doi:10.36849/JDD.84821

 ORIGINAL ARTICLE

USCOM V: A Practical Algorithm for the Prevention and Treatment of Cutaneous Side Effects of Hormonal Cancer Therapy

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ABSTRACT

Introduction: In 2024, over 2 million patients will be diagnosed with cancer in the United States, with prostate cancer and breast cancer representing the leading diagnoses in men and women, respectively. Hormonal therapy is a mainstay treatment for hormone-dependent cancers but is associated with cutaneous adverse events. These include accelerated signs of aging, xerosis and pruritus, brittle nails, androgenic alopecia, and hirsutism. All clinicians involved in the care of these patients play an essential role in managing treatment-related cutaneous adverse events to minimize the burden on patients and improve their quality of life.

Objectives: To develop a multidisciplinary, physician-developed algorithm to guide the care of patients who develop cutaneous hormonal therapy-related adverse events.

Methods: A panel of advisors was selected, and a systematic literature review generated evidence to develop a treatment algorithm for managing cutaneous hormonal therapy-related adverse events via a modified Delphi process. The algorithm was developed based on the assembled evidence coupled with the panel's experience and opinion.

Results: An algorithm that tailors the prevention and management of cutaneous hormonal therapy-related adverse events in cancer patients used the CTCAE v.5 grading of cancer therapy-related skin disorders. Suggested management recommendations supplement the algorithm.

Conclusions: Prevention, recognition, and treatment of cutaneous hormonal therapy-related adverse events through the use of a physician-developed algorithm may limit treatment interruption, improve patient outcomes, and optimize the quality of life in patients on hormonal cancer therapy.

J Drugs Dermatol. 2025;24:4(Suppl 2):s3-14.

INTRODUCTION

In 2024, an estimated 2,001,140 new cancer cases and 611,720 cancer deaths are projected to occur in the United States.[1] Hormone-dependent cancers, such as breast cancer and prostate cancer, are responsible for most new cancer cases. Breast cancer is the leading cancer diagnosis among women, with an estimated 310,720 women and 2,790 men expected to be diagnosed with breast cancer in 2024. Meanwhile, prostate cancer is the leading cancer diagnosis among men and the second most common diagnosis overall, with 299,010 expected cases.[2]

Although cancer incidence continues to rise, advancements in treatment options have contributed to the decline in cancer mortality.[1,3] Hormonal therapy is a mainstay treatment for the management of hormone-dependent cancers. In breast cancer, hormonal therapy often involves reducing estrogen levels or blocking estrogen receptors. For prostate cancer, therapy typically aims to lower testosterone levels or block its effects through androgen deprivation therapy or antiandrogens.

Hormonal therapies are associated with improved survival and prolonged time to disease progression but can also lead to treatment-related side effects. Cutaneous adverse events (cAEs) involving the skin, mucosa, hair, and nails are common and varied in patients treated with hormonal therapy. Although not typically life-threatening, these side effects can lead to suboptimal adherence and reduced quality of life. Appropriate preventative and management strategies are critical to optimize the comprehensive care of patients with cancer, help avoid unnecessary treatment discontinuation, and improve quality of life.[3-5]

Project Update

The US cutaneous oncodermatology management (USCOM) project was developed to improve the quality of life of cancer patients and survivors by offering tools for preventing and managing cAEs related to cancer therapy.

The USCOM consortium has previously published 4 foundational algorithms for skin management in cancer patients: 1) an algorithm to reduce the incidence of cAEs, treat cAEs, and maintain healthy skin using general measures and over-the-counter agents, 2) an algorithm to prevent and treat acute radiation dermatitis, 3) an algorithm to prevent and treat immunotherapy-related cAEs, and 4) an algorithm for the prevention and treatment of targeted therapy-related cAEs. These algorithms aim to support all healthcare providers (HCPs) treating oncology patients, including physicians, nurses, pharmacists, and advanced providers.

The next step in the project is to develop a practical, evidence-based algorithm for the prevention and treatment of hormonal therapy-related cAEs, which we propose here. This project aims to improve patient comfort during/after treatment, reduce and treat cAEs, and promote the healing of affected skin areas using prescription medication and skincare. The target audience is not only dermatologists but also a broad range of HCPs, including nurses, physician assistants, and pharmacists.

METHODS

A selected group of multidisciplinary advisors used the AGREE II instrument following the modified Delphi method to develop the USCOM V practical algorithm for preventing and treating hormonal-therapy-related cAEs. The modified Delphi method is a communication technique for interactive decision-making for medical projects.

During a face-to-face meeting on March 7, 2024, the outcome of a structured literature review identifying the spectrum of cAEs 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 practical algorithm and prepare and review the publication.

Literature Review

The systematic literature review included guidelines, consensus papers, reviews, and best practices on cAEs related to hormonal therapy published in English from January 2010 to January 2024. Articles were excluded if they contained no original data, did not deal with prescription treatment and/or skincare for cAEs related to hormonal therapy, or if the publication language was other than English.

A dermatologist and a physician-scientist conducted the searches on January 25 and 26, 2024. PubMed was the primary search engine, with Google Scholar as a secondary source. The search criteria used were as follows: *cAEs related to hormonal therapy AND QoL of patients/survivors OR education of staff and patients/survivors OR communication strategies OR prescription medications OR skincare OR topical regimes for prevention OR treatment OR maintenance OR adjunctive skincare OR adherence OR concordance OR efficacy OR safety OR tolerability OR skin irritation.*

The searches yielded 197 publications. After excluding duplicates and articles not deemed relevant (poor quality), 128 papers remained. Of these, 99 addressed hormonal treatment, 6 guidelines included hormonal therapy, and 23 discussed hormonal therapy-related cAEs, treatment, and skincare (9 hot flashes, 1 alopecia, 1 erythema, 2 urticarial vasculitis, 10 skincare, and other).

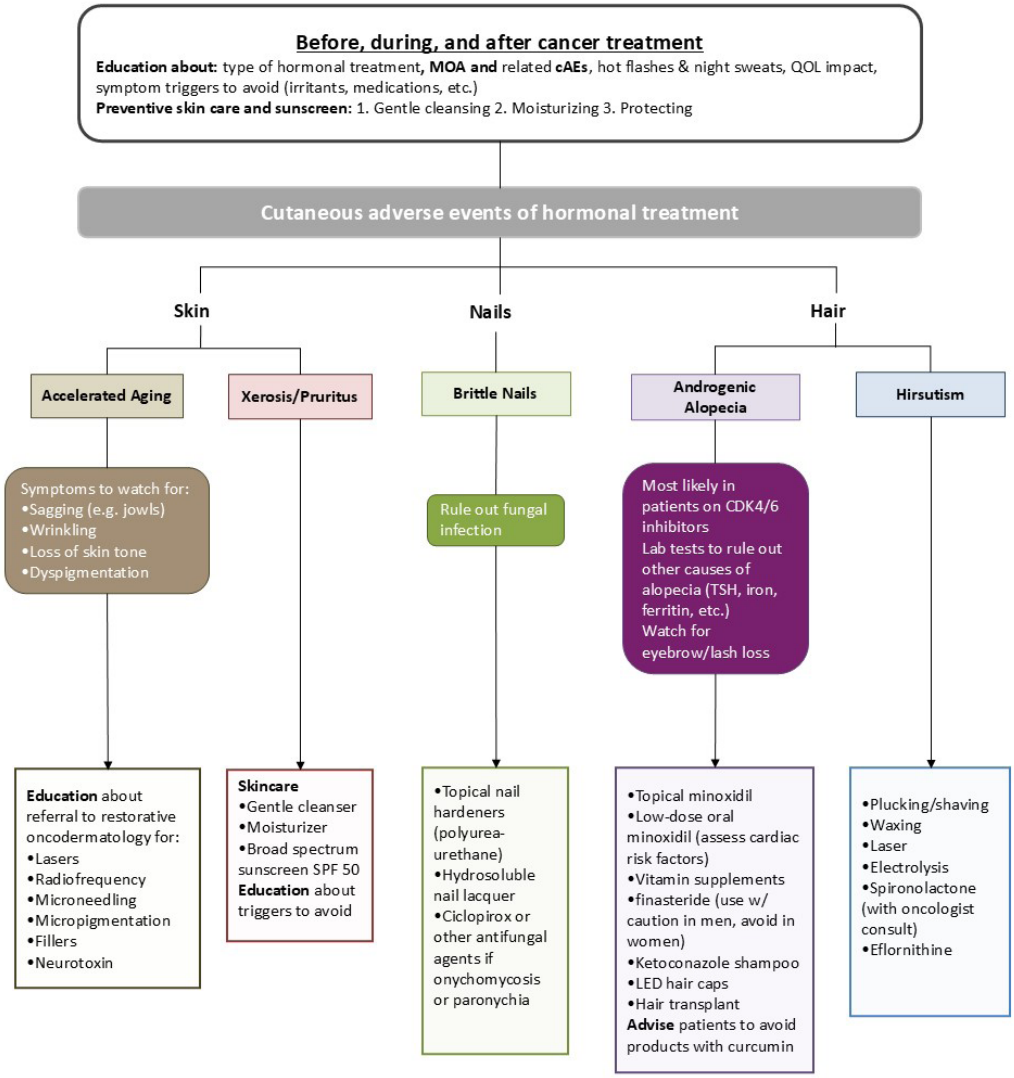
The results of the literature review were evaluated independently by 2 reviewers. Each clinical publication was graded by study type and quality (grade A to C) and level of evidence (level 1 to level 4) based on reviewer consensus. Any discrepancies were resolved by discussion. The reviewers then drafted an algorithm to improve patient comfort during and after treatment, reducing and treating cutaneous adverse events and promoting healing of affected skin areas using prescription treatment and skincare.

The Algorithm

An algorithm for preventing and managing hormonal cancer therapy-related cAEs was created based on the results of the structured literature review and expert experience and opinion (Figure 1). As with previous USCOM algorithms for the prevention and management of cutaneous targeted therapy-related adverse events, which utilized the Common Terminology Criteria for Adverse Events (CTCAE) grading system v.5,6, the proposed algorithm expands upon the algorithm for cancer-treatment-related cAEs (Table 1).

Early identification of severe cAEs, which may be detected by signs and symptoms including fever, skin pain, epidermal changes, high body surface area involvement, or laboratory abnormalities, is an important first step because, regardless of the cutaneous reaction, the patient will require immediate evaluation by a dermatologist

FIGURE 1. USCOM V Algorithm for the prevention and management of hormonal therapy-related cutaneous adverse events.



cAE = cutaneous adverse event; MOA = mechanism of action; QOL = quality of life; TSH = thyroid stimulating hormone.

and often inpatient or ICU level care. When emergent signs or symptoms are absent, recommendations become specific to the type of cutaneous reaction with therapeutic distinctions.

Treatment recommendations for specific cAEs are expanded upon below. Interventions are stepwise based on cAE severity and offered alongside grade-based recommendations for discontinuation or interruption of hormonal therapy.

Types of Cancers Treated with Hormonal Therapy

Hormonal therapy is often given as adjuvant treatment for breast cancer and prostate cancer to reduce levels of hormones that can stimulate the growth of cancer cells.[7,8] Approximately two-thirds of breast cancers are hormone receptor-positive; patients diagnosed with this subtype often receive hormonal therapy to reduce the risk of cancer recurrence. Hormonal treatment for breast cancer consists of aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), selective estrogen receptor degraders (SERDs), rash, and high-dose hormones.[7,9] Prostate cancer cells need androgens to grow, so hormonal therapies for prostate cancer decrease androgen levels by interfering with androgen production or blocking androgen actions. Hormonal treatment for patients with prostate cancer includes luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, androgen receptor blockers, and androgen synthesis inhibitors.[8]

Hormonal Therapies and Associated Cutaneous Adverse Events

Hormonal therapies for breast and prostate cancer are associated with various cutaneous adverse events that can affect the skin, hair, and mucosal surfaces (Table 2).[10] Breast cancer patients and survivors are known to experience adverse effects attributed to estrogen deprivation from hormonal therapy.[11] Signs of accelerated aging, xerosis and pruritus, nail changes, alopecia, and vulvovaginal atrophy are experienced by many patients taking SERMs and AIs. In addition to symptoms associated with reduced estrogen levels, these medications can also cause androgenic alopecia and hirsutism.[12,13] Meanwhile, the most common cAEs

TABLE 1.

Common Terminology Criteria for Adverse Events (CTCAE v.5) Grading of Skin Disorders[6]

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Accelerated Aging	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	--	--	--
Xerosis	Covering <10% BSA and no associated erythema or pruritus	Covering 10 to 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	--	--
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	--	--
Brittle Nails	Present	--	--	--	--
Androgenic Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psycho-social impact	-	-	-
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	--	--	--

BSA: body surface area; ADL: activity of daily living

TABLE 2.

Hormonal Therapies and Associated Cutaneous Adverse Effects[5,12,13,15]

Drug Class	Drug Name	Oncologic Indication	Cutaneous Adverse Events
Aromatase inhibitors	Anastrozole, exemestane, letrozole	Breast	Accelerated aging, xerosis, pruritus, alopecia, nail changes, vulvovaginal atrophy, rashes
SERMs	Tamoxifen, raloxifene, toremifene	Breast	Accelerated aging, xerosis, alopecia, hirsutism, nail changes, vulvovaginal atrophy
SERDs	Fulvestrant	Breast	Alopecia
High-dose hormones	Ethinyl estradiol, fluoxymesterone, megestrol acetate	Breast	Alopecia, hirsutism
Androgen receptor blockers	Bicalutamide, flutamide, nilutamide, enzalutamide, apalutamide, darolutamide	Prostate	Alopecia, xerosis, pruritus
LHRH agonists	Goserelin, histrelin, leuprolide, triptorelin	Prostate	Alopecia, pruritus
LHRH antagonists	Degarelix, relugolix	Prostate	Alopecia, pruritus, rashes
Androgen synthesis inhibitors	Abiraterone, ketoconazole, aminoglutethimide	Prostate	Xerosis, pruritus, rashes

LHRH, luteinizing hormone-releasing hormone; SERMs, selective estrogen receptor modulators; SERDs, selective estrogen receptor degraders.

with androgen deprivation therapy (ADT) for prostate cancer are alopecia, xerosis, pruritus, and hirsutism.[12,14]

Skin reactions associated with hormonal therapy for breast and prostate cancer can significantly reduce patient quality of life and threaten treatment adherence. Therefore, counseling patients before treatment initiation is essential to assess patients for risk factors, inform them about possible cAEs, and identify effective interventions to promote treatment adherence. By aiding in the prevention, recognition, and management of cAEs, dermatologists can limit treatment interruption, improve patient outcomes, and improve the quality of life in patients on hormonal therapy.[5]

All patients should be educated on the value of a proactive and preventive skin care regimen that includes the use of gentle cleansers, moisturizers, and sun protection (Table 3). Gentle skin cleansing and maintaining compromised skin hydration is an important element of skin care management during cancer therapies. One approach is to recommend that patients moisturize twice daily with emollients such as lotions, creams, or ointments.[16] Emollients that include ingredients such as niacinamide may help restore the skin barrier function. Patients should also be counseled to minimize scrubbing and avoid potential allergens and irritants, such as products with fragrance.[5]

If cAEs arise, the decision to discontinue or interrupt hormonal therapy should be made in consultation with an oncologist and/or dermatologist for grade 3 reactions, while grade 4 reactions are life-threatening and require immediate treatment discontinuation, in addition to urgent care and hospitalization. Therefore, recognizing adverse events and assessing the degree of severity remain essential.[6]

Event-Specific Treatment Recommendations

Accelerated Signs of Aging

Premature/accelerated aging is a significant yet often overlooked side effect of hormonal anticancer therapies (Table 4). The mechanism behind this process is closely tied to the reduction in estrogen levels experienced with breast cancer treatment. Diminished estrogen levels affect facial skin by causing a decrease in sebum production, collagen content, dermal thickness, and elastin fibers.[19] This can lead to skin changes, including decreased elasticity, increased dryness, epidermal thinning, fine wrinkling, and impaired wound healing.[20-22] In women with breast cancer, changes in physical appearance have been identified as 1 of the most significant causes of distress.[23]

It is important to educate patients about the need to use broad-spectrum sunscreen with UVA and UVB filters along with sun avoidance practices (eg, long-sleeved clothing, hats) to protect the skin and prevent the appearance of new wrinkles.[24] Patients who experience sunscreen irritation can be advised to use sunscreens with physical blockers, such as zinc oxide or titanium dioxide.[17] Topical retinoids may be recommended to increase collagen and improve wrinkles.

Communication with the patient's primary oncologist is necessary to discuss potential aesthetic interventions. Although active cancer treatment may not be an absolute contraindication to performing neuromodulation, dermal filler, or laser resurfacing treatments, these treatments must be approached with caution. A comprehensive review of the patient's medical history, including current treatments and potential immune system impairment, should be conducted. If the patient is neutropenic (ie, after bone marrow transplant and pre-engraftment), elective procedures

TABLE 3.

General Skin, Hair, and Nail Care Recommendations[17,18]		
Dermatologic Process	**Products/Ingredients To Look For**	**Products/Ingredients To Avoid**
Cleansing	Mild cleanser that is mildly acidic to neutral pH (4-6.5)	Abrasive ingredients, alkaline cleansers, fragrances
Moisturizing	Moisturizers with emollients or occlusives	Fragrances
Sun protection	Broad-spectrum sunscreen with SPF of 30 or higher	--
Hair care	Minoxidil	--
Nail care	Topical emollients, FDA-approved nail lacquers	--

SPF, sun protection factor; FDA, Food and Drug Administration.

TABLE 4.

Treatment for Accelerated Aging[12]		
Signs Of Accelerated Aging	**First-Line**	**Second-Line**
Premature Aging (Rhytides, dyschromias)	Sunscreen, topical retinoids	Rhytides: Neuromodulators, laser resurfacing Dyschromias: Chemical peels, laser resurfacing, or vascular/pigment- specific laser, topical hydroquinone
Volume Loss	Dermal fillers	--

should be delayed. Antimicrobial prophylaxis may be considered for individuals with an impaired immune system or on active treatment undergoing more invasive cosmetic procedures. Post-procedure wound care should be thoroughly reviewed, particularly in patients with a higher risk of infection, bruising, or delayed healing. Additional data regarding safety and optimal timing of treatment is needed.[12]

Topical retinoids are recommended as a first-line option to improve skin texture and reduce noticeable signs of photoaging. Ablative and non-ablative laser resurfacing can address skin laxity and fine rhytides in patients reporting accelerated skin aging.[12]

Neuromodulators and dermal fillers can improve facial rhytides and restore volume loss. A small study demonstrated the safety and efficacy of hyaluronic acid (HA) fillers and neuromodulators at least 6 months post-chemotherapy. However, injecting exogenous HA in areas of known active cancer should be avoided as the interaction between exogenous HA and tumor microenvironment has not been fully elucidated. Dermal fillers and neuromodulators for specific cancer-related issues may be performed on a case-by-case basis; a complete medical history review is necessary.[12]

Xerosis and Pruritus

Xerosis and pruritus are common side effects of anticancer therapies, often leading to significantly reduced health-related quality of life.[4,25] These conditions are associated with many types of cancer treatments, but they are most prevalent in EGFR inhibitor therapy, with studies reporting xerosis rates up to 90% and pruritus rates of up to 60% in patients taking EGFR inhibitors, with increasing numbers in long-term therapy of up to 100% for both xerosis and pruritus in patients treated at least 6 months.[26]

Xerosis and pruritus have also been reported in breast cancer patients receiving hormonal therapy, such as AIs or tamoxifen.[27,28] Since estrogen plays a crucial role in maintaining skin hydration, elasticity, and barrier function, its depletion can exacerbate skin dryness and itching. A systematic review and meta-analysis of clinical trials found that the incidence of all-grade xerosis was 1to 4% with aromatase inhibitors and the incidence of high-grade xerosis was up to 0.6% with aromatase inhibitors.[28]

Patients undergoing prostate cancer treatment also commonly experience xerosis and pruritus. In a study of 303 prostate cancer patients treated with apalutamide, 32.4% of patients reported xerosis and 28% experienced associated grade 1/2 pruritus.[14] Similarly, xerosis has been observed following antiandrogen treatments such as flutamide and ketoconazole.[29] The prevalence of these skin conditions in prostate cancer patients can be attributed to the role of androgens in skin health. Androgens significantly influence lipid and sebum production, which are crucial for maintaining proper skin barrier function. Consequently, a reduction of androgen levels or the blocking of androgen activity may explain the incidence of xerosis in these patients.[30]

Xerosis

The burden of xerosis in oncology patients cannot be understated. In a quantitative study that asked cancer survivors (n=379) which dermatologic toxicity was particularly damaging or caused a negative effect, the most frequent answer (63%) was skin dryness.[25] In practice, xerosis often presents as diffuse fine scaling.[17] However, it is often the precursor to more significant skin complications, such as fissuring,[17] infections,[5] sensitization to allergens, and pruritus. Timely identification and treatment are important to halt the evolution into more serious skin complications.

The successful management of xerosis begins with prevention. Regular use of moisturizers may mitigate dry skin and help maintain skin integrity, thus minimizing the risk of cracks and fissures, pruritus, and skin infections.[16,17] Emollients, particularly those containing urea and niacinamide, help maintain maximal skin hydration and decrease transepidermal water loss.[17] Providers should also educate patients on avoiding hot showers, scrubbing, and products containing fragrances, alcohol, or elevated pH.[17]

Pruritus

Pruritus is common with many anticancer therapies. In most cases, patients will have no visible skin lesions other than xerosis. However, possible skin alterations include excoriations from scratching or prurigo nodules.[4]

As dry skin is a common precursor to pruritus, it is important to implement preventative measures to prevent skin dryness.[31] Many cases of pruritus can be avoided by diligent skin care with non-fragranced creams and lotions containing ingredients like ceramides, niacinamide and shea butter. Triggers such as ultraviolet (UV) radiation exposure, extensive washing and other stress to the skin (mechanical, heat, humidity, occlusion) should also be avoided.[4]

If pruritus occurs, skin care with the above emollients is central to treatment.[4] For mild to moderate pruritus, a topical corticosteroid (eg, mometasone furoate 0.1% ointment or betamethasone valerate 0.1% ointment) could be considered (Table 5).[31] Non-sedating, second-generation antihistamines (eg, loratadine 10 mg daily) may be recommended as the first choice for systemic therapy for pruritus during daytime, while first-generation antihistamines (eg, diphenhydramine 25 to 50 mg daily) may be considered in patients who suffer from pruritus during night time, based on their sedative properties.[31] Due to limited evidence in oncology patients treated with hormonal therapy, antiepileptic agents (eg, pregabalin 25 to 150 mg daily and gabapentin 900 to 3600 mg daily) may be considered as second-line treatment in patients who fail antihistamines and those who continue to

TABLE 5.

Hormonal Therapies and Associated Cutaneous Adverse Effects[5,12,13,15]

Symptom	CTCAE Grade	Intervention	Notes
Pruritus	Grade 0 (prevention)	Gentle skin care	--
	Grade 1	Topical moderate/high potency steroids	Continue drug at current dose and monitor for change in severity. Reassess after 2 weeks (either by HCP or patient self-report); if reactions worsen or do not improve, proceed to next step.
	Grade 2	Topical moderate/high potency steroid OR Oral antihistamines OR GABA agonists (pregabalin/gabapentin)	Continue drug at current dose and monitor for change in severity. Reassess after 2 weeks (either by HCP or patient self-report); if reactions worsen or do not improve, proceed to next step.
	Grade >3 (or intolerable grade 2)	Topical moderate/high potency steroid OR Oral antihistamines OR GABA agonists	Interrupt treatment until G0/1 and treat skin reaction. Reassess after 2 weeks; if reactions worsen or do not improve, discontinuation may be necessary.

HCP, healthcare provider.

experience clinically significant pruritus.[31] In severe cases, the patient should be referred to a dermatologist to optimize the treatment. Systemic corticosteroids (0.5 to 2 mg/kg daily) may be considered for temporary relief of particularly severe pruritus.[31] Dupilumab has been increasingly used in cancer patients who experience dermatitis, bullous pemphigoid or pruritus and may be considered in recalcitrant cases after oncology consultation.[32]

Brittle Nails

Nail toxicity represents one of the most common cutaneous adverse effects of both classic chemotherapeutic agents and new oncologic drugs, including targeted treatments and immunotherapy.[33] While nail changes are more commonly associated with chemotherapy or targeted therapies,[4] they can also occur as a side effect of hormonal therapies. In a study of 152 patients diagnosed with breast cancer and undergoing treatment with chemotherapy, radiotherapy, hormone therapy and/or surgery, 7.9% of those receiving hormone therapy complained of nail changes.[34]

Onychorrhexis is one potential change to nail health, characterized by nails that split, flake, become soft, and lose elasticity.[35] Other common nail manifestations of cancer treatment include Beau's lines (deep ridges that form horizontally across the nail because treatment temporarily stopped the nail from growing), koilonychia (indented or concave nails), onycholysis, paronychia, and nail infections including bacterial and fungal etiologies.[13]

Drug-associated nail changes are almost never life-threatening, but they can significantly impair patients' quality of life, often restricting their daily life and self-care activities.[33] Dermatologists, oncologists, and other physicians should be aware of these burdensome adverse effects in order to guide management and prevent impairment of patients' quality of life.[33]

Counseling patients on the prevention of nail adverse effects is essential. Patients should be provided with clear and detailed information on appropriate prevention strategies. These include using protective gloves and comfortable, wide-fitting footwear and cotton socks, avoiding repeated trauma, friction, and pressure, avoiding prolonged water contact and harsh chemicals, and trimming nails regularly.[18,36] Nails should be kept straight/squared and not too short. Manicures and pedicures should be avoided due to the risk of infection and potential exacerbation of treatment side effects.[36]

Gentle hand and foot care is recommended. Patients should keep their hands and feet moisturized with emollients like plain, white petrolatum that do not contain perfumes or active ingredients. Nail lacquers are also recommended to limit water loss from the nail plate, especially for brittle nails.[33] Both topical emollients and FDA-approved nail lacquers can be used daily.[18]

If nail toxicities occur, early recognition and treatment can minimize their impact, allowing better adherence to conventional and newer oncologic treatments.[33] Nail manifestations that are fungal in origin (eg, onychomycosis or candidal paronychia) can be treated with ciclopirox or other antifungal agents.[37] The management of brittle nails involves continuing or intensifying all preventive measures, including moisturization of the nail plate, not just the skin around the nails.[4] In addition, some patients may benefit from local application of urea-containing nail polish for brittle nails.[4] Patients with brittle nails should take caution to avoid prolonged continuous exposure of their nails to water, such as washing dishes without the use of protective gloves.

Androgenic Alopecia (AGA)

A reversible, androgenic pattern of alopecia, usually of mild-to-moderate severity (grades 1 to 2) may develop with a number of anticancer therapies.[39] Alopecia is also a common yet underreported adverse event of hormonal cancer therapies.[40] In a meta-analysis of 35 studies with over 13,000 patients treated with hormonal therapy, the overall incidence of all-grade alopecia was

FIGURE 2. Androgenetic alopecia (AGA).

Graphic reproduced from Belgravia Centre

4.4%, with the highest incidence (25%) in patients treated with tamoxifen, followed sequentially by treatment with anastrozole (14.7%).[40] The risk for alopecia was increased when endocrine therapies were used in combination and with targeted therapies such as CDK4/6 inhibitors, supporting an additive or synergistic effect in the development of alopecia when agents are combined.[40]

Alopecia has been cited as the most traumatic dermatologic adverse event in approximately 58% of women receiving breast cancer treatment,[40] with up to 8% of survivors indicating they would discontinue therapy due to this dermatological adverse effect.[41] Women experiencing alopecia also report lower self-esteem, poorer body image, and lower quality of life (QoL).[39] In 112 patients diagnosed with endocrine-induced alopecia, 93% had mild alopecia (grade 1, <50% of hair loss), yet these patients reported a negative emotional impact when compared to the other psychological domains. This highlights the importance of considering the distress that any grade of alopecia may have on cancer survivors' quality of life.[11]

Androgenic alopecia typically manifests as female pattern hair loss, with diffuse thinning over the top of the scalp without a recession of the frontal hairline and the "Christmas tree pattern" along the center part (Figure 2).[10,31] This pattern of alopecia may result from increased androgen levels caused by hormonal therapies, which shorten the anagen (growth) phase of the hair cycle, causing the follicles to shrink and leading to hair thinning and eventual hair loss. Tamoxifen may also increase androgen receptor signaling in the hair follicle and contribute to follicular miniaturization.[10]

Before starting hormonal therapy, clinicians need to communicate the risk of alopecia with patients. As there are limited preventative options, patients should be informed about aids, such as hats, scarves, or wigs.[4,31] Automated scalp cooling systems can also be used in breast cancer patients receiving anthracycline and taxane-containing chemotherapies to minimize chemotherapy-related alopecia, but not for hormone therapy-related alopecia.[42,43] Scalp cooling works by narrowing the blood vessels beneath the skin of the scalp, which reduces the amount of chemotherapy medicine that reaches the hair follicles. With less chemotherapy medicine in the follicles, the hair may be less likely to fall out. The cold also decreases the hair follicles' metabolic activity, which makes the cells divide more slowly and protects the follicles from the chemotherapy. The FDA initially approved this system for breast cancer in 2015, and later expanded its use to patients with any solid tumor. Patients should also be encouraged to seek consultation immediately if they notice hair loss.[5] Digital photography can be used to help monitor hair changes.

If patients on hormonal therapy present with alopecia, other causes of hair loss should first be ruled out by evaluating serum iron, serum ferritin, total iron binding capacity, TSH levels, vitamin D, zinc levels, and a complete blood count.[5,31] After ruling out other causes of alopecia, individuals with mild alopecia can use over-the-counter (OTC) topical minoxidil 2% to 5% twice daily (Table 6). While 5% minoxidil foam was first approved for men, it is now approved for both men and women.[44] Patients have flexibility to select their preferred strength and formulation, with some clinicians recommending the 5% minoxidil formulation for women.[45] Low-dose oral minoxidil can also be considered following a patient assessment for cardiovascular risk factors. Since minoxidil acts a systemic vasodilator, it can lead to reflex tachycardia that can provoke myocardial ischemia. Therefore, oral minoxidil should be avoided in patients who have angina or recent myocardial infarction. Furthermore, minoxidil can promote substantial fluid retention and should thus be avoided in patients

TABLE 6.

Hormonal Therapies and Associated Cutaneous Adverse Effects[5,12,13,15]

Line of treatment	Medication	Formulation/Dosage	Comments
First-line treatment	Topical minoxidil	2 to 5% BID	Before starting treatment, check TSH, iron, ferritin, vitamin D, zinc.
Second-line treat-ment	Oral minoxidil	Variable doses, can start at 1.25 mg/day	Topical treatments can be started during chemotherapy. Wigs, hats, and camouflage powders may be recommended. Regarding spironolactone, decision should be made in consultation with oncologist due to the potential risk of hormonal stimulation in patients with HR+ tumors
	Oral minoxidil	Variable doses, can start at 1.25 mg/day	

BID, twice daily; TSH, thyroid stimulating hormone.

with heart failure or those at high risk for it. Minoxidil is best avoided in patients with left ventricular hypertrophy because it can promote ischemia and fluid retention. Patients who develop symptoms of chest pain, dyspnea, or persistent edema while taking low-dose oral minoxidil for alopecia should undergo prompt investigations.[46,47] In patients with grade 2 alopecia or in cases refractory to topical or oral minoxidil, spironolactone may be considered after discussion with the oncologist. Spironolactone in doses ranging from 50 to 200 mg daily is used to treat AGA and hirsutism and has been used in women with breast cancer on endocrine therapy. Oncology consultation is recommended given the potential risk for hormonal stimulation in patients with HR+ tumors. Further studies are needed to assess the long-term safety in this population.[48] In addition to medical approaches, wigs, tattooing, tinted powders, or extensions may help conceal low-grade hair loss.[5,31] Bimatoprost ophthalmic solution (0.03% daily) may be considered if eyelash hair loss occurs but is not generally recommended.[31]

Low-level laser therapy (LLLT) is a new device-based modality for stimulating hair growth in men and women in AGA.[49] Randomized controlled trials demonstrated statistically significant hair regrowth by terminal hair count in both males and females. Therefore, LLLT is a potential option for patients with androgenic alopecia who do not respond or are intolerant to standard treatment. However, the level of evidence in the studies is still low, and more research is needed.[49]

Platelet-rich plasma (PRP) has shown promise in treating androgenetic alopecia; however, there is limited evidence regarding its efficacy for endocrine therapy-induced alopecia. A randomized controlled trial that evaluated the effect of PRP in patients with endocrine therapy-induced alopecia or chemotherapy-induced alopecia and a history of breast cancer found that PRP may increase hair density in this patient population. Nevertheless, further investigations are needed.[50]

Finasteride should be used with caution in men; however, finasteride is not recommended for use in breast cancer patients or survivors. Finasteride has been used off-label to treat AGA in women with breast cancer, but further controlled studies are needed to confirm the long-term safety in this population.[10] In addition, biotin supplements are not recommended due to a lack of supporting data and the potential to interfere with lab results, such as thyroid function and cardiac enzyme studies.[51] Topical ketoconazole can be considered as a low-risk adjunctive or alternative therapy in the treatment of AGA. Although there is a low level of efficacy, a systematic review found positive results to support the use of 2% ketoconazole shampoo for the treatment of AGA, even with the most infrequent use of 2 to 3 times per week.[52]

Hirsutism

Hormonal therapies can cause excessive hair growth in androgen-dependent areas of the body in women (hirsutism).[31] Hirsutism has been shown to bother patients considerably and contribute to discomfort in social situations.[53] While hirsutism has been reported with anti-estrogen agents, it is likely underreported.[12] Local therapies such as plucking, shaving, waxing, or bleaching can be helpful to treat mild hair growth (grade 1 hirsutism), but may be too harsh for patients with skin sensitivity after cancer treatment (Table 7).[12] For prominent thick hairs (grade 2), long-pulsed alexandrite, Nd:YAG, or diode lasers may be used with the patient's Fitzpatrick skin type guiding wavelength selection.[12] Topical eflornithine cream has been shown to reduce the rate of hair growth and significantly diminish unwanted facial hair, leading to improvement in QoL.[53,54] Topical eflornithine is applied to affected areas of the face and chin twice daily, at least 8 hours apart. If used in conjunction with local hair removal methods, topical eflornithine should be applied at least 5 minutes after hair removal. Cosmetics or sunscreens may be applied over treated areas after the cream has dried.[54] Spironolactone can be considered in doses up to 200 mg/day, although caution is warranted due to the potential risk of hormonal stimulation in patients with hormone-receptor-positive breast cancer.[41,55] Finasteride is not recommended for use in breast cancer patients or survivors.[10] Eyebrows and eyelashes should be regularly trimmed to avoid corneal abrasion.[12]

TABLE 7.

Treatment for Hirsutism[12,41,55]

Grade	Treatment	Notes
Grade 1 (mild hair growth)	Depilatories, shaving, waxing, electrolysis, bleaching	--
Grade 2 (prominent thick hairs, associated with psychosocial impact)	Laser therapy	--
	Eflornithine topical cream BID	Can be combined with local hair removal methods
	Spironolactone, 50 to 200 mg/QD	Decision should be made in consultation with oncologist due to the potential risk of hormonal stimulation in patients with HR+ tumors

BID, twice daily; QD, once daily; HR+, hormone receptor-positive.

TABLE 8.

Treatment for Vaginal Atrophy		
Drug Class	**Treatment**	**Notes**
Hormone-free moisturizers	Water-based gel, HA gel, HA vaginal suppositories	Used routinely to improve moisture and pH
Lubricant	Hormone-free vaginal lubricant	Used as needed before intercourse
Topical hormone products	Low-dose estrogen rings, creams	May be considered for severe symptoms after consultation with oncologist

HA, hyaluronic acid.

Other Eruptions

Vaginal Atrophy

Vulvovaginal dryness and atrophy are experienced by many patients taking hormonal therapy for breast cancer. In a cross-sectional study of postmenopausal patients with breast cancer, 40% of those on tamoxifen and 74% of those taking AIs reported insufficient vaginal lubrication.[10] Hypoestrogenism results in a thinner vaginal epithelium, increased vaginal pH, and degeneration of collagen and elastin fibers in the underlying connective tissue, resulting in less tissue elasticity and greater mucosal fragility.[56] As a result, patients may experience vaginal dryness, burning, soreness, itching, and irritation, which can lead to dyspareunia.[56] Loss of estrogen also predisposes patients to subsequent urinary symptoms (urgency and dysuria) or recurrent urinary tract infections.[56]

Prevention of vulvovaginal atrophy should be discussed at the onset of hormonal therapy. Patients should be educated about maintaining vaginal health through regular sexual activity, which increases blood flow to the vaginal tissue, or the use of vaginal dilators, which gently stretch the vagina walls. Pelvic floor exercises may also be helpful for some patients.[10]

Mild symptoms of vulvovaginal atrophy can be treated with non-hormonal vaginal moisturizers and lubricants to help maintain moisture and elasticity (Table 8).[10] Patients should be educated on the difference between moisturizers – which are used continuously to increase vaginal moisture and improve pH – and lubricants, which are used as needed before intercourse. When moisturizers and lubricants are not effective, low-dose vaginal estrogen therapy may be considered after consultation with the oncologist to discuss the potential benefits versus the risks of estrogen exposure.[10,57] Dissolvable hyaluronic acid vaginal suppositories can also help hydrate vaginal tissues. They can improve vaginal moisture, reduce discomfort, and potentially enhance sexual function. Although the use of hyaluronic acid vaginal suppositories in oncology patients is limited, studies in postmenopausal women suggest that hyaluronic acid has comparable efficacy to vaginal estrogens for the treatment of the signs of vaginal atrophy and dyspareunia. While there was initial concern about using vaginal estrogen in women with a history of breast cancer due to the potential for increased cancer recurrence, current research indicates that low-dose vaginal estrogen is generally considered safe for most breast cancer survivors, particularly when non-hormonal treatments for vaginal atrophy have failed, as the minimal amount of estrogen absorbed systemically poses a negligible risk of cancer recurrence.[58] The American College of Obstetricians and Gynecologists (ACOG) supports the use of vaginal estrogen in breast cancer survivors when non-hormonal options are ineffective for managing severe symptoms.[59] However, careful discussion with a healthcare provider is critical in weighing individual risks and benefits, particularly based on the patients' age and breast cancer subtype.

Miscellaneous Rashes

Rashes are a common adverse effect of ADT for prostate cancer. An analysis of 303 patients with prostate cancer treated with apalutamide found that 33.8% experienced maculopapular rashes, 8.5% experienced an erythematous rash, 4.2% experienced an acneiform rash, and 2.8% experienced a psoriasiform rash. Most grade 1/2 rashes were effectively managed with moderate to high potency topical steroids +/– oral antihistamines. Few cases required oral steroids. In the SPARTAN and TITAN trials, the rash incidence was 23.8% and 27.1% in apalutamide vs 5.5% and 8.5% in placebo groups, respectively. While rash incidence was high, dose interruption occurred in 6.8% of patients in the SPARTAN and 8.4% in the TITAN clinical trials, rarely causing dose reduction or discontinuation. If drug interruption is necessary, dose reductions may help prevent recurrence.[14]

CONCLUSION

Hormonal therapies play an instrumental role in the treatment of hormone-receptor positive breast cancer and prostate cancer. Therefore, recognizing and managing cAEs that may occur with treatment is critical to improving the patient experience. Dermatologic adverse effects of hormonal therapy can significantly diminish oncology patients' quality of life and threaten treatment adherence. By integrating skincare into hormonal therapy and encouraging patients to adopt a proactive approach to skincare, clinicians can help prevent and manage cAEs, improve the patient experience, and support adherence to cancer treatment. Close collaboration between dermatologists and oncologists is essential for early recognition, prevention, and management of these adverse events.

DISCLOSURES

The authors disclosed receipt of the following financial support for the research, authorship, and manuscript publication. This work was supported by an unrestricted educational grant from La Roche-Posay US. All authors contributed to the development of this work and its review and agreed with its content.

MEL has a consultant role with Johnson and Johnson, Novocure, Bicara, Janssen, Novartis, EMD Serono, AstraZeneca, Innovaderm, Deciphera, DFB, Azitra, Kintara, RBC/La Roche Posay, Trifecta, Varsona, Genetch, Loxo, Seattle Genetics, Lutris, OnQuality, Oncoderm, NCODA, Apricity. Dr. Lacouture also receives research funding from Lutris, Paxman, Novocure, J&J, US Biotest, OQL, Novartis and AZ is supported funded in part by the NIH/NCI Cancer Center Support Grant P30 CA008748. JNC receives clinical trial research funding from OnQuality and has served on advisory boards for Regeneron, Parexel/Rockefeller, and PraHealth Sciences. AYH receives research funding from Merck, Natera, Glaxo Smith Kline, The Breast Cancer Research Foundation, NIH, and Department of Defense and has served as a consultant for Astra Zeneca. BNM receives clinical trial research funding from OnQuality and Pfizer, and has served on advisory boards for La Roche Posay and Paula's Choice. JL receives clinical trial research funding from OnQuality and Azitra, and has served on advisory boards for La Roche Posay and Sanofi Regeneron. AD, AA, and EM have no conflicts of interest to disclosure.

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