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Casmo Algorithm for Management of Hormonal Therapy-Related Cutaneous Adverse Effects in Oncology Patients

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ABSTRACT

Introduction: Breast and prostate cancer patients frequently use hormonal therapy to improve treatment outcomes and survival. However, these medications can be associated with numerous dermatologic adverse effects. If not appropriately managed, these cutaneous reactions can reduce the quality of life and interfere with treatment adherence.

Objectives: The Canadian skin management in oncology (CaSMO) algorithm was developed to improve the quality of life for cancer patients and survivors who experience hormonal therapy-related dermatologic toxicities.

Methods: The CaSMO advisory board created a practical algorithm for preventing and treating hormonal therapy-related cutaneous adverse effects based on the results of a literature search and their clinical expertise.

Results: Skin toxicities related to hormonal therapy include symptoms of menopause/andropause, androgenic alopecia, rosacea, hirsutism, and other eruptions. The algorithm provides practical steps for preventing and treating these cutaneous conditions.

Conclusions: The CaSMO algorithm provides information for all healthcare providers who treat oncology patients receiving hormonal therapy and can be used to help prevent and manage common dermatologic toxicities, thereby improving patient adherence, quality of life, and treatment outcomes.

Keywords: Hormonal cancer therapy, cutaneous adverse events, algorithm for hormonal therapy-related cutaneous adverse events

Introduction

An estimated 229,200 Canadians were diagnosed with cancer[1] in 2021. Excluding non-melanoma skin cancer, the most commonly diagnosed types are lung, breast, colorectal, and prostate, making up almost half of all new cancer diagnoses in Canada. Advances in treatment have contributed to a reduction in breast and prostate cancer mortality over the past couple of decades. The five-year survival rate for both cancer types is around 90%. However, with a growing number of survivors, providers should be aware of the potential health effects these patients may experience. It is imperative to be familiar with the adverse effects of hormonal therapies, typically used long-term by many breast and prostate cancer patients. These treatments have been associated with numerous skin toxicities, usually not life-threatening but can reduce the quality of life, limit treatment adherence, and potentially affect health outcomes.

Scope of the Canadian Skin Management in Oncology Project

The CaSMO project was developed to improve the quality of life for cancer patients and survivors by offering tools to prevent and manage cutaneous adverse effects (cAEs).[2-4] A general management algorithm to reduce the incidence of all cutaneous toxicities and maintain healthy skin using general measures and over-the-counter agents[3] and an algorithm to reduce and treat acute radiation dermatitis[4] were previously published. These algorithms aim to support all health care providers (HCPs) treating oncology patients, including physicians, nurses, pharmacists, and advanced providers.[3,4] The algorithms were followed by a practical primer on prevention, identification, and treatment, including skin care for cutaneous immune-related adverse effects (AEs), focusing on isolated pruritus, psoriasiform eruptions, lichenoid eruptions, eczematous eruptions, and bullous pemphigoid. The next step in the project was to develop an algorithm for cAEs in oncology patients receiving hormonal therapy.

Methods

The advisors convened for a meeting to develop the CaSMO hormonal therapy-related cAEs algorithm. The advisors used a modified Delphi approach following the AGREE II instrument.[5-7]

Literature Review

The literature review included guidelines, consensus papers, and publications on the prevention and management of hormonal therapy-related cAEs published in English from January 2010 to January 2022. A dermatologist and physician/scientist conducted searches on PubMed and Google Scholar for English-language literature on January 25 and 26, 2022, using the following AND OR search terms:

Hormonal therapy; Hormonal therapy-related cAEs AND oral prescription medications OR topical regimes OR skincare, for prevention OR treatment OR maintenance; Hormonal therapy-related cAEs AND adjunctive skincare use, OR education of staff and patients, OR communication strategies, OR adherence, OR concordance, OR efficacy, OR safety, OR tolerability, OR skin irritation

Two reviewers independently evaluated the results of the literature search. Of the one hundred and ninety-one papers identified in the search, sixty-six were excluded for duplication or poor quality. The remaining one hundred and twenty-five publications included ninety-nine papers on hormonal therapy, six guidelines that included hormonal therapy, and twenty papers that discussed hormonal therapy-related cAEs, treatment, and skin care.

Hormonal Therapy

Breast cancer and prostate cancer are the most diagnosed cancers in females and males. In Canada, breast cancer accounts for 25.0% of all new cancer cases in females, and prostate cancer accounts for 20.3% of all new cancer cases in males.[1] Hormonal therapy is often given as adjuvant treatment for these cancer types to reduce levels of hormones that can fuel the growth of cancer cells.[8,9] These medications are used for extended periods, and adherence is threatened by AEs and their effect on patient quality of life.[10]

Approximately two out of three patients with breast cancer have hormone receptor-positive disease[8] and will receive hormonal therapy for five to ten years to decrease the risk of disease recurrence and improve survival (Table 1).[11] Hormonal treatment for breast cancer consists of aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), selective estrogen receptor degraders (SERDs), and high-dose hormones. Prostate cancer cells need androgens to grow, and hormonal therapies decrease androgen levels by interfering with androgen production or blocking androgen actions.[9] Hormonal treatment for patients with prostate cancer includes luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, androgen receptor blockers, and androgen synthesis inhibitors.[9,12]

Type of Skin Reactions Associated with Hormonal Therapy

Hormonal therapies for breast and prostate cancer are associated with numerous dermatologic effects involving the skin, hair, and mucosal surfaces.[13] Due to the decrease in estrogen or androgen levels, they can induce menopause or andropause, respectively, leading to various general and skin-specific symptoms. Flushing, reversible alopecia, and vulvovaginal atrophy are experienced by many patients taking SERMs and AIs. In general, tamoxifen causes more frequent and severe hot flashes and higher alopecia rates than AIs. Conversely, vulvovaginal atrophy is more common in patients receiving AI therapy.[13,14] In addition to symptoms of menopause/andropause, these medications can also cause androgenic alopecia, exacerbation of rosacea, hirsutism, and rashes.

The most common dermatologic AEs with androgen deprivation therapy (ADT) for prostate cancer are hot flashes, pruritus, and rash.[9] Generally, men do not typically visit their doctor concerning skin issues associated with hormonal therapy. Instead, they are more likely to present with complaints of hot flashes, sweating, and changes to libido.

Patient and Caregiver Education

Most skin reactions associated with hormonal therapy for breast and prostate cancer are not life-threatening; therefore, providers may view them as minor or cosmetic issues.[15] However, cAEs associated with these medications can profoundly affect the quality of life and are often not anticipated by patients. Almost 70% of patients who experienced cAEs reported that their reactions significantly limited their daily activities.[16] Additionally, most patients reported that cAEs were worse than expected before starting therapy.[17] As a result, these toxicities can threaten treatment adherence. Pretherapy counseling is critical to identify risk factors for skin toxicities, educate patients about potential cAEs, and identify helpful interventions that can enhance adherence.[10]

All HCPs who treat oncology patients receiving hormonal therapy should be involved in managing skin toxicities. Ideally, the oncology team should provide pretherapy counseling to all patients, so they are aware of potential dermatologic toxicities, know what symptoms they should report, and are familiar with preventive strategies. In addition, they can advise patients about which products to use or avoid, provide key messages about skincare, and potentially distribute skincare starter kits. When skin concerns arise, patients are likely to contact their family doctor, and they should be prepared to discuss preventive measures, offer

Drug Class	Drug Name	Oncologic Indication	Cutaneous Adverse Events
Aromatase inhibitors	Anastrozole, exemestane, letrozole	Second-line	Third-line
SERMs		Breast	Vulvovaginal atrophy, hot flashes/flushing, alopecia
SERDs	Fulvestrant	Breast	Hot flashes/flushing
High-dose hormones	Ethinyl estradiol, fluoxymesterone, megestrol acetate	Breast	Hot flashes/flushing
Androgen receptor blockers	Bicalutamide, flutamide, nilutamide, enzalutamide, apalutamide, darolutamide	Prostate	Hot flashes/flushing
LHRH agonists	Goserelin, histrelin, leuprolide, triptorelin	Prostate	Hot flashes/flushing
LHRH antagonists	Degarelix, relugolix	Prostate	Hot flashes/flushing
Androgen synthesis inhibitors	Abiraterone, ketoconazole, aminoglutethimide	Prostate	Pruritus, rashes

Table 1: Hormonal Therapies and Associated Cutaneous Adverse Effects[8-10,12,13]

Details on the cancer drug, oncological indication, and cAEs

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

treatment recommendations, assess the severity of cAEs, and refer severe cases to a specialist. Finally, dermatologists will see patients with more severe reactions and should be familiar with possible skin toxicities in patients receiving hormonal therapies and recommended treatment options.

Quality-of-life studies indicate that women are affected by dermatologic toxicities more than men.[13] Ferreira and colleagues noted the potential impact of cAEs, stating, "These toxicities can affect a woman's self-image, cultural identity, femininity, sexuality, and mental health."[13] Although women are more likely than men to contact their doctor with skin complaints, educating all patients on ways to prevent and treat skin toxicities associated with hormonal therapy is important. In addition, because they have less experience with skincare and are less likely to present with skin complaints, it is imperative to develop messages and visuals targeted explicitly to men receiving hormonal therapy for prostate cancer.

Algorithm on the Management of Hormonal Therapy-Related Cutaneous Adverse Effects

The algorithm aims to improve patient comfort during and after treatment, reduce the incidence of skin toxicities, and treat cAEs using prescription medication and skin care. After a systematic search for relevant publications, a dermatologist and a physician/scientist reviewed the literature and created a draft algorithm. Next, the advisors met to workshop the draft algorithm, incorporating their collective feedback and reaching a consensus through blinded votes. The final algorithm provides a high-level overview of the management of skin reactions associated with hormonal therapy (Figure 1).

The algorithm highlights the importance of educating patients before initiating hormonal therapy on the type of medication they will receive, its mechanism of action, and potential cAEs associated with the treatment. Additionally, the algorithm emphasizes the value of preventive skin care throughout hormonal cancer treatment (Table 2). This daily skin care regimen should include the use of gentle cleansers, moisturizers, and sun protection by all patients. Practitioners should continue to educate and assess patients for skin toxicities throughout treatment to improve adherence to therapy.

Menopause/Andropause Symptoms

Hormonal therapies can induce menopause or andropause by interfering with hormone production or blocking hormone action. Patients receiving these treatments may present with general symptoms, including hot flashes, flushing, sleep disturbances, and hyperhidrosis. Additionally, they may experience skin-specific symptoms such as vulvovaginal atrophy, facial atrophy, and xerosis (Table 3).

General symptoms of menopause/andropause:

Hot flashes, described as brief episodes of intense and uncomfortable heat, have been reported in 46% to 73% of breast cancer survivors.[18] The feeling of overheating is often accompanied by facial flushing and blotchy erythema that spreads over the face, neck, and chest. Hot flashes typically have a quick onset and resolution and may be accompanied by sweating, palpitations, and anxiety.[19,20] Occurring at night can lead to night sweats and affect sleep quality.[20] Breast cancer survivors report higher rates of vasomotor symptoms than women without breast cancer, possibly due to the rapid transition to menopause during breast cancer treatment and exacerbation of estrogen deficiency

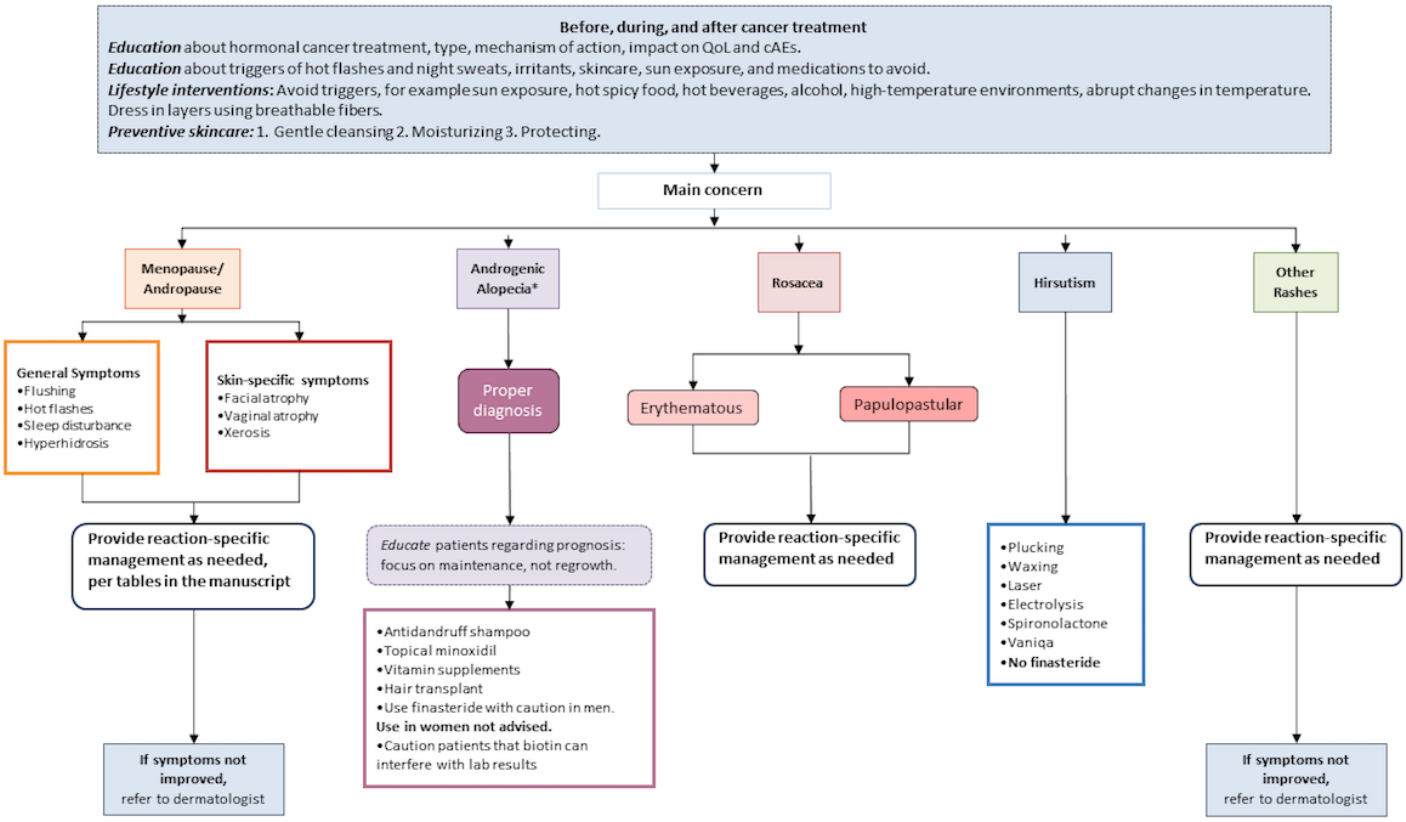

Figure 1: CaSMO algorithm for management of hormonal therapy-related cAEs

Products/Ingredients to Use	Products/Ingredients to Avoid
Mild cleanser	Abrasive ingredients
Fragrance-free	Fragrances
Cleanser that is mildly acidic to neutral pH (4-6.5)	Alkaline cleanser
Broad-spectrum sunscreen with SPF of 30 or higher	
Moisturizers with emollients or occlusives	

Table 2: General Skin Care Recommendations[35]
SPF, sun protection factor

caused by hormonal therapy.[14] A population-based survey found that breast cancer survivors were over 5.3 times more likely to experience menopausal symptoms than women in the general population.[21]

All patients who will be treated with hormonal therapy should receive pretherapy counseling on lifestyle interventions and environmental modifications to prevent hot flashes and flushing. It may be helpful to wear lightweight clothing and dress in layers, use fans and other cooling aids, and avoid triggers, such as heat, stress, hot beverages, spicy food, and alcohol.[13,21] Additional nonmedical approaches that may be beneficial for some patients include exercise, yoga, hypnosis, acupuncture, and cognitive behavioral therapy that teaches relaxation and paced breathing.[14]

Although hormone-replacement therapy is the most effective treatment for vasomotor symptoms, it is contraindicated in patients with breast cancer.[22] Nonhormonal management of hot flashes in breast cancer patients and survivors consists of low-dose antidepressants, anticonvulsants, clonidine, and oxybutynin.[18] Recommended antidepressants include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), which have shown a 20% to 65% reduction in the severity and frequency of hot flashes in randomized clinical trials.[23] Paroxetine is the only nonhormonal therapy approved for treating vasomotor symptoms.[14,23] However, because paroxetine is a potent inhibitor of CYP2D6, its use should be avoided in patients taking tamoxifen. Instead, citalopram and escitalopram are the preferred SSRIs for patients taking tamoxifen.[23] SNRI venlafaxine is widely used in clinical practice because it has been well studied and has shown effectiveness in reducing hot flashes.[11,23] Venlafaxine and desvenlafaxine, another possible SNRI option, are safe to use in tamoxifen patients.[23] For vasomotor symptoms, doses of SSRIs and SNRIs are typically lower than antidepressant doses, and effects can be seen as soon as two weeks after treatment initiation.[18,23]

Other than antidepressants, the anticonvulsant gabapentin is another first-line treatment option that has been associated with reductions in hot flash frequency and severity. As an added benefit, it may also help improve sleep quality.[23] Alternatively, pregabalin may be used, although it has been studied less than gabapentin.[23]

Second-line agents for hot flashes include clonidine and oxybutynin. Clonidine is somewhat effective, although its use is limited by AEs such as hypotension, dizziness, xerostomia, and constipation.[14,23] The dose of clonidine should be titrated to the desired effect on vasomotor symptoms and effect on blood pressure.[14] Long-acting transdermal clonidine is preferred to avoid AEs associated with oral clonidine. The anticholinergic agent oxybutynin may also be used to help manage vasomotor symptoms.[18] Data are limited on the safety and efficacy of phytoestrogens, botanicals, and dietary supplements in breast cancer patients and survivors, and their use is not recommended.[14,18]

Between 50% and 80% of men treated with ADT for prostate cancer report vasomotor symptoms.[18] For most patients, hot flashes increase in frequency three months after initiating ADT therapy and persist throughout treatment.[24] It is important for clinicians to talk to their prostate cancer patients about this potential AE, as it can be debilitating and lead to treatment discontinuation. In fact, between 15% and 27% of patients receiving ADT indicate that hot flashes are the AE with the most significant impact on their quality of life. Prevention and treatment of ADT-related hot flashes in men is similar to what is recommended for women. Venlafaxine and gabapentin have both been studied in males experiencing hot flashes; the other agents are used in clinical practice but have not been tested in this population.[18] Hormonal treatment using megestrol acetate, depot medroxyprogesterone, or transdermal estrogen may also be considered in male patients, but the benefits of these agents should be weighed against the risk of weight gain, sexual dysfunction, cardiovascular complications, and potential progression of prostate cancer.[24] Additionally, intermittent administration of ADT may be an option for some patients dealing with vasomotor symptoms.[12]

Sleep disturbance affects nearly 60% of patients receiving hormonal therapy for breast cancer[25] and is also commonly associated with the use of ADT for prostate cancer.[18] Effects on sleep may result from changes in hormone levels, hot flashes, or night sweats.[25] Treating hot flashes may improve sleep quality, and gabapentin may be particularly helpful at bedtime. For patients who experience nighttime vasomotor symptoms that disrupt sleep, it is recommended to take gabapentin as a single dose one hour before bedtime to reduce hot flashes and help with sleep initiation.[14] Alternatively, patients who experience vasomotor symptoms during the day and night can take gabapentin twice daily, with one dose in the morning and the second dose is taken one hour before bedtime. Melatonin may be beneficial for patients experiencing sleep disturbances, although it has not been studied explicitly in cancer patients or survivors taking hormonal therapy.[22] Additionally, mind-body interventions, such as exercise, yoga, meditation, acupuncture, and cognitive behavioral therapy, may also have benefits for sleep.[22,25]

Patients receiving hormonal therapy for breast and prostate cancer may also experience hyperhidrosis due to decreasing estrogen and androgen levels. Additionally, the SERMs raloxifene and tamoxifen are known to cause secondary hyperhidrosis.[26] Treatment recommendations depend on the severity and location of hyperhidrosis. Topical 20% aluminum chloride is recommended as first-line therapy for patients with hyperhidrosis. Intradermal administration of onabotulinumtoxinA can be used for patients who fail treatment with aluminum chloride or as first-line treatment for patients with severe symptoms; these treatments can be used in combination when patients fail monotherapy with the individual agents. Additional first-line options include iontophoresis for plantar or palmar hyperhidrosis and compounded topical 2% glycopyrrolate for craniofacial hyperhidrosis. When hyperhidrosis does not resolve using the above approaches, oral anticholinergic agents, such as oxybutynin and glycopyrrolate, may decrease sweating and disease severity.

Skin-specific symptoms of menopause/andropause:

Vulvovaginal atrophy is a common AE associated with hormonal therapy for breast cancer, with symptoms reported in up to 40% of patients taking tamoxifen and 74% of patients taking an AI.[13] Hypoestrogenism results in thinner vulvar and vaginal epithelium, loss of glycogen, and increased vaginal pH.[27] As a result, patients may experience dryness, burning, irritation, and itching that can lead to dyspareunia. Vulvovaginal atrophy is also associated with urinary incontinence and urinary tract infections. These changes

Symptom	Drug Class	Treatment	Common Dosage	Notes
Hot flashes	SNRI	Venlafaxine	37.5-150 mg/day	Frequently used in clinical practice; best-studied agent in men
		Desvenlafaxine	100-150 mg/day	
	SSRI	Paroxetine	7.5-25 mg/day	Approved for hot flashes; not for patients receiving tamoxifen due to potent CYP2D6 inhibition
		Citalopram	10-20 mg/day	Preferred
		Escitalopram	10-20 mg/day	Preferred
		Fluoxetine	10-30 mg/day	Potent CYP2D6 inhibitor; avoid use with tamoxifen
		Sertraline	25-100 mg/day	Moderate CYP2D6 inhibitor
	Anticonvulsant	Gabapentin	300-900 mg/day	Can cause drowsiness, best-studied agent in men
		Pregabalin	150-300 mg/day	Less studied than gabapentin
	Anticholinergic	Oxybutynin	2.5 mg BID	
	Antihypertensive	Clonidine	0.1 mg/day	Clinical use is poor due to significant AEs; transdermal patch preferred over oral tablets.
Sleep disturbances	Anticonvulsant	Gabapentin	100 mg to 1200 mg single dose/ bedtime	May help with sleep
	Supplement	Melatonin	Not specified	No studies on patients with cancer
Hyperhidrosis	Astringent	Aluminum chloride	20% topical solution	First-line treatment for all patients
	Neurotoxin	OnabotulinumtoxinA	Intradermally into affected areas	Use when patients fail aluminum chloride or in severe cases
		Iontophoresis		First-line option for plantar or palmer hyperhidrosis
	Anticholinergic	Topical glycopyrrolate	2%	First-line option for facial hyperhidrosis
	Anticholinergic	Oxybutynin	2.5%/day or BID	Second-line option
	Anticholinergic	Oral glycopyrrolate	2mg /BID	Second-line option
Vaginal atrophy	Hormone-free moisturizers	Water-based gel, HA gel	-	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 the oncologist

Table 3: Treatments for Menopause/Andropause Symptoms[13,14,18,21-23,26,29]

Continued on next page

Symptom	Drug Class	Treatment	Common Dosage	Notes
Facial atrophy	Sun protection	Broad-spectrum sunscreen, SPF 30 or higher	-	Protects skin, reduces further thinning, prevents new wrinkles
	Moisturizer	Moisturizer containing HA or glycerin	-	Helps reducing xerosis
		Retinol	-	Increases collagen
Xerosis	Moisturizer	Moisturizer containing HA or glycerin	-	Helps reducing xerosis

Table 3: Treatments for Menopause/Andropause Symptoms[13,14,18,21-23,26,29] *(Continued)*

Details on cancer treatment, cAEs (Hot flashes/flushing, sleep disturbances, hyperhidrosis, vaginal atrophy, facial atrophy, and xerosis) and treatment of cAEs; *Consider other causes. Medication for androgenic alopecia: Topical minoxidil 2% to 5%/BID; spironolactone 5mg to 200mg/QD

AEs, adverse effects; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; SPF, sun protection factor; BID, twice a day; HA, hyaluronic acid.

can significantly impact patient relationships and quality of life.[11,27]

Mild symptoms of vulvovaginal atrophy can be treated with vaginal moisturizers and lubricants.[13,22] It is important to inform patients of the difference between moisturizers used continuously to increase vaginal moisture and improve pH and lubricants used as needed before intercourse.[14] Vaginal dilators and pelvic floor physical therapy may also be helpful for some patients.[13] When moisturizers and lubricants are not effective, low-dose vaginal estrogen therapy may be considered after consultation with the oncologist to discuss the benefits and risks of treatment.[13,14]

Estrogen deficiency also affects facial skin by causing a decrease in sebum production, collagen content, dermal thickness, and elastin fibers.[28] When estrogen levels decrease, women may notice dryness, decreased firmness, thinning of the skin, fine wrinkling, and poor wound healing. For skin-specific symptoms of menopause, it is important to use a broad-spectrum sunscreen with SPF 30 or higher to protect the skin and prevent new wrinkles.[29] A mild cleanser and a moisturizer with hyaluronic acid or glycerin can help manage dryness. Retinoids may be recommended to increase collagen and improve wrinkles.

Androgenic Alopecia:

A meta-analysis10 including data from over 13,000 patients treated with hormonal therapy indicated that tamoxifen was the single-agent treatment associated with the highest incidence of all-grade alopecia (9.3%) and grade 2 alopecia (6.4%). Hair loss was observed in 2.2% to 2.5% of patients receiving single-agent AI therapy. The incidence of alopecia was highest for patients who received a combination of hormonal treatments. With hormonal therapies that lower estrogen levels, alopecia is thought to be caused by decreased estrogen stimulation and increased androgen stimulation of the hair follicles,[15] which leads to an increase in hair loss during the telogen phase and a decrease in hair shaft diameter that leads to fragility, breakage, and subsequent hair loss.[10] Androgenic alopecia typically presents as female pattern hair loss, with diffuse thinning over the scalp and the "Christmas tree pattern" along the center part.[13]

Most cases of alopecia associated with hormonal therapy are grade 1, which is defined as hair loss of less than 50% of normal for that individual that is not obvious from a distance.[13] Alopecia associated with hormonal agents is generally reversible, but it tends to last for the duration of treatment.[10,13] While HCPs may view hair loss as a temporary or cosmetic issue; alopecia can be very distressing to cancer patients and survivors.[15] Even low-grade alopecia has been associated with decreased quality of life and negative emotional impact.[13]

Before starting hormonal therapy, providers need to discuss the risk of alopecia with patients and encourage them to report any increase in hair loss that is not normal for them.[30] Although there are currently no preventive strategies for alopecia caused by endocrine therapies, it is essential that diagnosis and treatment start as soon as possible to improve prognosis. Once patients seek medical help for alopecia, the goal of treatment is to stop or reduce hair loss. Patients must be educated on their prognosis and understand that therapy focuses on maintenance, not hair regrowth.[15]

When a patient on hormonal therapy presents with alopecia, it is important first to rule out other causes, such as thyroid dysfunction or low iron, vitamin D, or zinc levels.[10] Occasionally, scalp biopsy can be helpful to exclude early scarring alopecia or telogen effluvium, especially when patients present with alopecia that does not follow the typical androgenetic pattern.[10,31] After ruling out other contributing factors, patients with mild alopecia can use topical minoxidil 2% to 5% twice daily.[10] Camouflaging sprays, powders, wigs, or extensions may also help conceal low-grade hair loss. Spironolactone may be considered after discussion with the oncologist for cases refractory to topical or oral minoxidil.[13,32] In abundance of caution, finasteride is not recommended for use in breast cancer patients or survivors.[13] Although supplementation is recommended for patients with alopecia and low levels of vitamin D and iron, there is insufficient evidence to support the use of most other vitamin supplements. Of particular interest, the use of biotin supplements is not recommended because of a lack of supporting data and the fact that it can interfere with lab results.[33]

Rosacea

Rosacea, an inflammatory dermatologic condition characterized by facial flushing that persists for at least three months, is classified into several subtypes based on clinical signs and symptoms (Table 4).[34]

Patients with rosacea need to identify exacerbating factors to avoid these triggers.[34] Patients should be instructed on the importance of using mild, fragrance-free, non-alkaline cleansers and moisturizers that contain emollients and occlusives. Additionally, daily use of sun protection using a broad-spectrum sunscreen with SPF 30 or higher is recommended.[19,35]

Treatment of rosacea varies according to the presentation. To treat erythema and inflammation, patients can use topical metronidazole, azelaic acid, ivermectin, or brimonidine.[35] Additionally, vascular laser therapy can treat erythema and telangiectasias. Patients who present with papulopustular rosacea can use the above treatments alone or in combination. Anti-inflammatory doses of doxycycline can also be used as monotherapy or in combination with topical treatment. If oral therapy with low-dose doxycycline is ineffective, other options include antimicrobial doses of doxycycline, various other antibiotics, or oral isotretinoin.

Hirsutism

Hirsutism is reported in less than 10% of breast cancer survivors receiving hormonal therapy[15]; however, this AE is likely underreported (Table 5).[30] For mild hair growth (grade 1 hirsutism), local therapies such as plucking, waxing, and electrolysis may be helpful.[15,36] For prominent thick hairs that are associated with psychosocial impact (grade 2), laser therapy or pharmacologic treatment may be considered. Eflornithine (Vaniqa) topical cream can slow terminal hair growth rates on the face and under the chin.[37] It is applied to affected areas of the face and chin twice daily, at least 8 hours apart, and can be combined with local hair removal methods.[36,37] Spironolactone up to 200 mg per day can be considered, but this decision should be made in consultation with the oncologist due to the potential risk of hormonal stimulation in patients with hormone-positive breast cancer.[36] Finasteride should not be used in breast cancer patients or survivors.[13,32]

Other Eruptions

Aside from the above cAEs that are commonly observed with hormonal therapy for breast and prostate cancer, some of the individual medications can cause other skin toxicities.

Especially, a newer androgen receptor antagonist, apalutamide has been associated with high rates of dermatologic reactions. An analysis of 303 patients with prostate cancer treated with apalutamide showed that 23.4% experienced a dermatologic AE of any grade, most commonly maculopapular rashes, and xerosis.[38] In both the SPARTAN and TITAN trials, apalutamide was associated with a higher incidence of skin rash compared

	Medication	Formulation and Dosage	Type of Rosacea	Symptoms Treated	Adverse Effects
First-line treatment	Metronidazole	Gel, cream, or lotion 0.75%/BID, Gel 1%/QD	EPP	Erythema, inflammation	Mild; pruritus, irritation, dryness
	Azelaic acid	Gel 15%/QD or BID			
		EPP	Erythema, inflammation	Mild; include transient burning, stinging, irritation	Third-line
	Brimonidine	Gel 0.33%/QD	EPP	Background erythema (reduced via vasoconstriction)	Mild; irritation, burning, dry skin, pruritus, erythema
Second-line treatment	Ivermectin	Cream 1%/QD	PP	Inflammation, antiparasitic	Burning, skin irritation
	Benzoyl peroxide	Gel 5%/ QD or BID	PP	Antibacterial	Burning, stinging, pruritus
	Erythromycin	Gel 2%/ BID	PP	Antibiotic	Pruritis, erythema, irritation, dryness
	Clindamycin	Gel 1%/BID	PP	Antibiotic	Pruritus, burning, irritation, dryness
	Doxycycline	Oral: 100 mg/QD	PP	Anti-inflammatory	Photosensitivity, candidal vaginitis, diarrhea

Table 4: Treatment for Rosacea[35]

QD, once daily; BID, twice daily; EPP, Erythematous, papulopustular; PP, Papulopustular

with placebo (23.8% vs. 5.5% for SPARTAN and 27.2% vs. 8.5% for TITAN).[39] An integrated analysis of data from Japanese patients in these two studies, plus the PCR1008 study, indicated that the incidence of rash with apalutamide was nearly double in the Japanese population compared with the global population. Rash associated with apalutamide was easily managed with drug interruptions, dose reductions, and supportive medication, including oral antihistamines, topical corticosteroids, or systemic corticosteroids. The median time to resolution was one month. Treatment discontinuation was required in 14.3% of the integrated Japanese population, 9.9% of the global SPARTAN population, and 8.5% of the global TITAN population.

Rash, pruritis, and xerosis can occur with AI therapy.[40] There have also been rare reports of cutaneous vasculitis, erythema nodosum, subacute cutaneous lupus erythematosus, lichen sclerosus vulvae, erythema multiforme, and erythema multiform-like eruption associated with use of AIs.

While tamoxifen is generally well tolerated, it has been associated with a wide range of less frequent dermatologic AEs. Approximately 19% of patients receiving tamoxifen will experience a cAE during treatment.[41] These reactions can vary from the common occurrence of flushing to the rare and serious development of Stevens-Johnson syndrome. Other potential skin toxicities that have been associated with tamoxifen include urticaria, vasculitis, hypersensitivity reactions, and subacute cutaneous lupus erythematosus. Cutaneous reactions typically occur within the first couple of weeks to months after initiating therapy, but there have been reports of delayed reactions that present years after starting tamoxifen. Treatment for cAEs includes discontinuation of tamoxifen and use of antihistamines, topical corticosteroids, or systemic corticosteroids when appropriate. Depending on the severity of the reaction, tamoxifen may be gradually restarted under close observation, or the patient may be switched to another hormonal therapy.

Combination Treatment:

The risk of dermatologic AEs is even higher when hormonal therapies are combined with other anticancer treatments.[42] Targeted therapies, such as phosphoinositide 3-kinase (PI3K) inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, and cyclin-dependent kinase (CDK) inhibitors, are often used in combination with hormonal therapy and can contribute to skin toxicities.

Rash is common when patients begin treatment with the PI3K inhibitor alpelisib in combination with fulvestrant. Therefore, the ESO-ESMO guidelines recommend the use of a nonsedating antihistamine for the first four weeks of therapy.[22] Alpelisib labeling includes a warning for severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms. Alpelisib should be held when patients present with signs or symptoms of SCARs and should be permanently discontinued if SCARs are confirmed.[43] Additionally, when alpelisib is added to fulvestrant, the rates of stomatitis, rash, alopecia, pruritis and xerosis are increased compared with fulvestrant plus placebo.[43]

mTOR inhibitors can cause paronychia and stomatitis.[13] To prevent paronychia, patients should be instructed on gentle nail care, including regular trimming, avoiding manicuring, and wearing shoes that fit correctly. Topical corticosteroids can be used to treat chronic paronychia, and topical antibiotics and antiseptic washes can be used for bacterial infections. Oral or intravenous antibiotics may be necessary to treat more serious secondary infections. A steroid mouthwash containing dexamethasone can be used to prevent stomatitis.[22] Treatment delays and dose reduction should be considered for stomatitis higher than grade 2. Additionally, dental steroid paste can be considered for the treatment of ulcers.

A high incidence of alopecia was seen in studies involving the CDK 4/6 inhibitors palbociclib, abemaciclib, and ribociclib.[44] Other dermatologic AEs observed with CDK 4/6 inhibitors include mild rash, as well as rare cases of Stevens-Johnson syndrome.

Corticosteroid-related cAEs:

High-dose corticosteroids are frequently used in the treatment of cancer and are associated with various adverse effects, including cAEs. The use of systemic corticosteroids can cause acne, skin atrophy, impaired wound healing, and ecchymosis.[45] Additionally, corticosteroids can result in hirsutism or thinning of hair.

	Treatment	Effectiveness	Notes
Treatment recommendations (grouped into 1st, 2nd, and 3rd line)	Plucking, waxing, electrolysis	For mild hair growth (grade 1)	
	Laser therapy	For more severe hair growth (grade 2)	
	Eflornithine topical cream BID	For more severe hair growth (grade 2)	Can be combined with local hair removal methods
Systemic treatment	Spironolactone, 50 to 200 mg/QD	For more severe hair growth (grade 2)	Decision should be made in consultation with oncologist

Table 5: Treatment for Hirsutism[36]
QD, once daily; BID, twice daily

Conclusion

Patients receiving cancer treatment and survivors live longer. They require information on risk factors of clinically significant events, preventive strategies, and treatment, which would contribute to the optimal care of patients with cancer. This algorithm aims to provide HCPs with information on various skin toxicities associated with hormonal therapies for breast and prostate cancer, including preventing and treating these AEs. With this knowledge, providers will be better equipped to manage cAEs in this population, thereby contributing to improved quality of life, treatment outcomes, and therapy adherence.

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