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Xerosis as the toxicity of novel anti-cancer therapies — pathophysiology and management

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ABSTRACT

In the systemic treatment of modern oncology, novel anti-cancer therapies are becoming increasingly important. The toxicity profile of these therapies is different from that of standard chemotherapy and has become an emerging challenge for clinicians and patients. Among the most common adverse events are skin toxicities, including xerosis, that might be debilitating and have a negative effect on patients' quality of life. Untreated or treated ineffectively can necessitate dose modification or treatment withdrawal. Xerosis is a symptom stemming from a skin barrier dysfunction caused by a variety of different mechanisms, which differ depending on the therapy. Patients indicate xerosis as an unexpected symptom that significantly decreases their quality of life. Even so, it is a complication often neglected in clinical practice. Prevention and treatment of xerosis include avoiding irritating factors, bathing in lukewarm water, and applying emollients. Early treatment prevents inflammation and secondary bacterial infections.

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Key words: immunotherapy, xerosis, molecularly targeted therapy

INTRODUCTION

Systemic treatment in modern oncology, in addition to conventional chemotherapy that is still used particularly in palliative therapy, includes immunotherapy and molecularly targeted therapy. Due to the increasing number of cancer patients and the growing knowledge of the molecular pathomechanisms of carcinogenesis, newer therapies are being sought that will be specific to individual types of cancers or even selected specifically for a patient's cancer [1]. By learning the exact pathomechanisms and mutations present in specific tumor types, molecularly targeted drugs can be developed. This is a large and growing group that includes, among others, epidermal growth factor receptor inhibitors (EGFR inhibitors), angiogenesis inhibitors — vascular endothelial growth factor inhibitors (VEGF inhibitors), BRAF tyrosine kinase inhibitors, MEK inhibitors, and mTOR inhibitors. The main drugs used in immunotherapy are immune checkpoint inhibitors (ICIs). This therapy is used in the treatment of many types of cancers, particularly lung cancer, renal cell carcinoma (RCC), breast cancer, colorectal cancer, melanoma, and others [2].

Such types of therapy are associated with adverse events whose profile differs from the toxicity of classical chemotherapy. This poses a new challenge for both patients and medical staff providing care for oncology patients.

The group of adverse events of molecularly targeted therapy, like immunotherapy, includes a large proportion of dermatological complications that occur more frequently compared to chemotherapy and significantly reduce patients' quality of life [3]. If left untreated, or treated ineffectively, they can lead to the need for dose modification or complete cessation of treatment. The most common skin toxicities include exanthema, xerosis, mucositis, inflammatory skin lesions, pigmentary disorders, hand-foot syndrome, and changes in body hair (alopecia, hirsutism, trichomegaly) or nail apparatus (paronychia, onycholysis, pyogenic granuloma) [4, 5]. Adverse events vary in profile depending on the drug used and have different pathogenesis. Complications that are easily diagnosable, such as hair loss and exanthema, receive considerable attention in clinical trials. The incidence of less visible but equally persistent lesions, such as xerosis, is still underestimated. In clinical trials involving patients treated with EGFR inhibitors, the reported incidence of xerosis ranges from 10% to 33%. The retrospective analysis, in which patients treated with EGFR inhibitors for more than six months

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Table 1. The severity of xerosis, eczema, and pruritus according to the CTCAE v5 scale

CTCAE term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Xerosis	A condition characterized by flaky and dull skin; generally, without pore problems, skin texture resembles a thin sheet of paper	Coverage < 10% of BSA and non-associated erythema or pruritus	Coverage of 10–30% of BSA and association with erythema or pruritus; limited significant ADLs	Coverage > 30% of BSA and association with pruritus; limited self-performance of ADLs	–	–
Eczema	A condition characterized by itchy skin, redness, inflammation, scabs, thick, flaky skin, and/or blister formation	Asymptomatic or mild symptoms; additional medical interventions in addition to standard management not advisable	Moderate; topical or oral intervention indicated; additional medical intervention in addition to standard management advisable	Severe or medically significant but not immediately life-–threatening; intravenous intervention is advisable	–	–
Pruritus	A condition characterized by an intense itching sensation	Mild or localized pruritus; topical intervention advisable	Extensive and sporadic; skin lesions associated with scratching (e.g. edema, papulae, abrasions, lichenification, oozing/scabs); oral intervention advisable; limited significant ADLs	Extensive and chronic; limiting self–performance of ADL or limiting sleep; systemically administered steroids or immunosuppressive therapy advisable	–	–

BSA — body surface area; ADL — activities of daily living

underwent a dermatological examination, revealed that the incidence of the above-mentioned complication was 100% [6–8]. In a survey of 379 patients who were cured of their cancer, up to 63% indicated xerosis as the most negative dermatological adverse event [9]. This study aims to provide insight into xerosis as a common dermatological problem faced by oncology patients and present its suggested pathogenesis, prevention of occurrence, and treatment.

XEROSIS — DEFINITION AND CTCAE GRADING

Xerosis is a condition that affects patients not only in the course of other diseases, such as atopic dermatitis but is also a clinical problem on its own [10]. It mainly affects the elderly, which is related to the fact that the activity of sweat and sebaceous glands is reduced with age. Lesions are most commonly seen on the anterolateral lower legs but also on the back, abdomen, and shoulders [11].

Xerosis is primarily associated with water loss from the stratum corneum. Depending on the severity of the lesions, they may take the form of a reticular pattern accompanied by an uneven distribution of pigment, scales, and cracking of the skin, which frequently leads to fissures and bleeding, thereby weakening the skin barrier and facilitating penetration by pathogens and allergens [10, 11]. Dryness is often accompanied by pruritus, causing patients to scratch, which exacerbates the condition and may lead secondarily to excoriation, asteatotic eczema, or lichen simplex chronicus. Factors such as cold or dry air and inadequate skin care also contribute to exacerbations [11].

The CTCAE (Common Terminology Criteria for Adverse Events Version 5.0) grading plays an important role in the assessment of complications of anticancer therapy. Depending on the severity of the adverse event, it is graded from 1 to 5 according to specific criteria. Among other things, xerosis, eczema, or pruritus can be assessed according to these criteria (Tab. 1).

EGFR INHIBITORS

EGFR inhibitors are modern molecularly targeted drugs that find their use in the treatment of many types of cancers, particularly solid tumors such as colorectal cancer and lung cancer. EGFR inhibition can occur in two ways — through monoclonal antibodies such as cetuximab or panitumumab, or small-molecule EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib or afatinib. Cutaneous adverse events occur in up to 50–90% of patients using EGFR inhibitors [12]. The most common cutaneous adverse events can be classified into three groups: folliculitis (involved in acne-like exanthema), changes in the skin barrier (leading to xerosis, subsequent cracking, and pruritus), and changes in epidermal structures (paronychia, changes in hair texture) [13].

The very mechanism of action is responsible for the high incidence of cutaneous adverse events in this group of drugs. The EGFR receptor plays an important role in maintaining skin homeostasis and its barrier function and enables normal cell proliferation [14]. Blockade of EGFR on keratinocytes inhibits epidermal cell renewal. It also results in increased expression of pro-inflammatory and pro-apoptotic genes and decreased expression of loricrin, a protein that is present in corneocytes, which has an important role

in maintaining the integrity of the skin barrier [15]. These processes result in thinning of the epidermis and stratum corneum, increased permeability, water loss, and reduction in the protective capacity of the skin. Pruritus, which accompanies xerosis, arises as a result of the increased number of histamine-secreting mast cells identified in the skin of patients treated with EGFR inhibitors [16].

Xerosis appears during the first months of therapy in up to 55% of patients receiving EGFR inhibitors. After 6 months, up to 100% of patients may be affected [8, 17, 18]. Xerosis most commonly appears on extremities or in areas previously affected by disease processes. Elderly patients, those with atopic dermatitis, and patients previously treated with chemotherapy are particularly at risk. One-third of patients with xerosis develop pruritus and cracking of the skin that most commonly develop in the sixth to eighth week of therapy and are found within the fingers [8, 19].

IMMUNOTHERAPY

Immunotherapy is a method of cancer treatment that has its basis in the use of the immune system and its components in fighting the disease [20]. In terms of drugs that belong to the class of immunotherapeutics, PD-1, PDL-1, and CTLA-4 checkpoint inhibitors should be noted [21]. Immunotherapy was found to be effective in the treatment of patients with advanced melanoma and other cancers such as non-small cell lung cancer, RCC, or bladder cancer [22]. In immunotherapy, among the main groups of used drugs are antibodies against the programmed cell-death protein-1 (PD-1) receptor, which include pembrolizumab and nivolumab. By blocking the PD-1 pathway, they enable an increased anti-tumor response from the body's natural immune cells [23]. During treatment with anti-PD-1 antibodies, skin reactions occur in approximately half of the patients, the most common being pruritus which is often accompanied by xerosis, exanthema, mucositis, or changes in the nail apparatus (mainly paronychia) [24]. Cutaneous complications are mediated by non-selective activation of immune cells in the patient's body, particularly by cytotoxic T lymphocytes of the skin [21]. Nivolumab is one of the PD-1 inhibitors that is used, among others, in the treatment of melanoma. In one meta-analysis, it was found that xerosis occurred in 5.3% of patients during treatment with this antibody [22]. Pembrolizumab, another drug in this group, caused xerosis in 2.4% of patients [25]. Pruritus, a symptom that is often accompanied by xerosis, was present in 18% of patients. As one of the registered therapies for patients with stage IV melanoma, nivolumab is used in combination with ipilimumab (anti-CTLA-4 antibody). In this situation, the frequency and severity of dermatological adverse events increase [22]. Ipilimumab, an anti-CTLA-4 antibody, is another checkpoint inhibitor commonly used in modern oncology. CTLA-4 silences the immune system by competitive binding to the CD80/CD86 co-receptor. Blockade of the CTLA-4 receptor with a monoclonal antibody enables the CD28 receptor to bind to the CD80/CD86 molecule, thereby enhancing T-cell proliferation and migration into the tumor microenvironment [26]. The anti-CTLA-4 antibody is characterized by the occurrence of more severe adverse events compared to the PD-1 and PD-L1 inhibitors, which are less toxic. Adverse events of CTLA-4 inhibitors include diarrhea, inflammatory bowel disease, hepatitis, opportunistic infections in the form of pneumonia, and skin lesions. Adverse events are positively correlated with the drug dose and occur with higher frequency when high therapeutic levels are used [27]. It was found that 40% of patients taking ipilimumab experience dermatological adverse events, which include pruritus (approximately 30% of patients), vitiligo, and exanthema (10–40% of patients) [28]. Those adverse events most commonly occur during the first 4 to 8 weeks of therapy. Xerosis and concomitant pruritus secondary to skin damage are under-reported adverse events, as they are often associated with the appearance of exanthema. Rare adverse events may include Stevens-Johnson syndrome or bullous pemphigoid (< 1%) [29].

OTHER MODERN ONCOLOGY THERAPIES

VEGFR inhibitors

Proliferation and the formation of new blood vessels are essential for the growth of cancerous tumors. Those processes also contribute to metastasis through blood vessels. Vascular endothelial growth factor (VEGF) not only causes the formation of new vessels but also changes their phenotype. Inhibitors of the receptor for VEGF (VEGFR) include bevacizumab, a monoclonal antibody against VEGF, or multi-kinase inhibitors such as sunitinib, sorafenib, pazopanib or axitinib. The most common cutaneous adverse advents of this group of drugs include petechiae, ecchymoses and impaired wound healing (bevacizumab), or hand-foot syndrome, hair loss, depigmentation, and skin inflammatory lesions (multikinase inhibitors). Xerosis occurs most frequently with therapy with cabozantinib, axitinib, or sorafenib (19.2%, 17.7%, and 14.3%, respectively) [30]. No cases of xerosis were reported in clinical trials regarding bevacizumab, which may indicate that the etiology of xerosis in this group of drugs is not directly related to inhibition of the VEGF signaling pathway but to other effects of the multikinase inhibitors, although the exact mechanism is not yet known.

BRAF and MEK inhibitors

Activating mutations of the BRAF protein can occur in malignant neoplasms such as melanoma, lung cancer, or colorectal cancer. The combination therapy with BRAF and MEK inhibitors is applied in systemic therapy of cancers

in which the BRAF V600E mutation is present. The MEK protein is another transmitter in the "RAS–RAF–MEK–ERK" signaling pathway, whose activating mutations occur with BRAF inhibitor monotherapy [31]. Many adverse events are observed, with up to 90% of patients experiencing one or more skin toxicities [32]. The most common include pseudo-tumorous conditions associated with increased epidermal proliferation. Xerosis occurs in 16–19% of patients taking vemurafenib (BRAF inhibitors) and 23% of patients taking sorafenib (a multi-kinase inhibitor with BRAF inhibitor activity) [33–36]. Xerosis, which occurs with a frequency of 22–30%, is often accompanied by pruritus which occurred in 8–19% of cases. Therapy with the MEK inhibitor, trametinib, caused xerosis in 22.6% of patients [37]. The concomitant use of those drugs, which often occurs in clinical practice, may increase the incidence of this adverse event, although precise data to support this fact are lacking.

mTOR inhibitors

The mTOR (*the mammalian target of rapamycin*) signaling is important in terms of the regulation of survival, metabolism, growth, protein synthesis, autophagy, and cell homeostasis. Abnormalities in the regulation of the mTOR pathway may thus result in neoplastic processes, for which mTOR inhibitors have found their use in treatment [38]. From this group of drugs, everolimus, sirolimus and temsirolimus were classified for the treatment of cancers [39]. The dermatological symptoms reported during treatment with mTOR inhibitors include acne-like lesions, folliculitis, exanthema, stomatitis with associated aphthae, or edema. Leukocytoclastic vasculitis was also rarely observed during therapy with sirolimus [40]. Therapy with mTOR inhibitors also carries a high risk of xerosis — it is experienced by 10.8% of everolimus-treated patients and 17.6% of temsirolimus-treated patients [30].

BCR-ABL inhibitors

BCR-ABL tyrosine kinase inhibitors are used in the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). The following drugs from the indicated group are currently used in clinical practice: imatinib, nilotinib, dasatinib, bosutinib, and ponatinib [41]. Dermatological adverse events such as exanthema, edema, pigmentary changes, or pruritus are observed during therapy with the indicated drugs [42, 43]. However, in terms of xerosis, special attention should be paid to ponatinib — a drug that is effective in patients who have the T315I point mutation in BCR-ABL, which is one of the most common mutations in CML [44]. Depending on the study, xerosis was observed in 10% up to 32% of patients on ponatinib therapy, making it one of the most commonly reported adverse events [41, 45]. Xerosis usually occurred at CTCAE grade 1–2 (version 4) [45]. During nilotinib therapy, xerosis was reported in 13% of patients [46].

Prevention of xerosis

All patients undergoing treatment that may cause xerosis should use agents to prevent the onset of this symptom. In daily skin care, suitable cleansing and moisturizing products that do not irritate the skin and contain humectants such as urea, glycerol or lactic acid should be used [47]. Moreover, it is important to avoid additional factors that can cause xerosis, such as exposure of the skin to low and high temperatures, UV radiation, detergents containing surfactants or low air humidity. The optimum humidity level for patients to be in should be 45–60%, so the use of a humidifier is recommended during the winter months. Following these rules helps to maintain the integrity of the skin barrier [47, 48].

In terms of the prevention of xerosis, it is also important to identify and eliminate additional risk factors as effectively as possible. These include radiotherapy, end-stage renal disease, nutritional deficiencies, hypothyroidism, or diseases associated with excessive sweating [47]. People at risk are also advised to follow dietary recommendations, such as avoiding the consumption of spicy foods, excessive alcohol, or citrus fruit [48]. Recommendations for the prevention and treatment of xerosis are summarised in Table 2.

Treatment of xerosis

In terms of the treatment of xerosis, both the use of topical substances and the observance of correct hygiene and care procedures are of fundamental importance. Prolon-

Table 2. Recommendations for the prevention and treatment of xerosis

Prevention	Treatment	
	Good hygiene and care procedures	Topical and systemic agents
• Gentle cleansing agents, humectants (urea, glycerol, lactic acid), keratolytic agents (salicylic acid) • Avoiding exposure to irritants (detergents, low humidity, high and low temperatures) • Avoiding additional risk factors • Appropriate dietary recommendations (limiting the consumption of spicy foods, alcohol, and citrus fruit)	• Reduction of the number and duration of baths • Avoiding detergents • Clothing made of soft fabrics	• Emollients • Cyanoacrylate tissue adhesives • topical GCS (from G3) • GCS + topical antibiotic (in case of lichenification) • Antihistamines (in patients with associated pruritus)

GCS — glucocorticosteroids; G3 — grade 3 adverse event

ged contact of water with the skin may lead to exacerbation of adverse skin lesions. For this reason, patients should limit the number and duration of baths and the water should be warm but not hot. This is particularly important because, initially, water can reduce the pruritus experienced by the patient. Cosmetics and cleansers containing substances that may cause irritation and dryness of the skin, such as soaps and detergents, should also be avoided. The patient's choice of clothing should be limited to clothes made of soft and smooth materials (e.g. cotton) that will not damage sensitive skin [47]. Topical agents applied to the skin mainly include emollients to prevent further drying by evaporation and restore damaged skin fragments. Their composition may vary; however, the most important ingredients include lipids (i.a. oils, waxes, ceramides, cholesterol), the aforementioned humectants or antipruritic agents (e.g. glycine, polidocanol, cold-sensitive receptor activators TRPM8 [menthol]). Emollients should be applied in large quantities (250–500 g/week), several times a day, especially after bathing, while the skin is still wet [47–49]. Another way to prevent excessive xerosis is the use of cyanoacrylate tissue adhesives. However, it should be kept in mind that those may cause folliculitis due to their occlusive effect [50]. In case of worsening symptoms accompanied by inflammation, the addition of topical glucocorticosteroids (in very advanced forms including oral glucocorticosteroids) is recommended. In case of lichenification, cracking of the skin, and superinfection of skin lesions, it is necessary to include combination preparations — glucocorticosteroids combined with an antibiotic and antihistamines that block the second-generation H1 receptor for antipruritic purposes [51].

CONCLUSIONS

Undoubtedly, the problem of xerosis affects a significant number of patients undergoing oncology treatment. Therefore, it is extremely important for clinicians to be aware of the extent of this phenomenon, particularly during EGFR inhibitor therapy. Given the possible prevention of the condition, attention should be paid to the education of patients during therapy and rapid response in the event of complaints. Simple steps, such as changing the care of sensitive skin, make it possible to improve the quality of life of patients undergoing oncology treatment. The problem of underestimation of this adverse event when reporting skin toxicities of modern oncology therapies is evident in research studies. In addition to easily observable changes such as hair loss or exanthema, xerosis seems to be of less importance to clinicians, with a high impact on the quality of life of patients.

Conflict of interest

The authors report no conflicts of interest.

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