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Skin Care in Oncology

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This review is a concise summary of skin care in cancer therapy. It is intended as an educational resource for healthcare professionals involved in the field of oncology. The review discusses the adverse effects of systemic chemotherapy and radiotherapy on the skin and the supportive skin care necessary, with a focus on over-the-counter products. Expert commentaries by Associate Professors Marius Rademaker (Hamilton) and Pablo Fernández-Peñas (Sydney) discuss the different types of cutaneous toxicities and their management from a clinical practice standpoint. This review does not cover allergic type cutaneous adverse reactions.

Introduction

Systemic chemotherapy and radiotherapy have resulted in increased survival rates in patients with cancer. However, they are also the cause of cutaneous adverse reactions in cancer patients, which can be itchy or painful as well as disfiguring.[1-3] With ongoing cancer treatment, the associated skin toxicity increases in frequency and can significantly impair quality of life,[4,5] potentially leading to dose reduction or delays or discontinuation of therapy and a compromised treatment outcome.[1-3,6,7] Patients may also face an economic burden associated with dermatological complications of cancer therapy.[8]

The management of cutaneous adverse reactions is thus becoming an increasingly important part of the supportive care for cancer patients.[1,2,6] In this clinical setting, close collaboration between oncologists and dermatologists is recommended to better manage cutaneous toxicities and to minimise the need for changes to chemotherapy or radiotherapy regimens.[1]

Skin Barrier Function

The primary function of the skin is to act as a barrier to protect the body from infection, desiccation, chemical insult, ultraviolet (UV) radiation, and mechanical stress, as well as being the major component of the innate immune system.[9,10]

Skin barrier function is primarily the responsibility of the stratum corneum, which forms the outermost layer of the epidermis. It is composed mainly of corneocytes and intercellular lipids. In addition to its vital role as a physical barrier, the stratum corneum is involved in the maintenance of hydration and contributes to innate immunity.[10,11] When skin barrier function is disrupted, trans-epidermal water loss (TEWL) increases and innate immunity is compromised, which can result in dry skin and cutaneous disorders such as irritant dermatitis.[9,10]

Cutaneous Effects of Cancer Treatment

Systemic chemotherapy and radiotherapy can disrupt skin barrier function, resulting in dry skin (xerosis), itching (pruritus), red rash (erythema), and changes in pigmentation, etc. Disruption of skin barrier function can also result in heightened sensitivity to topical substances and UV radiation, and increased vulnerability to skin infections. Furthermore, chemotherapy and radiotherapy used in combination can exacerbate these effects and produce severe skin dryness, inflammation (dermatitis), skin thinning, bullous eruptions and possibly necrosis.[1,12]

Systemic chemotherapy

Systemic chemotherapy primarily involves the use of conventional cytotoxic drugs, such as alkylating agents and antimetabolites, and targeted therapy with monoclonal antibodies (e.g. epidermal growth factor receptor [EGFR] inhibitors) and small molecules (e.g. BRAF inhibitors).[2,6,13]

Dry skin is a frequent cutaneous side effect of EGFR inhibitors and other systemic chemotherapeutic agents.[12,14,15] However, the most commonly reported cutaneous reaction to chemotherapy is rash,[1,2] especially in patients receiving targeted chemotherapy,[12,16,17] which can result in significant morbidity.[3] Rash is a poor term that comprises multiple different skin reactions (e.g. maculopapular exanthems, acute generalised pustulosis, acneiform reactions, eczema), induced by a variety of mechanisms. As an example, rash occurs in 45-100% of patients treated with EGFR inhibitors,[3,18] with papulopustular (acneiform) rash being the most clinically-significant dermatological toxicity caused by EGFR inhibitor chemotherapy.[12] Hence, rash is a term that should be avoided.

Hand-foot syndrome is a serious cutaneous adverse reaction that can occur with certain classes of chemotherapeutic agent, including the anthracyclines, antimetabolites and tyrosine kinase inhibitors.[1,2] As the name suggests, the palms of the hands and soles of the feet are primarily involved. In severe cases, patients may have difficulty walking and using their hands due to burning pain and skin cracking, blistering, and sometimes ulceration.[19] There are two main mechanisms: erythrodysaesthesia syndrome[20] and acute

keratoderma.[21] The first is a toxic effect on the epidermis of palms and soles and the second is increased epidermal proliferation secondary to trauma.

A relatively new cutaneous complication of chemotherapy is the development of new skin cancers, such as squamous cell carcinoma associated with BRAF inhibitor therapy.[6,22] Aggressive management of these skin cancers with resection, chemoprophylaxis with systemic retinoids, and regular follow-up is recommended.[6]

All patients receiving EGFR inhibitors are at risk of developing nail changes, the most common of which is nail fold inflammation (paronychia). Paronychia is characterised by tender, oedematous, often purulent inflammation of the nail folds, and has the potential to result in infection.[1,2,12]

Radiotherapy

Radiotherapy mainly involves the use of high-energy radiation, including X-rays and gamma rays, to destroy cancer cells and reduce tumour size.[2,13] The cutaneous adverse effects associated with radiotherapy are commonly referred to as radiodermatitis.

Radiotherapy will result in a moderate to severe skin reaction, ranging from mild erythema to severe ulceration, in approximately 85% of patients treated.[7] The most common forms of radiodermatitis are: i) dry desquamation, in which the stratum corneum becomes thick and is shed in clusters causing the skin to become dry and scaly; and ii) moist desquamation, in which the stratum corneum becomes thin and the skin begins to weep, due to loss of skin barrier integrity.[1,2] Longer-term radiotherapy-induced cutaneous toxicity can include telangiectasia, atrophy, fibrosis and ulceration.[23] Delayed effects include skin cancer.

Modern radiotherapy technologies allow the skin to receive a fraction of the total dose that is delivered to the intended target.[23] Nonetheless, radiodermatitis is difficult to avoid when treating certain tumour sites where the skin or very superficial tissues are the intended target. In such cases, radiodermatitis may be expected to occur in most, if not all, patients. Tumour sites that are commonly associated with radiodermatitis include the brain, breast, head and neck, soft tissue, perineum, and anal canal.[23]

Assessment of Cutaneous Toxicities

Accurate assessment and grading of dermatologic adverse events due to cancer treatment is important for monitoring and documentation in clinical practice, including drug toxicity determination and adjustment of supportive skin care treatments.[23,24]

The US National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) is the most widely used tool for grading cutaneous toxicities.[23,24] The CTCAE 4.0 provides some descriptive terminologies and a grading scale (grade 1 = mild to grade 5 = death) that can be used to rate the severity of some cutaneous adverse effects, including rash, xerosis, and paronychia (**Table 1**). A potential disadvantage of the CTCAE 4.0 is that it is a non-treatment specific grading tool, which could result in under-reporting and poor grading of distinctive adverse events. It also supports the use of generic terms, such as rash, generating data of little use for diagnostic and treatment purposes as it aggregates very different cutaneous conditions. For these reasons, a drug class-specific grading scale to standardise assessment and improve reporting of EGFR inhibitor-associated dermatologic adverse effects has been proposed,[24] and better tools for skin conditions should be developed.

In addition to the non-treatment specific CTCAE 4.0, the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) grading systems, and the Late Effect on Normal Tissue (LENT)/Symptom Objective Measures, Management, Assessment (SOMA) are widely used treatment-specific tools for rating of radiotherapy-induced cutaneous adverse reactions (**Table 1**). Similar to the CTCAE 4.0, they categorise a broad range of adverse events, with a structured description and rating of severity supplied for each event type. It is worth noting, however, that, despite providing specific criteria for grading skin toxicity and being widely used, reliability and validation data for these tools is lacking.[23]

Disfiguring Effects of Cancer Treatment

As well as the itch, pain and discomfort of the dermatological toxicities secondary to chemotherapy and radiotherapy, the associated skin changes can be highly visible and aesthetically disfiguring and lead to negative self-image and quality of life.[1,2,6] For example, health-related quality-of-life studies have shown increased levels of emotional, psychosocial, and functional impairment in cancer patients with EGFR inhibitor-induced rash and painful, burning and itchy skin.[6]

Skin Care in Cancer Patients

A large range of potential treatments to manage cutaneous adverse reactions associated with chemotherapy and radiotherapy have been studied. Due to a lack of randomised controlled trials, however, the recommendations of management guidelines are largely empirical, being based mainly on individual physician and clinic experience, expert opinion and consensus, and published case studies,[7,12,25] as well as being based on the treatment of similar skin conditions in patients not treated with anti-cancer therapies.

In general, treatment of the skin reaction is preferable to chemotherapy or radiotherapy dose reduction, delay, or termination.[3] A suggested algorithm for the management of cutaneous toxicities associated with cancer treatment is presented in **Figure 1**.[2,13] The main issue is that a specific diagnosis is

	RTOG/EORTC	LENT/SOMA	CTCAE 4.0
0	No change from baseline/no symptoms	No change from baseline/no symptoms	No change over baseline/no symptoms
1	Follicular, faint or dull erythema, hair loss, dry desquamation, decreased sweating	Minor symptoms present that require no treatment	Faint erythema or dry desquamation
2	Tender or bright erythema, patchy moist desquamation, moderate oedema	Moderate symptoms present that require conservative treatment	Moderate to brisk erythema, patchy moist desquamation, mostly confined to skin folds and creases, moderate oedema
3	Confluent moist desquamation other than skin folds, pitting oedema	Severe symptoms, which have a significant negative impact on daily activities, and which require more aggressive treatment	Moist desquamation other than skin folds and creases, bleeding induced by minor trauma or abrasion
4	Ulceration, haemorrhage necrosis	Irreversible functional damage, necessitating major therapeutic intervention	Life-threatening consequences, skin necrosis or ulceration of full thickness dermis, spontaneous bleeding from involved site, skin graft indicated
5	Death related to treatment effects	Death or loss of organ	Death

Table 1. Commonly used tools for the grading of cancer treatment cutaneous toxicities.[23] CTCAE 4.0 = Common Terminology Criteria for Adverse Events version 4.0; LENT/SOMA = Late Effect on Normal Tissue/Symptom Objective Measures, Management, Assessment; RTOG/EORTC = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer

not required, and the algorithm is deficient to treat many adverse skin reactions. For example, an acneiform reaction or a maculopapular exanthem will not benefit from sun protection, moisturisers, or camouflage, and while eczema may improve with moisturisers, it usually gets better with moderate sun exposure. A word of caution, systemic complimentary medicines used to attenuate the toxic effects of chemotherapy or radiotherapy may also reduce their therapeutic effects.

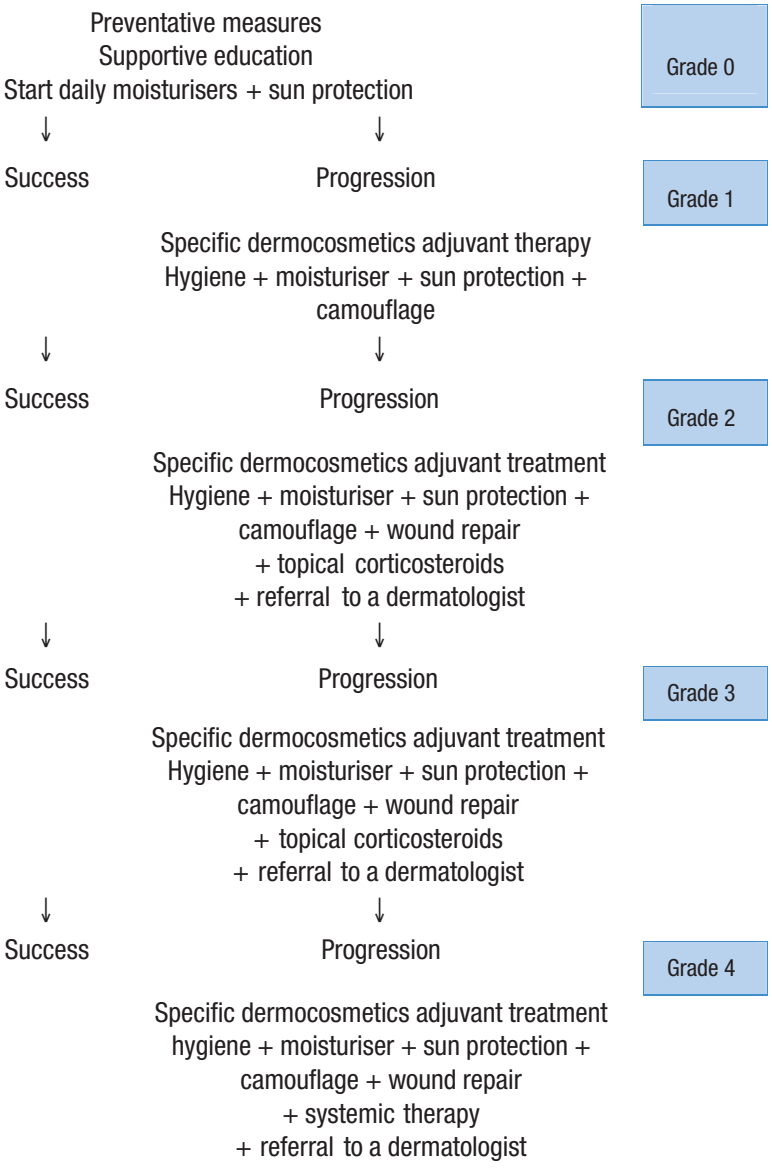


Figure 1. A suggested algorithm for the management of cutaneous toxicity secondary to cancer treatment based on the National Cancer Institute's Common Toxicity Criteria (0 = no toxicity to 4 = exfoliative or ulcerating dermatitis).[2,13]

Mild cutaneous adverse reactions associated with cancer therapies can usually be effectively managed by the treating physician if they are familiar with the clinical presentation (e.g. acneiform reactions induced by EGFR inhibitors). However, when the reactions are unusual or worsen, especially when they are disseminated and painful, with pustules or blisters, or when necrosis develops, the involvement of a dermatologist and, possibly, other medical discipline expertise is recommended (**Figure 1**).[13] In particular, multi-disciplinary teams, including medical and radiation oncologists, nurses, dermatologists, pharmacists, and wound care specialists, are recommended for management of EGFR-inhibitor–associated dermatologic toxicities.[12]

Cosmetics

The use of cosmetics to camouflage appearance changes in the skin can help to improve the quality of life of cancer patients.[1,2] Hence, providing patients with professional advice on cosmetic products that are specially formulated for and clinically tested on sensitive damaged skin is important in this regard.[1,2] Prospective studies have shown that training seminars on appropriate skin care, including camouflage and dressing techniques, and provision of beauty care services, improve measures of patient quality of life, including reduced anxiety and enhanced self-esteem.[2]

Skin cleansing

Skin cleansing is a standard part of personal hygiene and there is no evidence to suggest that skin cleansing in cancer patients with cutaneous reactions should be avoided. Washing with water, with or without a mild soap or soap-free cleanser, is supported, although excessive bathing, particularly in hot rather than tepid water, is not advised.[1,2,12,13,23]

It is worth noting that the use of hygiene products that remove sebum in addition to impurities can further aggravate already dry and damaged skin in cancer patients whose skin barrier function has been disrupted by their cancer treatment.[1,2] Therefore, providing professional guidance so that patients avoid using unsuitable self-care skin products is essential.[26] Gentle skin cleansing with soap-free cleansers that are free of fragrances or perfumes is generally recommended.[1,2,12,23]

Skin hydration

Topical application of emollients or moisturisers can help to repair damaged skin by binding water within the stratum corneum thereby facilitating skin barrier function and skin hydration.[1,2] Moisturisers can reduce TEWL and replace skin lipids and other factors that help to maintain the integrity of skin barrier function.[9] Given that the use of clinically-tested emollients or moisturisers helps to improve barrier function and skin hydration, their application prior to, during, and after cancer treatment can be beneficial in the prevention and treatment of cutaneous reactions.[2,13] For example, the use of moisturisers contributed to the effectiveness of a pre-emptive skin treatment regimen, which also included topical steroids and oral doxycycline 100mg twice daily, in preventing EGFR inhibitor-induced skin toxicity.[27]

There is broad consensus that use of alcohol-containing lotions or skin products that may dehydrate the skin should be avoided.[1,2,12] For the same reason, avoidance of severe, cold, dry weather or significant heat has also been advocated.[12]

Sun protection

Photoprotection is important in patients receiving radiotherapy or EGFR inhibitors to prevent the rash and pigmentation changes that can result from the skin's heightened sensitivity to UV radiation, particularly in patients with lighter skin types.[3,18] A pre-emptive skin treatment regimen that included an SPF≥15 (UVA/UVB protection) sunscreen has been shown to be effective in reducing skin toxicity caused by EGFR inhibitor chemotherapy in a regimen with topical steroids and oral doxycycline 100mg twice daily.[27]

In general, treatment guidelines recommend the use of alcohol-free broad-spectrum SPF≥15 sunscreens, preferably physical rather than chemical sunscreens (i.e. zinc oxide, titanium dioxide).[3,13,28]

Treatment Recommendations

The following are general recommendations for basic skin care in cancer patients receiving cancer treatment, with specific detail provided in **Table 2**:

1. Daily use of non-comedogenic moisturisers or emollients from several days before the first session of chemotherapy or radiotherapy.
2. Gentle skin cleansing with water, with or without mild soaps or soap-free cleansers.
3. Refrain from using alcohol-containing skin care products and those containing perfume or fragrance.
4. Avoidance of direct sun exposure and application of a broad-spectrum SPF≥15 sunscreen to the face and other exposed areas.
5. Patient well-being is improved by covering aesthetically-disfiguring skin reactions with non-comedogenic make-up.[1,2,12,13,23]

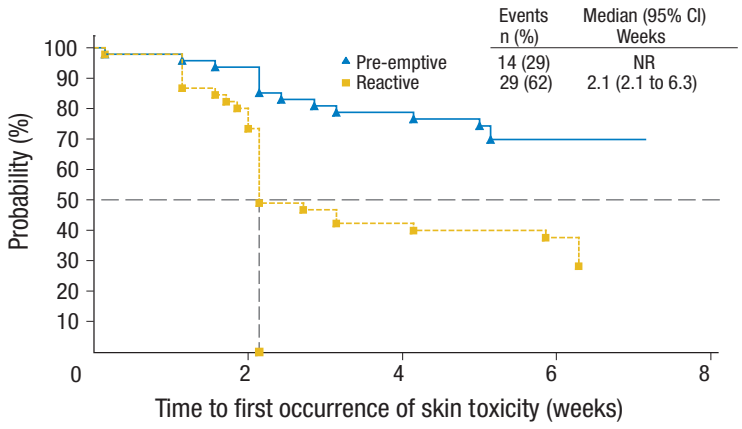
	Recommended Skin Care
Dry skin	• Gentle skin cleansers
	• Moisturising creams
	• Emollients
	• Oil-in-water moisturisers
	• Exfoliants (if very scaly)
	• 1-10% urea or topical salicylic acid in emollient base (may irritate)
	• Topical zinc oxide
	• Photoprotection
	• Topical corticosteroids
Fissures	• Protective footwear, gloves
	• Moisturisers, glycerine, zinc oxide cream
	• 1-10% urea or topical salicylic acid in emollient base (may irritate)
	• Liquid glues or cyanoacrylate
	• Topical antiseptics/antibiotics
	• Topical corticosteroids
	• Hydrocolloid dressings
Hand and foot	• 1-10% urea or topical salicylic acid in emollient base (may irritate)
Radiodermatitis	• Gentle skin cleansers
	• Moisturisers
	• Photoprotection
	• Drying gels, antiseptics, dusting powders
	• Antiseptics, topical antibiotics
	• Silver sulphadiazine
	• Topical corticosteroids
Radiotherapy-induced telangiectasia	• Pulse dye laser therapy
Radiotherapy-induced fibrosis	• Pentoxifylline and vitamin E
Rash	• Gentle skin cleansers
	• Moisturisers/emollients
	• Photoprotection
	• Topical corticosteroids
Papulopustular rash	• Antiseptics
	• Topical corticosteroids
	• Photoprotection
	• Low-dose isotretinoin (acneiform eruptions)
Paronychia	• Topical antiseptics
	• Topical corticosteroids
	• Liquid bandages or glue for nail splitting
Pruritus	• Gentle skin cleansers
	• Topical menthol (1-3%)
	• Topical corticosteroids
	• Systemic antihistamines
	• Systemic gabapentin/pregabalin
	• Topical and systemic doxepin

Table 2. General recommendations for treatment of some cutaneous reactions to chemotherapy or radiotherapy.[1,2,12,13,23]

Pre-Emptive Skin Care

The effectiveness of a pre-emptive skin treatment regimen in patients with advanced colorectal cancer who received systemic chemotherapy with the EGFR inhibitor, panitumumab, was evaluated in STEPP, a multicentre, randomised, open-label, clinical study conducted by Lacouture and colleagues.[27] The use of a regimen of skin moisturisers, SPF≥15 (UVA/UVB) sunscreen, topical steroid, and doxycycline 100mg twice daily prior to administration of panitumumab resulted in a 50% lower incidence of grade 2 or higher skin toxicities (graded using a modified CTCAE 3.0) compared with reactive treatment (any skin treatment deemed necessary for management of emergent skin toxicity) during the 6-week skin treatment period. In addition, the median time to first occurrence of specific grade 2 or higher toxicities was not reached in the pre-emptive skin care group versus 2 weeks in the reactive skin care group (**Figure 2**).

Lacouture et al concluded that these findings demonstrate the benefits of establishing a comprehensive pre-emptive skin toxicity programme in patients treated with panitumumab, which may be generalisable to other EGFR inhibitors given that the toxicities are considered a class-based effect.[27]



Pre-emptive n	48	44	36	27	0
Censored	0	1	1	5	27
Reactive n	47	36	18	16	0
Censored	0	2	1	0	15

Figure 2. Median time to first occurrence of specific grade ≥2 skin toxicity with pre-emptive versus reactive skin treatment.[27] CI = confidence interval; NR = not reached; n = number

Expert's Concluding Comments – Pablo Fernández-Peñas

Cutaneous adverse reactions are a complex diagnostic dilemma for most physicians. Eczema, psoriasiform dermatitis, bullous diseases, photo-induced dermatitis, maculopapular exanthems, acneiform reactions, Grover's disease, lichenoid reactions, etc., are some of the multiple presentations on the skin associated with oncology medications. Treatments differ from one condition to another, and some are suggestive of more aggressive disease that could lead to Stevens-Johnson syndrome or toxic epidermal necrolysis. In this context, the use of generic, non-descriptive terms, such as rash, hinders the possibility of a mechanistic explanation and more directed therapy.

Oncologists should get familiar with the most common manifestations of the anti-cancer therapies they use and learn the proper treatment for them. Acneiform reactions induced by EGFR inhibitors, plantar keratoderma induced by BRAF inhibitors, and erythrodysesthesia induced by cytarabine or docetaxel are good examples of easily identifiable and easily managed adverse events. Other generalised exanthems and most rashes will need proper dermatological diagnosis to provide the best treatment possible. Multidisciplinary teams with dermatologists will provide proper cutaneous care and will avoid dose reduction or treatment changes due to skin toxicities.

Expert's Concluding Comments – Marius Rademaker

Adverse reactions to drugs can be divided into type A, expected, dose-dependent side-effects, which make up approximately 80-90%, and type B, unexpected allergic-type reactions, which make up 10-15% (there are also type C, D, E and F adverse reactions). Physicians tend to concentrate on the allergic reactions as being more serious, but often the type A give rise to more severe reactions, and from the patient point of view, are often more significant. Cutaneous toxicity is often forgotten when dealing with neutropenic crisis or failing kidneys, but to the patient an unhappy skin is unrelenting. The reduction in quality of life from significant skin dysfunction is often greater than that seen with chronic diseases, such as diabetes, cardiac disease and even cancer itself.

Whilst allergic reactions are often unavoidable, cutaneous toxicity can be ameliorated with reduction in treatment dose and good skin care. As the former is undesirable, the importance of good skin care, from before the start of cutaneous toxicity, cannot be over stressed.

As the nature of cancer therapies shifts to more immunological-based treatments, the range of skin toxicities and cutaneous adverse reactions is also changing. Our increasing understanding of the vital role of the skin in the innate immune system only emphasises the importance of good skin care.

It may seem inappropriate use of your valuable time discussing with your patient which soap to use, or which shampoo or cosmetic, but these are often higher up in the mind of your patient than what their creatinine level or neutrophil counts are. The suggested algorithm and recommendation for skin care in this article should serve as a good starting point in the management of your patient's skin during their cancer treatment.

Take-Home Messages

1. Chemotherapy and radiotherapy are associated with cutaneous toxicity and adverse reactions.
2. Prevention and treatment of dermatological toxicities is important to maintain cancer patients' treatment intensity and quality of life.
3. General consensus-based treatment guidelines support the use of mild skin cleansers and emollients.
4. Oncologists should familiarise themselves with the most common cutaneous manifestations of the anti-cancer therapies that they use and learn to treat them appropriately, as different skin reactions require specific therapies.

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