00% (9). According to the type of local reaction, chemotherapeutic agents are classified as irritants or vesicants. Irritants are agents that cause an inflammatory reaction, pain, erythema, paresthesia, or phlebitis at the injection site or along the venous pathway. The symptoms are generally of short duration and leave no necrosis or any other skin sequelae. The drugs most frequently associated with this adverse event (AE) are fluorouracil, cisplatin, carboplatin, cyclophosphamide, paclitaxel, docetaxel, and etoposide. In contrast, vesicants agents, such as doxorubicin, daunorubicin, vinblastine, vincristine, vinorelbine, paclitaxel, and docetaxel, can cause long-lasting and more severe tissue damage, including necrosis of the surrounding area. The initial symptoms are often subclinical and may include local burning, paresthesia, edema, erythema, and pruritus, whereas increased erythema, pain, dry desquamation, blisters, necrosis, and local skin destruction may appear later, after 2-3 days (14,15). Chemotherapeutic agents do not always belong to a specific category because clinical presentation depends on the drug's concentration, volume, and solvent. For example, taxanes, which belong to the category of irritants, appear to show low vesicant potential (16). Finding appropriate venous access and avoiding small caliber or fragile veins is of the utmost importance in preventing extravasation. Treatment begins with immediate cessation of the infusion and elevation of the affected limb to decrease hydrostatic capillary pressure. Cold and warm compresses may be applied because the warmth causes vasodilatation and absorption of the extravasated drug, whereas coldness causes constriction of the veins, reducing the drug's further spread. Antidotes for specific drugs can also be administered (17).

Alopecia

Alopecia is the most common dermatologic AE of chemotherapy, with an estimated incidence of 65%. Clinical presentation depends on the drug dose, combination regimen, duration of treatment, and patient-related aspects such as age, comorbidities, and hormonal and nutritional status. Based on the type of chemotherapeutic agent used, incidence of alopecia higher than 80% has been reported with anti-microtubule agents, 60-100% with topoisomerase inhibitors, more than 60% with alkylating agents, and 10-50% with antimetabolites (18,19). Since 90% of scalp hairs are in the anagen phase, chemotherapeutic agents most commonly produce anagen effluvium with a diffuse pattern within 7-10 days of initiation of chemotherapy. Hair loss is almost always reversible, and regrowth begins within 1-3 months after cessation of chemotherapy, although it can present with a difference in texture, color, and thickness (7,19,20). However, if hair growth is absent six months after cessation of chemotherapy, permanent alopecia occurs, with a higher risk with busulfan and cyclophosphamide, taxanes and radiotherapy (19). In addition, permanent alopecia can be associated with depression, anxiety, and increased somatization and thus significantly affect a patient's QoL (21). Topical 2% minoxidil solution shortens the duration of drug-induced alopecia, but it is ineffective in preventing alopecia (22). Scalp cooling is a valuable option to prevent alopecia. It causes local vasoconstriction, hypoperfusion, and reduction of intrafollicular metabolic rate,

leading to reduced follicular exposure to harmful cytotoxic effects. However, headaches, nausea, and dizziness can occur, and it is not indicated for patients with cryoglobulinemia and hematologic tumors, who are at higher risk for cutaneous metastases (19,22).

Mucositis

Mucositis is a significant, often dose-limiting AE. Specific drugs most frequently associated with mucositis are bleomycin, doxorubicin, daunorubicin, docetaxel, fluorouracil, and topotecan. Changes in nonkeratinized mucosa are observed 4 to 7 days after administration of the chemotherapeutic agent and present with erythematous, edematous, and ulcerated oral mucosa. Initial symptoms include pain, burning, and xerostomia, followed by bleeding, infection, weight loss, and malnutrition. Moreover, focal ulcerations may become diffuse and confluent, and occasional vesicles and blisters may appear. Patients at a higher risk of mucositis include those with hematologic malignancies, other comorbidities, patients under 20 years of age (high mitotic activity of the epithelium), and those who do not practice adequate oral hygiene. Resolution of lesions often occurs spontaneously after 3-4 weeks (7,23). Prevention includes maintaining adequate oral hygiene. For preventing and treating mucositis, dexamethasone mouthwash formulation has shown effectiveness and suitability, along with palifermin, chlorhexidine, royal jelly, zinc supplement, cryotherapy, and laser therapy (24,25).

Acral erythema

Acral erythema is also known as palmoplantar erythema, hand-foot syndrome, Burgdorf's syndrome, and toxic erythema of the palms and soles (23). It occurs most commonly in patients treated with cytarabine, fluorouracil, doxorubicin, and less commonly with cisplatin, cyclophosphamide, paclitaxel, and docetaxel (7). Although the pathogenesis is not well understood, it is believed that direct tissue damage occurs due to the high concentration and accumulation of cytotoxic drugs in eccrine sweat glands in palms and soles (26). Acral erythema affects the palmar and dorsal surface of the hands more often than the soles and dorsa of the feet. Clinical manifestations of the prodromal phase include dysesthesia and a tingling sensation on the palms and soles, which progresses to pain, tenderness, and edema associated with symmetric and well-demarcated erythema (23). The erythema develops on lateral phalanges or the thenar or hypothenar eminences, whereas the swelling appears on distal phalanges (7). If therapy continues, lesions tend to aggravate, causing pain and edema limiting the movement of fingers. With the cessation of therapy, lesions usually disappear within two weeks (23). There is no specific treatment other than dose reduction, prolongation of the dosing interval, and withdrawal of the drug. Symptoms can be relieved by applying cold compresses, emollients, topical corticosteroids, and oral analgesics (9). Celecoxib appeared to be a promising agent for preventing acral erythema, whereas pyridoxine showed no advantage (27).

Pruritus

Almost all chemotherapeutic agents can cause pruritus, most commonly due to drug effects on the sebaceous and sweat glands, resulting in dry skin and itching. Patients present with secondary cutaneous lesions, including excoriations, lichenification, and differences in pigmentation. Prurigo nodularis can also develop due to chronic skin scratching, which generally appears on the extensor surfaces of extremities. Topical treatment for pruritus includes emollients, menthol and capsaicin creams, topical corticosteroids, topical local anesthetics, and topical immunomodulators tacrolimus and pimecrolimus. Systemic treatment includes antihistamines, antidepressants, opioid agonists and antagonists, GABA agonists, gabapentin, and pregabalin (28).

Eccrine squamous syringometaplasia

Eccrine squamous syringometaplasia histologically describes the transformation of the cuboidal epithelium of the eccrine duct into squamous epithelium. Although this AE was reported in other conditions such as chronic ulcerations, malignant and inflammatory dermatoses, it may also be associated with chemotherapy. It commonly develops with pegylated liposomal doxorubicin and rarely with cyclophosphamide, gemcitabine, and taxanes. Clinically, it presents within the first 30 days of chemotherapy as macular lesions and erythematous plaques located axillary, inguinal, inframammary, and on the neck or eyelids. Applying topical corticosteroids for ten days is usually a sufficient treatment (9).

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis is considered a part of the spectrum of neutrophilic dermatoses and is most commonly associated with acute myeloid leukemia and cytarabine. Clinically, it presents with disseminated erythematous plaques, urticaria-like appearance, and febrile illness (9). Skin changes develop approximately ten days after starting chemotherapy and tend to resolve spontaneously (29).

The diagnosis is histological, and the biopsy demonstrates a neutrophilic infiltration around the eccrine ducts and necrosis of ductal cells. The pathogenesis is unknown, but a drug-induced toxic effect on the ductal cells has been suggested (9). Although it is a self-limiting condition, symptoms can be managed using ibuprofen, corticosteroids, and dapsone (29,30).

Hyperpigmentation

Pigmentary changes can be diffuse or circumscribed and may affect the skin, mucosa, and nails. The time of onset varies from the first week to several months after therapy (31). Diffuse hyperpigmentation may occur due to the use of busulfan, fluorouracil, doxorubicin, and daunorubicin, and it appears in large skin folds, acral areas, light-exposed areas, and areas previously affected by inflammatory dermatoses (9). Some chemotherapeutics show a distinctive skin pattern. Bleomycin causes characteristic flagellate hyperpigmentation on the trunk and at pressure points. Supravenous hyperpigmentation is rare and can appear in the infusion site on the forearm after administration of fluorouracil, alkylating agents, and taxanes. Reticulate hyperpigmentation can rarely appear following fluorouracil, bleomycin, cytarabine, and paclitaxel. It can be associated with pruritus or erythema affecting the back, shoulders, or buttocks. In children and young adults, eruptive naevi are common following treatment for hematological malignancy with fluorouracil, capecitabine, methotrexate, or doxorubicin. The palms and soles are especially prone to being affected, and melanoma can develop occasionally. Mucosal hyperpigmentation is a rare sequela of alkylating agents, antimetabolites, anthracyclines, or bleomycin. Nail pigmentation in the form of melanonychia can develop after several months of therapy. Hyperpigmentation rarely requires treatment discontinuation and subsides soon after cessation of therapy (9).

Inflammation of preexisting keratoses

Inflammation of actinic and seborrheic keratoses may occur with the administration of certain chemotherapeutic drugs. Pathogenesis is unknown; however, it is believed that chemotherapeutics cause DNA damage in dysplastic keratinocytes which were previously damaged by ultraviolet radiation. Both lesions generally develop in the first week of chemotherapy, appearing predominantly on sun-exposed areas. The lesions are characterized by erythema, pruritus, and inflammation (14). The drugs associated with inflammation of actinic keratoses are fluorouracil, docetaxel, doxorubicin, vincristine, cytarabine, cisplatin, and paclitaxel, whereas cytarabine and gemcitabine are associated with seborrheic keratoses (14,32,33). Discontinuation of chemotherapy is not necessary because lesions respond well to corticosteroid therapy (14).

Photosensitivity reactions

Photosensitivity reactions develop due to the interaction between chemotherapeutic drugs and ultraviolet (UV) light. The drugs most often involved are fluorouracil, capecitabine, tegafur, dacarbazine, and vinblastine. Clinical cutaneous manifestations are similar to an exaggerated sunburn with erythema, edema, pain, and pruritus. In severe cases, blister formation and desquamation may occur. This condition is observed on sun-exposed areas such as the face, neck, nuchal region, extensor surfaces of the forearms, dorsa of the hands, and anterior portions of the legs, sharply demarcated from unexposed skin areas (7,34). Treatment includes cessation of causing agents and avoidance of direct sunlight. Cold compresses, topical or oral corticosteroids, and systemic antihistamines can also be administered (14).

Nail alterations

Nearly all chemotherapy agents can lead to nail growth rate reduction, nail fragility, Mees' lines of discoloration, and Beau's transversal depressions (23). Mees' and Beau's lines are signs of acute toxicity of the nail matrix, migrating distally with nail growth, and can occasionally be one of the first symptoms of chemotherapy (35). Melanonychia presents as brown or black nail discoloration caused by doxorubicin, cyclophosphamide, and fluorouracil (36). Onycholysis (distal detachment), onychomadesis (proximal separation), and subungual abscesses can appear due to taxanes and anthracyclines (9,23). Alteration in thickness can cause koilonychia (spoon nails), onychorrhexis (longitudinal grooves), onychoschizia (distal fragmentation), or trachyonychia (rough nails). Paronychia and periungual pyogenic granulomas can appear following capecitabine, methotrexate, and doxorubicin (9).

RADIOTHERAPY-RELATED ADVERSE EVENTS

Radiation dermatitis

Acute radiation dermatitis develops within 90 days of radiation exposure if a one-time dose is higher than 7 Gy or after cumulative application of lower radiation doses (37,38). After the acute phase, hypopigmented or hyperpigmented skin lesions may

be observed. In addition, higher radiation dose delivery can lead to telangiectasis, edema, atrophy, and fibrosis (37-39). Conversely, chronic radiation dermatitis may develop months to years following the completion of radiation treatment (40). Skin reactions include dermal atrophy, hypopigmentation or hyperpigmentation, telangiectasis, and fibrosis (38-40).

Furthermore, there is an increased risk of developing non-melanotic cutaneous malignancies later in life (40). Approximately 95% of patients receiving radiotherapy will ultimately develop radiation dermatitis, significantly affecting QoL and limiting radiation delivery. However, recent evidence suggests that topical products may treat, prevent, or delay higher grades of radiation dermatitis. Those topical approaches include silver sulfadiazine, laser therapy, topical corticosteroids, and non-pharmaceutical agents such as hyaluronic acid cream, topical Calendula officinalis, glutamine, and lactokine. Moreover, regular skincare assessment, following standard hygiene practices, wearing loose-fitting clothes, avoiding extreme temperatures, sun exposure, and perfumes should also be advised (40).

Radiation recall

Radiation recall dermatitis is an acute inflammatory reaction confined to areas previously exposed to radiation and triggered by a specific chemotherapeutic agent or sun exposure. It can occur weeks, months, or even years after irradiation. This condition clinically manifests with erythema, maculopapular or vesicular lesions, pain, and dry desquamation of the affected area (41). Although radiation recall is a rare phenomenon, numerous chemotherapeutics have been implicated in its development, including doxorubicin, capecitabine, gemcitabine, docetaxel, and paclitaxel (41-43). The precipitating agent should be withdrawn or delayed to allow skin healing. Topical or systemic corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce inflammation, and antihistamines can alleviate the symptoms. Protection of the recently irritated skin is essential, and patients should be advised to avoid sun exposure (43).

Mucositis

Mucositis is a common AE of radiotherapy, particularly oral mucositis affecting up to 100% of patients with head and neck cancer. Radiation-induced oral mucositis develops after 1-2 weeks of radiotherapy due to cumulative radiation exposure, and in most cases resolves spontaneously without scarring. However, oral mucositis can have a detrimental effect on patient QoL. Painful ulcerations appear after cumulative doses of 30 Gy, affecting the patient's ability to eat, swallow and absorb nutrients, leading to nutritional deficiencies and weight loss. It can extend beyond the local oral AE and negatively affect physical, emotional, and psychological aspects of the paitient's life. Oral glutamine may mitigate radiation-induced oral mucositis (44-46).

Alopecia

Alopecia is a common AE of radiotherapy for primary or metastatic brain cancer. As with chemotherapy-induced alopecia, hair follicles in the anagen phase are most susceptible to radiation damage. By introducing megavoltage energy radiotherapy (2-40 MV) instead of orthovoltage energy (90-500 kV), the incidence of dermatologic AEs decreased due to deeper tissue penetration of the former, although the probability of dermatologic AEs development cannot be entirely excluded (47).

Pruritus

Radiation therapy may cause dry desquamation, xerosis, and pruritus. The severity of skin changes and symptoms depends on radiation energy and the dose applied, duration of the treatment, size of the exposed area, skin type, and the presence of comorbidities such as diabetes. Xerosis and pruritus develop early in the treatment due to damage to the dermal barrier and consequent increase in the transepidermal water loss. Later in the course of treatment, a reduction in the number of stem cells in the basal layer stimulates non-proliferating stem cells with shortened cell cycle, which results in dry desquamation (28).

ADVERSE EVENTS RELATED TO HORMONAL THERAPY

Hot flashes are a common AE of hormonal therapy. Agents most often implicated in the development of hot flashes include tamoxifen, raloxifene, anastrozole, letrozole, leuprolide, flutamide, bicalutamide, and progestin. Estrogen is the best treatment option for hot flashes, but its use is contraindicated in patients with a history of breast cancer, deep vein thrombosis, pulmonary embolism, or coronary artery disease. Treatment with vitamin E may alleviate mild symptoms, whereas antidepressants and anticonvulsives have shown efficacy in moderate and severe symptoms.

Alopecia occurs with tamoxifen, exemestane, and rarely with fulvestrant and letrozole. Fulvestrant, exemestane, anastrozole, and leuprolide can cause hyperhidrosis. Moreover, exemestane may cause acne-like rash, while anastrozole, letrozole, and progestin

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may cause a skin rash. Pruritus and xerosis may occur with the use of anastrozole and letrozole. Flutamide may be associated with papulovesicular erythema on sun-exposed skin areas. Fluoxymesterone has a strong androgenic effect and can thus cause acne and hirsutism. Apart from few cases of erythema nodosum, no significant dermatologic AEs of estrogen therapy have been noted (48).

ADVERSE EVENTS RELATED TO IMMUNOTHERAPY

Maculopapular rash

The rash appears almost immediately upon therapy initiation and presents with erythematous macules, papules, and plaques localized on the trunk and extremities (49,50). In response to anti-PD-1/PD-L1 treatment, eczema-like or psoriatic lesions along with lichenoid dermatitis have been described (51-53). Maculopapular rash may also be an early manifestation of other dermatologic toxicities related to immune response, such as lichenoid dermatitis, psoriasis, and bullous pemphigoid. Topical or systemic corticosteroids and oral antihistamines can be used depending on the severity of the rash. Discontinuation of therapy is not indicated except in severe cases (54).

Pruritus

Pruritus is generally concomitant with a maculopapular rash, but it may precede the rash or appear on healthy-looking skin. Although pruritus is not rare (10-30% of patients), it is usually underreported and thus commonly undiagnosed. Treatment includes regular use of topical emollients. In addition, topical corticosteroids, antihistamines, and GABA agonists can be used in moderate and severe cases. Patients with severe pruritus require discontinuation of therapy (49,53-55).

Lichenoid dermatitis

Unlike maculopapular rash, which appears after several days, lichenoid reactions appear after several weeks to months of treatment. It is most commonly seen in patients receiving anti-PD-1/PD-L1 treatment and can present as typical lichen planus, oral lichen planus, hypertrophic lichen planus, and pruritus. Skin lesions are usually manageable with topical corticosteroids; however, in more severe cases, oral corticosteroids, phototherapy, and acitretin may be prescribed (49,52,54).

Psoriasis

Psoriasis can develop de novo or as an exacerbation of a preexisting condition. With anti-PD1 treatment, a history of psoriasis is the main risk factor for developing psoriasis. Furthermore, the timeline to develop psoriasis in these patients is shorter than in patients without a history of psoriatic disease. This condition presents with typical erythematosquamous plaques, and patients can be managed with topical corticosteroids, phototherapy, and acitretin (54,56).

Vitiligo

Vitiligo occurs in patients with melanoma, with an incidence of up to 25% in patients receiving immune checkpoint inhibitors (ICI) therapy, and is more frequent during treatment with pembrolizumab than ipilimumab. It presents with bilateral and symmetric depigmented lesions several months after therapy initiation. Vitiligo is a positive prognostic factor for treatment response, especially in patients with melanoma treated with ipilimumab and anti-PD1 therapy (49,57,58).

Bullous pemphigoid

Bullous pemphigoid is a severe cutaneous AE of immunotherapy. The early phase manifests with pruritus and non-specific maculopapular rash, followed by the occurrence of pruritic blisters on erythematous plaques. Skin changes involve either the skin or the mucous membrane only, whereas the combination of cutaneous and mucous membrane pemphigoid is rare. Development of bullous pemphigoid requires discontinuation of therapy, usually in conjunction with topical or systemic steroids. In refractory cases, treatment with rituximab or omalizumab has been reported to be effective (54,59).

Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS) is a rare but severe cutaneous reaction with cutaneous, membranous, and ocular involvement. It is clinically characterized by febrile illness with atypical target-like lesions, blisters, and epidermal necrosis peeling involving less than 10% body surface area. SJS is most commonly triggered by medications, such as antibiotics, anticonvulsives, and NSAIDs, which are often combined with cancer therapy. Patients require immediate permanent discontinuation of therapy. In addition, application of systemic corticosteroids and immunoglobulins is necessary, along with fluid and electrolyte replacement (54,60).

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is a life-threatening AE of immunotherapy. It presents with extensive erythema, bullae, and exfoliation, accompanied by necrosis of skin and mucous membranes involving more than 30% of the total body surface area. Development of TEN requires immediate discontinuation of the ongoing therapy, fluid and electrolyte management, and administration of systemic corticosteroids and immunoglobulins. In severe cases, infliximab, mycophenolate mofetil, or cyclosporin may be used (54,60).

ADVERSE EVENTS RELATED TO TARGETED THERAPY

Papulopustular eruption

Papulopustular eruption occurs in approximately 91% of patients treated with EGFR inhibitors (61). This condition develops during the first or second week of therapy with pruritic papules and pustules typically distributed in seborrheic areas: the scalp, the face, and retro-auricular, sternal, and interscapular areas. Palmoplantar areas are always spared. It can be distinguished from acne by the absence of comedones and the presence of additional symptoms, such as pruritus or pain. The lesions tend to resolve after eight weeks despite continuation of therapy, leaving erythema and postinflammatory hyperpigmentation. If the skin lesions persist longer than eight weeks, bacterial superinfection is possible (Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella spp.) (62,63). Patients with this condition are advised to avoid sun exposure and use sunscreen. In mild cases, topical corticosteroids, antibiotics, and systemic retinoids can be used. In cases with severe pain, extreme pruritus, spontaneous bleeding, and bacterial superinfection, dose reduction or discontinuation may be necessary (49). The severity of the eruption may be an effective marker for predicting therapy response, with a 60% decrease in the risk of death in patients with a rash, compared with patients without a rash (64).

Non-specific rashes

Multikinase inhibitors (MKIs) give rise to non-specific morbilliform rashes, occurring in 20-30% of patients treated with sorafenib, regorafenib, or imatinib, 10-20% of those on sunitinib, and 5-10% of patients on pazopanib, during the first 6-8 weeks of therapy. The rash is distributed on the trunk and proximal extremities, involving less than 30% of the body surface area. Rarely, the rash can present with lichenoid lesions (62). In patients treated with sorafenib, an erythematous and squamous rash commonly appears on the face and scalp, simulating seborrheic dermatitis (65). If symptomatic treatment with oral antihistamines and topical corticosteroids is sufficient, discontinuation of the therapy is not required (62).

In 30-40% of patients, imatinib induces non-specific maculopapular rash on the trunk and extremities, appearing in the ninth week of therapy. In addition, it can be associated with pruritus, and antihistamines or topical corticosteroids provide a good treatment response (65,66). In patients treated with the BRAF inhibitor vemurafenib, 64-75% developed a maculopapular rash. Other BRAF inhibitors may cause erythematous papules on the face, chest, and upper extremities (62,67). MEK inhibitors may produce a maculopapular, papulopustular, or exfoliative rash, folliculitis, and erysipelas, usually within the first month of therapy (61). Morbilliform, eczematous, and papulopustular rash on the trunk and extremities may occur in patients treated with mTOR inhibitors (62).

Xerosis

Xerosis occurs in up to 50% of patients on EGFR inhibitors approximately 1-3 months after therapy initiation. The skin dryness develops due to alteration in keratinocyte differentiation and abnormal function of sebaceous glands, resulting in alteration of the epidermal barrier and increased transepidermal water loss (49,61). Xerosis presents as dry, scaly, and itchy skin, affecting the trunk and extremities, on which painful fissures and eczema may occur. Furthermore, it may become superinfected by S. aureus and rarely by herpes simplex virus 1. Elderly patients with a history of atopic eczema and patients previously treated with cytotoxic agents are more likely to develop xerosis (62,68). Xerosis may be observed three months after the initiation of MEK inhibitors (61). VEGF and mTOR inhibitors may also cause xerosis, in which emollients can alleviate the symptoms (66).

Pruritus

Pruritus can frequently be associated with papulopustular eruption and xerosis. Approximately 18-55% of patients treated with EGFR inhibitors experience pruritus, and the risk is highest when using panitumumab (62). Pruritus has also been described with BRAF and MEK inhibitors (49). Risk factors for developing pruritus include concomitant use of other medications, comorbidities, and the underlying malignant disease itself. In mild to moderate cases, symptoms can be managed by emollients containing

antipruritic substances, topical corticosteroids, and oral antihistamines. Patients with severe pruritus require other medication with antipruritic effects, such as antidepressants and anticonvulsives (62).

Acral erythema

MKIs most commonly cause acral erythema or hand-foot syndrome. The pathogenesis is unknown, although it is probably linked to inhibition of VEGFR. Unlike acral erythema caused by chemotherapy, MKI-induced acral erythema presents with hyperkeratotic lesions located on the palms and soles, with the highest severity at pressure points. Symptoms appear after 2-4 weeks of therapy and include pain, discomfort, paresthesia, and burning sensation. Preventive measures include wearing suitable footwear and applying emollient creams. Management is centered on keratolytic agents and topical corticosteroids, whereas NSAID or GABA agonists can be used for pain treatment. Patients with severe disease may require dose adjustments treatment or discontinuation (62,66).

Hair alterations

Various changes in quality, texture, and growth pattern of the hair are observed around the second month of EGFR inhibitors therapy. Paradoxical changes in hair growth may occur, such as hirsutism, trichomegaly, trichiasis, and androgenetic alopecia. Inward growth of eyelashes increases the risk of developing keratitis and blepharitis. Therefore, patients are advised to trim their eyelashes regularly. Topical minoxidil can be used for the treatment of alopecia (61,63). MKIs can also cause changes in texture, density, and color of the hair. Alopecia may develop in 21-44% of patients treated with sorafenib and less commonly with sunitinib and pazopanib. Moreover, regrowth of hair despite the continuation of sorafenib therapy is not uncommon (49,66). Alterations in the hair appearance and alopecia due to telogen effluvium have been described with BRAF and MEK inhibitors (62).

Nail alterations

EGFR inhibitors can cause nail changes such as growth reduction, nail fragility, onycholysis, paronychia, and changes in matrix pigmentation. In some cases, pyogenic granuloma-like lesions can develop, which may bleed even with minor trauma. If bacterial or mycotic superinfection occurs, antibiotics or antifungals may become necessary (49,63). Paronychia has been described with mTOR and MEK inhibitors (61,66). Splinter subungual hemorrhages may be noted in the first few weeks of VEGF inhibitor therapy, manifesting as painless black longitudinal lines on the distal nail matrix. Treatment is not required because hemorrhages resolve after therapy ends (66).

Mucositis

Compared with conventional chemotherapy, the use of EGFR inhibitors reduced the incidence and severity of mucosal changes considerably. However, mucosal surfaces are not entirely spared, and AEs, such as mucositis, stomatitis, conjunctivitis, and oral and genital ulcus, can still occur (63). Patients treated with mTOR inhibitors may experience stomatitis, which presents with well-demarcated, superficial, and painful aphthae localized on the nonkeratinizing epithelium. Associated symptoms of dysphagia and odynophagia can result in malnutrition and dehydration; consequently, dose modification or treatment interruption may be needed (49,53). Stomatitis has been associated with a better outcome in patients with metastatic renal cell carcinoma treated with everolimus (62,69).

Pigmentary changes

Imatinib may induce reversible, dose-related hypopigmentation. Cutaneous depigmentation can be localized or diffuse, appearing after several weeks of therapy, and usually resolving after the cessation of therapy (62,70). Skin discoloration has been reported in patients treated with sunitinib. It consists of yellow discoloration and hypopigmentation of the skin, occurring after the first week of therapy and resolving after treatment discontinuation (71). The multikinase inhibitor vandetanib can cause the appearance of blue-gray macules predominantly in perifollicular regions of the face, scalp, and trunk, which gradually subside 3-6 months after cessation of the treatment (72).

Impaired healing

VEGF inhibitors (bevacizumab) inhibit cancer angiogenesis. However, angiogenesis inhibition can cause mucocutaneous hemorrhage, commonly presenting as epistaxis and impaired wound healing (49). Bevacizumab increases the incidence of wound-healing complications (dehiscence and delayed healing), especially perioperatively in patients with colon cancer. Therefore, it is recommended to withdraw bevacizumab treatment at least 4-8 weeks before elective surgery and initiate the treatment after all wounds have completely healed (73).

Photosensitivity

Photosensitivity appears in 35-63% of patients treated with vemurafenib, and the drug also increases

erythrocyte porphyrin levels (62). In patients on vandetanib treatment, erythematous skin eruption on sun-exposed areas was associated with desquamation and pruritus (72). Patients should apply broad-spectrum sunscreens and wear protective clothing because sunburns can occur after only 10 minutes of UV exposure (49).

Secondary malignant cutaneous lesions

The most severe AE of BRAF inhibitors is the development of secondary premalignant and malignant lesions, especially keratoacanthoma and squamous cell carcinoma (SCC). In a study by Mattei *et al.*, 33 patients underwent BRAF inhibitor therapy, 30.3% developed actinic keratosis, and 18.2% developed SCC, at a higher frequency and with earlier manifestation in patients treated with vemurafenib (74). Development of keratoacanthoma and SCC has also been reported in patients on sorafenib therapy. Keratoacanthoma can regress spontaneously, while SCC does not regress without treatment and may metastasize (66). Therefore, regular dermatologic evaluation is extremely important for the early detection of cancer. Surgery is the first-line treatment of SCC, and other therapeutic options include radiotherapy, cryosurgery, intralesional fluorouracil, systemic retinoids, and photodynamic therapy (49).

Stevens-Johnson syndrome

SJS has been reported in patients treated with sorafenib, vemurafenib, and EGFR inhibitors (66,75). Immediate cessation of therapy is required. In addition, systemic corticosteroids, immunoglobulin, and fluid and electrolyte replacement are also necessary (60).

THE IMPACT OF DERMATOLOGIC ADVERSE EVENTS ON PATIENT QUALITY OF LIFE

Dermatologic AEs take a significant toll on the course of treatment and the patient's QoL, which was rarely considered and often neglected in the past (76,77). Negative impact on QoL manifests through increased distress, withdrawal from relationships, increased risk of mood disturbances, and non-adherence to treatment (76). In other words, those AEs negatively affect the patient's physical, functional, emotional, and social well-being and daily functioning. Therefore, it is essential to assess the severity of dermatologic AEs, connecting it to the type and clinical extent of the symptoms and their effect on QoL (46,78). For this reason, different questionnaire techniques for routine clinical use have been introduced, such as the DLQI (Dermatology Life Quality Index), Skindex-16, Skindex-29, FACT-G (Functional Assessment of Cancer Therapy – General), or FACT-EGFRI-18 (Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitors-18).

In a study conducted by Lee *et al.*, the impact of cutaneous AEs on QoL was evaluated in 375 patients on anticancer therapy using the DLQI questionnaire survey (77). DLQI is a simple and practical questionnaire technique, which includes questions about the impact on a patient's QoL over the previous week only, which is a short enough time to allow clear recall. A higher score means a more significant impairment of QoL (79). It was found that patients treated with targeted therapy had more distractions in QoL than patients receiving non-target therapy. Although the most frequently reported problem was hair loss, followed by dry skin and nail color and shape changes, the highest DLQI score was observed in patients experiencing periungual inflammation, followed by patients with palmoplantar lesions and papulopustules. This DLQI score could be explained by the presence of pain and limitation of the patient's instrumental and self-care daily activities. No additional distress in QoL was observed in patients with alopecia, presumably because hair loss is not associated with itching or pain and because patients expected hair loss but did not expect other cutaneous symptoms to emerge (77).

Suh Oh *et al.* selected several questionnaires, including FACT-G, DLQI, Skindex-16, and FACT-EGRI-18, which showed that hand-foot syndrome and rash had the greatest influence on QoL, while pigmentary changes, alopecia, and xerosis had the lowest. It was also suggested that alopecia did not cause additional reduction in the patient QoL. Unlike the study conducted by Lee *et al.*, this study did not find differences in QoL between conventional chemotherapy and targeted therapy (78).

Using DLQI and Skindex-29, Urakawa *et al.* found that hand-foot syndrome decreased QoL more significantly than rash, xerosis, paronychia, or pigmentation (80). Similarly, using Skindex-16, Oliveri *et al.* confirmed that hand-foot syndrome brought more distress and suffering and more frequently led to discontinuation of therapy (76). In addition, Oliveri *et al.* found that specialized aesthetic treatment protocols alleviated perceived symptoms and improved QoL in breast cancer patients with grade I adverse skin symptoms who underwent chemotherapy, radiotherapy, or targeted therapy (76).

In a qualitative study by Sibeoni *et al.*, the patients highlighted the importance of not only prolonging their life but also of living as well as possible in their everyday lives (81).

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CONCLUSION

In recent decades, the overall survival of cancer patients has significantly increased due to advances in oncologic therapy. Apart from chemotherapy, radiotherapy, surgery, and hormonal therapy, newer therapies, such as immunotherapy and targeted therapy, have been increasingly employed. However, all these therapies cause numerous AEs, among which dermatologic AEs are frequently observed. The most common dermatologic AE is alopecia, followed by mucositis, pruritus, xerosis, acral erythema, non-specific rashes, nail changes, and many others. These skin changes can significantly impact the patient QoL, which should be considered in therapy evaluation. Therefore, prevention, early detection, and management of dermatologic AEs are of utmost importance to improve the patient QoL and avoid the reduction or cessation of oncologic therapy. A multidisciplinary approach including different specialists (dermatologists, oncologists, psychologists) is vital to provide the best comprehensive care for patients.

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