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Nordic European Cutaneous Oncodermatology Management (NECOM) 4: A practical algorithm for the integration of skincare to improve patient outcomes and satisfaction with immunotherapy for cancer

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 ORIGINAL ARTICLE

NECOM 4: Algorithm Integrating Skincare for the Management of Immunotherapy-Related Cutaneous Adverse Events for Cancer Patients and Survivors

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ABSTRACT

Background: In the Nordic European Countries, cancer is the leading cause of death. The last decade has brought revolutionizing cancer treatments including immune checkpoint inhibitors (ICIs). Patients on ICIs have a high risk of developing cutaneous immune-related adverse events. Treating these side effects is of high importance to improve patient's quality of life (QoL) and continue the anti-cancer treatment.

Methods: The Nordic European Cutaneous Oncodermatology Management (NECOM) project develops tools to prevent and treat cancer therapy-related cutaneous adverse events (cAEs). The first 2 NECOM papers presented various cAEs and skincare regimens involving hygiene, moisturization, sun protection, and camouflage products for preventing and managing cAEs. The NECOM 3 practical algorithm was on the prevention and treatment of acute radiation dermatitis. This NECOM 4 practical algorithm is intended to prevent and manage cutaneous immunotherapy-related adverse events (cirAEs), improving cancer patients' QoL and outcomes.

Results: The NECOM advisors discussed the results of a systematic literature review and obtained consensus on the evidence and expert opinion-based practical algorithm for cirAEs to support all healthcare providers treating cancer patients in the Nordic European Countries. The algorithm starts with a simple skincare regimen of cleansing, moisturizing, and protection, followed by the exclusion of severe cutaneous adverse reactions, and then specific interventions to treat the most common cirAEs (pruritus, maculopapular eruption, eczematous eruption, psoriasis, lichenoid eruption, and bullous eruption).

Conclusions: CirAEs are the most common side effects induced by ICIs and may lead to cancer treatment interruption or even discontinuation. Patient education on the prevention of cirAEs using a skincare regimen and treatment recommendations given in the NECOM 4 algorithm may help prevent and manage cirAEs and improve the QoL and outcome of patients receiving ICIs.

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INTRODUCTION

Cancer is the leading cause of death in most countries, including Norway, Sweden, and Finland.[1] Cancer incidence and mortality are still growing worldwide with the aging and growth of the population.[1] The estimated global incidence of cancer per 100,000 population in 2020 in Denmark was 350, Norway 325, Sweden 285, Finland 270, and Iceland 260.[2] In these Northern European countries, prostate cancer and breast cancer are the most diagnosed cancers in males and females, respectively.[1] Breast, lung, colon, and prostate cancers are the most common cancers in the five Nordic European countries excluding non-melanoma skin cancers (NMSC).[3] According to mortality, lung and prostate are the leading causes of cancer death.[1] Cancer is an important cause of morbidity secondary to the cancer itself and adverse events induced by cancer treatments. Early detection and quality of cancer treatments have significantly improved cancer outcomes, leading to more patients living with cancer or surviving cancer.[3]

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, leading Professor Honjo and Professor Allison who discovered ICIs to be awarded the 2018 Nobel Prize in Physiology or Medicine.[4] ICIs are monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), or lymphocyte-activation gene 3 (LAG-3) (Table 1). There are numerous indications for ICIs in a neo-adjuvant, adjuvant, and curative setting. Immunotherapy is now approved for more than fifteen cancer sites such as melanoma, small cell and non-small cell lung cancer, renal cancer, and triple-negative breast cancer.[5,6] Indications for ICIs continue to grow.

Cancer cells have ways to evade body immune surveillance. ICIs are antibodies targeting negative regulators of T cell activation, thus removing the brakes on the immune system and leading to the activation of host T cells to attack cancer. ICIs-activated

TABLE 1.

Immunotherapy Classes and Molecules	
Anti-CTLA-4	Ipilimumab
Anti-PD-1	Tremelimumab
	Pembrolizumab
	Nivolumab
	Cemiplimab
	Dostarlimab
	Retifanlimab
	Toripalimab
Anti-PD-L1	Avelumab
	Durvalumab
	Atezolizumab
Anti-LAG3	Relatimab

T-cells may attack not just cancer cells, but also normal tissue, leading to immune-related adverse events (irAEs). IrAEs range in intensity from mild to life-threatening. They can occur within days of treatment initiation and at any time during the course as well as after discontinuation. Almost any organ system can suffer from irAEs.[7] Cutaneous immune-related adverse events (cirAEs) are the most common category of ICI side effects. Between 30 to 60% of cancer patients on ICIs will suffer from cirAEs.[8] Around 20% of patients on anti-PD-L1 will develop a cirAE, 34 to 42% on anti-PD-1, and 44 to 59% on anti–CTLA–4 monotherapy.[8] Concurrent PD-1 and CTLA-4 blockage leads to the highest rate of cirAEs occurring in 59 to 72% of patients.[8]

The most common cirAEs are pruritus with or without primary dermatologic findings, maculopapular eruption, eczema, psoriasis, and lichenoid eruption. In melanoma patients, vitiligo-like depigmentation is common and is a sign of better cancer outcome.[9] Rare cirAEs can be severe and life-threatening and need to be recognized. They include Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

CirAEs may indicate therapeutic response to ICIs. Patients who experience them have increased progression-free survival (PFS) and overall survival (OS).[10-14] Patients should be informed about the data showing that adverse events (AEs) predict better cancer response. However, despite their positive prognostic value, cirAEs come with a high burden of symptoms, cosmetic concerns, and impacts on quality of life (QoL). Some patients even discontinue ICIs because of cirAEs. With better cancer treatments, an increasing number of patients are cancer survivors and are living with cutaneous toxicities or sequelae of cancer or cancer treatments. The significant impact cutaneous toxicities can have on a patient's QoL needs to be recognized.

Managing cirAEs is often challenging. Many common medications used to treat cutaneous inflammatory diseases may not be prescribed in a cancer setting because of the lack of safety data or the potential interaction with ICIs. Most systemic medications have not been studied in a cancer setting with most clinical trials excluding patients with cancer or recent cancer. Immunosuppressive medications commonly used for moderate-to-severe dermatological conditions such as systemic steroids and cyclosporine could promote cancer recurrence or progression or could even interfere with ICIs. In current practice guidelines, the mainstay of treatment for moderate-to-severe irAEs are systemic steroids.[15] However, systemic steroids could potentially be detrimental and decrease ICI efficacy, but there is some conflicting data. Some studies have shown that systemic steroids used to treat irAEs are associated with decreased OS and PFS,[16-18] especially with higher doses,[19,20] but other publications have shown no difference.[21] Stronger immunosuppression using systemic steroids plus a second-line immunosuppressant was associated with worse OS and PFS compared to steroids alone.[22] There is a balance to be found between treating irAEs and improving the patients' symptoms without compromising cancer outcomes. Many cirAE could be more realistically attenuated or possibly prevented with a proper skincare routine. However, most guidelines do not include skincare measures. There is a gap between skincare recommendations in the literature and oncodermatology guidelines. The aim of the skincare algorithm (Figure 1) for patients with active cancers or survivors of cirAEs is to improve symptoms, QoL, and ICIs adherence and continuation whenever possible.

Project Update

The Nordic European Cutaneous Oncodermatology Management (NECOM) project was developed to improve cancer patients and survivors' QoL by offering tools to support all healthcare providers treating oncology patients, including physicians, nurses, pharmacists, and advanced providers for preventing and managing cutaneous adverse events (cAEs).

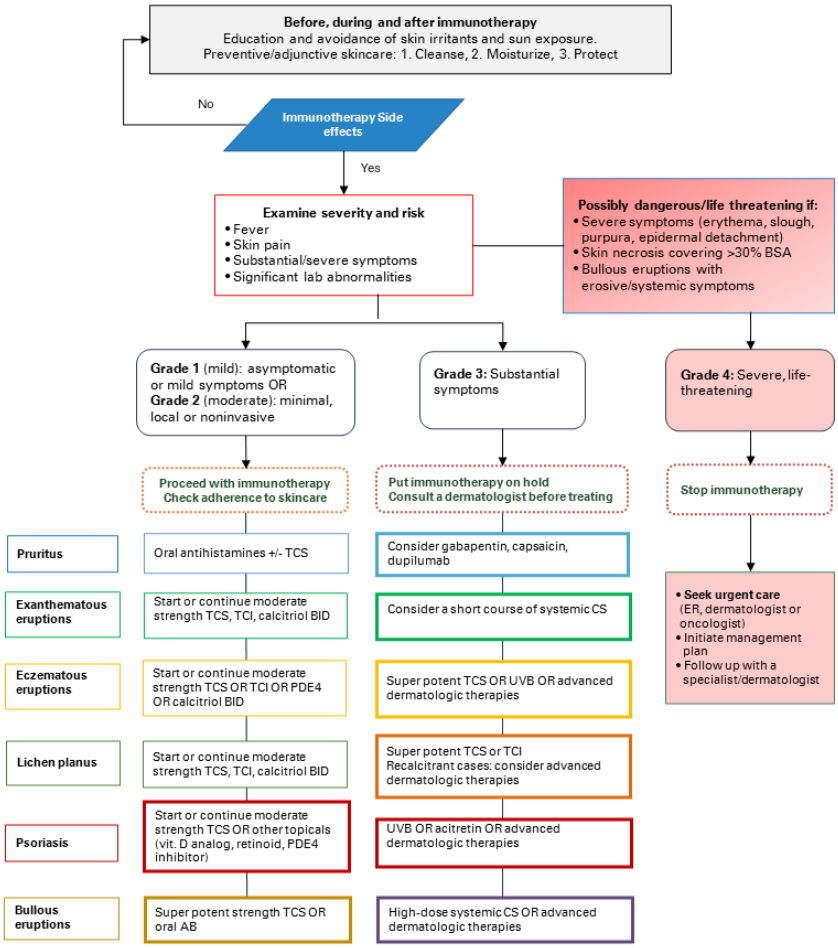
NECOM 1: A review paper and an algorithm to reduce the incidence of cAEs, treat cAEs, and maintain healthy skin using general measures and non-prescription agents was published.[23]
NECOM 2: A skincare algorithm for patients with cancer and survivors in Scandinavia was published.[24]
NECOM 3: A practical algorithm on skincare for the prevention and treatment of acute radiation dermatitis related to radiation treatment was accepted for publication.[25]
NECOM 4: The next step in the project was to develop a practical algorithm for skincare for the prevention and treatment of cirAEs induced by immunotherapy.

METHODS

An expert panel of clinicians who treat patients with cirAEs used a modified Delphi method to develop a practical evidence-based algorithm to treat patients with cirAEs. The algorithm aims to improve patient comfort during and after treatment, reducing and treating cirAEs, and promoting healing including using skincare.

During a face-to-face meeting on October 13, 2023, the outcome of a systematic literature review identifying the spectrum of cirAEs and addressing their prevention and treatment was discussed and the practical algorithm was developed based on the assembled evidence coupled with the panel's experience and opinion. An online process was used to fine-tune the algorithm and prepare and review the publication.

FIGURE 1. Supportive skincare for oncology patients receiving immunotherapy.



Literature Review

The systematic literature review included guidelines, consensus papers, and clinical or other research publications on the prevention and management of cirAEs published in English from January 2010 to July 2023. Articles were excluded if they contained no original data (unless a review article was deemed relevant), were not relevant to cirAEs, or the publication language was other than English.

A dermatologist and a physician-scientist conducted the searches on August 1 and 2, 2023. PubMed was the primary source and Google Scholar was the secondary source. The search criteria utilized were as follows: *cirAEs AND isolated pruritus OR psoriasis OR lichen planus OR eczematous eruptions OR bullous eruptions AND QoL OR prevention OR treatment OR maintenance with prescription therapy OR skincare OR adjunctive skincare OR education of staff and patients.*

The results of the searches were evaluated independently by two reviewers who resolved discrepancies through discussion. The searches yielded 106 publications. Ninety-four (94) papers remained after excluding duplicates and articles not deemed relevant (other subjects, low quality). The papers addressing cirAEs were comprised of 2 guidelines and algorithms, 8 systematic literature reviews, 10 consensus papers, 17 reviews, 42 clinical studies, and 15 other research studies. Case reports were included as they provide valuable information in this fast-developing field. Moreover, cirAEs possess complex issues, including their presentation and appropriate management on a patient-to-patient basis, that are difficult to capture in randomized controlled settings. Two reviewers evaluated the literature search results and graded the clinical publications. Grading and rating of evidence included study type and quality (grade A to C) and level of evidence (level 1 to level 4) using pre-established criteria.[11] The paucity of studies on cirAE treatment, with both general skincare and prescription medications, made grading less relevant; however, the guidelines, systematic literature reviews, and consensus papers provided valuable information.

The Algorithm

An algorithm for the prevention and management of cirAEs was created based on the results of the systematic literature review as well as expert experience and opinion (Figure 1). The proposed algorithm expands on the NECOM algorithm for cancer-treatment-related cAEs.[24]

The target audience is physicians and other healthcare providers who treat cancer patients receiving immunotherapy and developing related cirAEs such as: medical oncologists, primary care physicians, internists, dermatologists, oncology nurses, advance practice providers (nurse practitioner/physician assistant), and pharmacists.

The algorithm is organized by degree of severity and type of eruption.

Immune Checkpoint Inhibitors and Associated Cutaneous Immune-Related Adverse Events

Treating Cutaneous Adverse Events of Immunotherapy

cirAEs have impact and consequences on many levels of the patient's life. Treating them is crucial. cirAEs are visible, they may alter the self-image of patients and reveal the cancer they want to sometimes keep secret. Symptoms associated with cirAEs such as pruritus and pain can disturb sleep, alter mobility and daily activities, or cause anxiety or depression. cirAEs have an important psychological impact, affecting QoL and impeding interpersonal and emotional life.[26] Patients most frequently report that they do not anticipate cAEs prior to starting cancer therapy and 67% of them report that dermatologic AEs are worse than their initial belief.[26] Patients and physicians may want to discontinue ICIs because of skin side effects, albeit it is often not indicated. Treating cirAEs can improve the cancer journey for patients and increase adherence and thus the success of anti-cancer therapy.

cirAEs range from mild to life-threatening. Common Terminology Criteria for Adverse Events (CTCAE v.5) is the most common grading system of skin disorders induced by cancer treatments.[27] Most common cirAEs are pruritus with or without prurigo nodularis, maculopapular eruption, eczema, psoriasis, lichenoid eruption, and vitiligo. Less common cirAEs include bullous pemphigoid (BP), alopecia areata, vasculitis, and neutrophilic dermatoses among others. Although rare, urgent and even fatal cutaneous toxicities can occur, and they need to be recognized early. They include SJS, TEN, overlap SJS-TEN, progressive immunotherapy-related mucocutaneous eruption (PIRME), and rarely acute generalized exanthematous pustulosis (AGEP) or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.[28]

CTCAE v5.0 has specific grading for pruritus, maculopapular rash, eczema, and bullous dermatitis (including bullous pemphigoid) (Table 2).[27] Psoriasis and lichen planus are graded using the non-specific category Skin disorders – Other (Table 2). SJS and TEN are always grade 4.

Eruption-Specific Treatment Recommendations

The treatment of cirAEs may improve patients' QoL and thus could increase cancer outcome through improved adherence to ICIs. Figure 1 shows the algorithm for the prevention and management of cirAEs based on results of the systematic literature review and expert experience and opinion (Figure 1). The algorithm starts with skincare routine that should always be discussed with patients on ICIs and should be put in place before, during, and even after immunotherapy. The second step is to search for severe signs and symptoms. When assessing a patient with cutaneous toxicities, it is important to determine the degree of severity and recognize features concerning for severe cutaneous adverse reactions (SCARs). They include fever, facial edema, skin pain, widespread cutaneous involvement, skin detachment, pustules, blisters, erosions, and mucosal involvement in the eye, nose, mouth, and genitalia. Patients need to be aware of these concerning signs and should seek urgent care via an oncologist and/or emergency department (ER) if they develop one or more of them. A dermatologist should also be consulted for proper diagnosis and treatment. Patients with cirAEs who are evaluated by a dermatology specialist are less likely to receive systemic immunosuppression or be taken off ICIs specifically for their dermatologic irAEs compared with patients who are not assessed by a dermatologist.[29]

Immunotherapy rarely needs to be permanently discontinued because of cirAEs except if the patient develops life-threatening conditions. Grade 4 cirAEs are rare and may include severe bullous pemphigoid, overlap SJS-TEN, TEN, PIRME, DRESS, and AGEP. The decision to discontinue immunotherapy has important impacts. There should always be a discussion between oncologists, dermatologists, other involved healthcare members, and the patient himself before making this final decision.

If SCARs have been excluded, the algorithm continues to the third step which includes the most common cirAES: pruritus, exanthematous or maculopapular eruption, eczematous eruption, lichen planus, psoriasis, and bullous eruptions. The intensity of the cirAE should be determined according to the CTCAE grading and patients should be treated accordingly. We recommend continuing the anticancer therapy whenever possible, especially for CTCAE grade 1 and 2 AEs. Communication between dermatologists and oncologists is of high importance.

Pruritus

Pruritus has a high impact on QoL and must be treated accordingly. Pruritus induced by immunotherapy is common, affecting 14 to 47% of patients.[8] It is more commonly associated with CTLA-4 inhibitor and a combination of CTLA-4 inhibitor and PD-1 inhibitor. Pruritus occurs early during treatment, usually in the first 3-10 weeks. Pruritus can be isolated in normal-appearing skin individuals or associated with another cirAE such as psoriasis, exanthematous eruption, eczematous eruption, and lichenoid eruption. Patients with pruritus can demonstrate secondary skin findings including excoriations, lichen simplex chronicus, and prurigo nodularis. Baseline workup should include blood works to exclude other causes of systemic pruritus. If the patient has pruritus out of proportion to what would be expected, bullous pemphigoid in its pre-bullous phase should be considered and investigated. Pruritus can be multifactorial and can be induced or worsened by xerosis. All patients on ICIs should be counseled on xerosis and reinforced to use gentle skincare with pH balance cleansers daily as per the algorithm. The treatment of ir-pruritus is often very challenging, Table 3 outlines recommendations for management.

Exanthematous Eruption

Exanthematous eruption, also known as morbilliform eruption or maculopapular eruption, is the most common cirAE. It can be

TABLE 2.

Common Terminology Criteria for Adverse Events (CTCAE v.5) Grading of Skin Disorders					
CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching; oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	--	--
Maculopapular rash	Macules/papules covering <10% body surface area (BSA) with or without symptoms	Macules/papules covering 10-30% BSA with or without symptoms; limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	--	--
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	--	--
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10-30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self-care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or non-invasive, intervention indicated; limiting age-appropriate instrumental ADLs	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

triggered by all ICIs but it is slightly more common with anti-CTLA-4 and a combination of anti-CTLA-4 and anti-PD1.32 It usually occurs quickly after the initiation of ICIs. An exanthematous eruption can be the initial presentation of more serious cirAEs such as PIRME, TEN, DRESS syndrome, and bullous pemphigoid. We recommend reassessing the patient shortly after starting treatment to monitor the evolution.

Eczematous Eruption

Eczema is another common irAE induced by ICIs. It is more commonly associated with PD-1 inhibitors and it affects ≤ 17% of patients.[8] In patients receiving ICIs, there is often an overlap between exanthematous eruption and eczematous eruption. Same as for patients with atopic dermatitis,[33] gentle skin care and moisturizers are a mainstay of treatment for ir-eczema (Table 5). Dupilumab, a human monoclonal antibody targeting IL-4 receptor alpha, has been an effective treatment for patients with ICI-induced eczema.[34,35]

Psoriasis

All psoriasis subtypes have been described with ICIs. Immune-related (ir) psoriasis can be new or a flare of pre-existing psoriasis and can occur anytime during or even after immunotherapy. It can be associated with ir-psoriatic arthritis. Management of moderate-to-severe ir-psoriasis is challenging. There is a lack of effective, safe, and evidence-based treatment options in a cancer setting. Acitretin is the safest systemic medication for psoriasis in cancer patients. Cyclosporine should be avoided due to its pro-tumor effect. The use of methotrexate is controversial, and various specialists disagree on its safety in a cancer setting. Most recent studies have shown no increase in malignancy except cutaneous squamous cell carcinoma

TABLE 3.

Treatment of Immune-Related Pruritus	
Grades 1 and 2	Moisturizers
	Potent to ultra-potent topical steroids (TCS)
	Non-sedating anti-histamines
Grade 3	Topical capsaicin
	Gabapentin, pregabalin
	Dupilumab
	Omalizumab
	Mu-Opioid Receptor Antagonist[30]
	Aprepitant[31]
	Systemic steroids if severe and refractory

(SCC) with low-dose methotrexate.[36] There is a lack of data on the safety of apremilast and biologics in a cancer setting. Biologics include TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors. IL-17 inhibitors should be used with caution due to their potential gastrointestinal side effects and symptoms mimicking immune-related colitis induced by ICIs.[37] According to experts, IL-23 inhibitors are the safest biologics to use because of their very targeted mechanism of action.

Lichenoid Eruption

ICIs can induce cutaneous and oral lichenoid reactions. It occurs mostly in patients receiving anti-PD-1 and anti-PD-L1.[32] Lichenoid reaction is one of the most refractory and difficult to treat cirAEs (Table 7).

Bullous Eruption

Immunotherapy can trigger numerous bullous and/or epidermal detachment eruptions including SCARs (SJS, TEN, PIRME, bullous DRESS syndrome) and mild-to-severe inflammatory bullous diseases (BP, pemphigus vulgaris[38]). Rare cases of erythema multiforme have been described.[39]

SJS and TEN are rare cirAEs and they can be delayed, developing after several cycles of treatment. PIRME is a recently described entity characterized by a generalized dusky erythematous eruption mimicking SJS/TEN in patients receiving ICIs, but with a slower/subacute onset, rare ocular involvement, and better response to treatments if well-recognized and treated.[40] PIRME is characterized by a milder disease course and less mortality.

BP is a well-reported irAE, although less common than pruritus, psoriasis, lichenoid, maculopapular, and eczematous eruptions.[8] It has a delayed onset, starting on average 10,1 months after the initiation of ICIs.[41] It can present with typical tense blisters but can also start with a milder presentation of nonbullous urticoid plaques and severe pruritus. BP should always be considered in cancer patients on ICIs with out-of-proportion pruritus. Skin biopsies for histopathology and direct immunofluorescence (DIF) and blood work for anti-basement membrane antibodies should be done. BP is challenging to treat (Table 8). Dupilumab,[34,41-44] omalizumab,[41] and rituximab[45] have been used to treat patients with ir-bullous pemphigoid.

Skincare for Cutaneous Immune-Related Adverse Events

Attention to prevention and early diagnosis ruling out life-threatening cAEs can improve patients' QoL, adherence to cancer treatment, and, therefore, outcomes.[46-52] Although data is scarce to support the prevention of severe skin sequelae for cancer patients and survivors, the NECOM panel agreed that early education on

TABLE 4.

Treatment of Immune-Related Exanthematous Eruption	
Grades 1 and 2	Moisturizers Moderate strength topical steroids BID Topical calcineurin inhibitors
Grade 3	Non-sedating antihistamines if pruritus Systemic steroids (prednisone or prednisolone) Consider a short interruption of ICIs if necessary

TABLE 5.

Treatment of Immune-Related Eczematous Eruption	
Grades 1 and 2	Moisturizers Topical steroids Topical calcineurin inhibitors Topical phosphodiesterase 4 (PDE4) inhibitor
Grade 3	Dupilumab, tralokinumab Phototherapy narrowband UVB (NB-UVB)[a] Systemic steroids if severe and refractory

[a]We recommend avoiding phototherapy in patients receiving ICIs for melanoma or other serious skin cancers even if there is no proven increase in skin cancer with broadband or NB-UVB.[36]

TABLE 6.

Treatment of Immune-Related Psoriasis	
Grades 1 and 2	Topical steroids, vitamin D analogs, retinoids, PDE4 inhibitors, salicylic acid, and tar
Grade 3	Phototherapy NB-UVB[a] Acitretin Methotrexate Advanced dermatological treatments (apremilast, guselkumab, risankizumab, tildrakizumab)

[a]We recommend avoiding phototherapy in patients receiving ICIs for melanoma or other serious skin cancers even if there is no proven increase in skin cancer with broadband or NB-UVB.[36]

preventive measures using skincare is beneficial to patients.[23] The multidisciplinary oncology team ideally including a dermatologist should build a therapeutic relationship with the patient enabling their active participation in the cancer treatment plan.[23,49] Before initiating treatment, the treating physician and nurse, or other multidisciplinary oncology team members should have a detailed and lengthy conversation with the patient addressing the treatment protocol, potential cirAEs, hospital visits, diagnostic tests, management of cirAEs, and preventive measures.[23,50,51] Verbal information should be supported by printed or digital material to allow the patient to clarify and process the information.[23,50,51] Cancer patients may underreport their cAEs as they may not recognize it as potentially serious or assume the condition is not treatment-related, so informing them about the potential risk for cirAEs is of high importance. Patients should be encouraged to report new symptoms early and a member of the multidisciplinary oncology team should be available to assess these new findings rapidly. Frequent communication between the patient and the oncology team is of high importance in order for patients to be comfortable discussing any worries or symptoms. cirAEs are typically more responsive to therapies with lower severity grades. Thus, early identification and intervention of cirAEs is ideal.

Preventive measures for cirAEs, including a skincare regimen, should be used throughout cancer treatment and continued after that. It is recommended to initiate a skincare routine prior to the anticancer treatment. A daily skincare regimen should include three simple steps: cleanse, moisturize, and protect. It should comprise gentle cleansers, moisturizers that help restore skin barrier integrity and function, photoprotection using sun avoidance measures, and sunscreen.[23,50,51] According to the NECOM panel, the choice of skincare regimen needs to be tailored to the individual patient and may be dependent on the patients' individual preferences.

Skincare formulations should be safe, effective, easy to use, and cosmetically pleasant. Products that contain allergens and irritants such as common preservatives, fragrances, perfumes, or sensitizing agents are unsuitable for oncology patients. Gentle cleansers should be used instead of regular soap. Cleansers should have a near-physiological skin pH (4.0–6.0). Soaps, surfactants, and detergents, especially those with an alkaline pH (>7), remove skin lipids and elevate skin surface pH, triggering inflammation and lowering the diversity of the skin microbiome and should also be avoided. Showers and baths should be of limited time (5 minutes or less), using warm, not hot, water.

Moisturizers form a barrier that helps prevent transepidermal water loss, restore skin elasticity, and sustain skin homeostasis.[53] There is growing evidence on a skincare regimen for the prevention and treatment of cAEs that benefits cancer patients undergoing anticancer treatment and cancer survivors; however, the evidence on specific ingredients is scarce. Hydrophilic humectants, such as glycerol, propylene glycol, butylene glycol, and AHAs including lactic, glycolic, and tartaric acids, may help to retain moisture in the skin of patients in general, unrelated to cancer or cancer treatment. AHAs should be used with caution as they can change the skin surface pH and be irritants. Same as for cleansers, moisturizers should have a near-physiological skin pH (4.0–6.0). Creams and ointments are better choices than lotions because of their higher oil-to-water ratio content, especially in the winter. The NECOM panel recommends choosing a moisturizer vehicle based on skin condition, level of xerosis, and patient preference. Moisturizers

TABLE 7.

Treatment of Immune-Related Cutaneous Lichenoid Eruption	
Grades 1 and 2	Moderate strength topical steroids. Can increase to ultrapotent if refractory. Topical calcineurin inhibitors Intralesional steroids in localized or hypertrophic lesions
Grade 3	Advanced dermatologic therapies (phototherapy NB-UVB,[a] acitretin, hydroxychloroquine, immunosuppressants) Short course of systemic steroids

[a]We recommend avoiding phototherapy in patients receiving ICIs for melanoma or other serious skin cancers even if there is no proven increase in skin cancer with broadband or NB-UVB.[36]

TABLE 8.

Treatment of Immune-Related Bullous Pemphigoid	
Grade 1	Class 1 topical steroids Doxycycline and nicotinamide
Grade 2	Systemic steroids (prednisone or prednisolone 0.5 mg/kg/day)
Grade 3	Systemic steroids (prednisone or prednisolone 1 mg/kg/day) Dupilumab, omalizumab, rituximab, methotrexate, or other steroid-sparing agent Suspend ICI; restart when back to grade 1 and when prednisone 10 mg/day or less
Grade 4	Admission, inpatient care, consider burn unit Systemic steroids (methylprednisolone 2 mg/kg/day) Discontinue ICI

should be applied to a full body surface at least once a day, ideally several times daily, and immediately after bathing or showering and soft pat drying. Moisturizer effectiveness depends on the formulation, the vehicle, frequency, and compliance of applications. Some patients want to wait until cirAEs appear before moisturizing; clinicians should communicate with patients about the benefits of proactive prophylactic moisturization.

Sun protection is of high importance. Patients should apply sunscreen with a sun protection factor (SPF) of 30 or higher. We should also encourage them to avoid sun exposure between 10 AM and 4 PM and to wear long sleeves, ideally photoprotective clothing, a brim hat, and sunglasses.

Skincare product choices and regimens depend on the skin condition, availability, costs, and individual preferences. It is important to look at the patient holistically and acknowledge socioeconomic factors involved in their access to resources and willingness to adhere to recommended practices.

CONCLUSION

ICIs have revolutionized cancer treatment. Despite their positive impact on cancer outcomes, they commonly induce cirAEs ranging from mild to life-threatening and impacting patients' QoL. It is important to recognize and treat cirAEs to decrease unnecessary treatment delays or early discontinuation of potentially life-saving ICIs and to improve the overall care of cancer patients. Patient education, therapeutic relationships, and frequent, open communication between patients and oncology team members are essential. Patients should be encouraged to adopt a proactive approach to caring for their skin before, during, and after cancer immunotherapy using three simple steps; cleanse, moisturize, and protect. Simple skincare measures can prevent and attenuate cirAEs. Recommendations given in the NECOM 4 algorithm may help prevent and manage cirAEs and improve patients' cancer journey.

DISCLOSURES

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