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Casmo Prevention and Management of Four Common Cutaneous Toxicities Associated with Targeted Cancer Therapies: Papulopustular Eruption, Xerosis, Paronychia, and Hand-Foot Skin Reaction

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Acknowledgments and Disclosure: targeted cancer therapy, management of cutaneous adverse events:

ABSTRACT

Introduction: Advances in cancer treatment have contributed to a reduction in mortality but survivors and healthcare providers should be aware of the potential adverse effects of these advanced treatments.

Objectives: The Canadian skin management in oncology (CaSMO) practical recommendation was developed to improve the quality of life for cancer patients and survivors who experience targeted therapy-related cutaneous adverse events.

Methods: The CaSMO advisory board (advisors) identified four common cutaneous adverse events related to targeted therapy and gave practical recommendations for managing these cutaneous adverse effects based on the results of a literature search and clinical expertise.

Results: Papulopustular eruption, xerosis, paronychia, and hand-foot skin reaction were identified as common cutaneous adverse events related to targeted therapy. The advisors provide practical steps for preventing and treating these cutaneous conditions.

Conclusions: The CaSMO practical guidance is for all healthcare providers who treat oncology patients receiving targeted therapy and can be used to help prevent and manage common cutaneous adverse events, thereby improving treatment adherence, quality of life, and outcomes.

Key words: targeted cancer therapy, management of cutaneous adverse events

Introduction

Improved understanding of the molecular basis of numerous cancers has led to the development of targeted therapies. Epidermal growth factor receptor (EGFR) inhibitors, multikinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors, mammalian target of Rapamycin (mTOR) inhibitors, BRAF inhibitors, and MEK inhibitors (Table 1) are all molecular targeted agents that have emerged as effective cancer treatments. As opposed to conventional chemotherapies which usually target rapidly dividing cells and are not specific to cancer cells, targeted therapies more selectively attack cancer cells by inhibiting specific molecules involved in tumor pathogenesis.

The increased specificity of these therapies leads to an improved safety profile compared with conventional chemotherapy, with fewer systemic side effects. However, the most prevalent side effect of targeted therapies are skin and appendage toxicities. The targeted therapy cutaneous adverse events (ttCAEs) profile is broad and differs for each specific agent. In general, most common ttCAEs include papulopustular eruption, xerosis, pruritus, hand-foot skin reaction (HFSR), paronychia, and mucositis. Targeted therapies can also lead to uncommon but serious toxicities such as morbilliform exanthema, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Targeted Therapy Categories	Specific Agents
Epidermal Growth Factor Receptor (EGFR) inhibitors	• Cetuximab • Panitumumab • Erlotinib • Gefitinib • Lapatinib • Neratinib • Afatinib • Osimertinib • Pertuzumab • Dacomitinib • Mobocertinib • Canertinib
Multikinase inhibitors	• Sorafenib • Sunitinib • Regorafenib • Pazopanib • Cabozantinib • Axitinib • Vandetanib
Selective VEGF inhibitors	• Bevacizumab • Ranibizumab
Mammalian target of Rapamycin (mTOR) inhibitors	• Everolimus • Sirolimus • Temsirolimus
BRAF inhibitors	• Dabrafenib • Vemurafenib • Encorafenib
MEK inhibitors	• Trametinib • Cobimetinib • Binimetinib

Table 1: Targeted therapy categories and specific agents

ttCAEs can lead to severe symptoms with profound effects on cosmesis, quality of life, and compliance with cancer medication. Common ttCAEs are not life-threatening toxicities by themselves but can lead to targeted therapy dose reduction, therapeutic holidays, or even permanent discontinuation, which may compromise cancer outcomes.

Targeted therapy toxicities generally are a positive prognostic sign to therapeutic response. CAEs incidence as well as severity are associated with a longer time to progression of cancer (TTP) and increased overall survival (OS).[1] Most data show a positive relation between papulopustular eruption incidence and severity and TTP and OS in patients receiving EGFR inhibitors.[2-5] The goal for dermatologists and oncologists should be to treat the dermatological toxicities prior to considering dose reduction, interruption, or discontinuation, whenever possible.

While ttCAEs are common, treatments and guidelines are mostly based on reviews, expert consensus, and case series. Very few controlled studies are published on specific treatments to prevent or manage these CAEs. Even more, in most published clinical trials studying targeted therapies, cutaneous side effects are reported as "rash" without details about the clinical appearance and management of specific cutaneous toxicities.

Mechanisms underlying these ttCAEs are poorly understood. Most explanations come from literature on EGFR inhibitors. EGFR is overexpressed in some cancer cells, but is also expressed in normal basal keratinocytes, the outer layers of hair follicles, sebaceous epithelium, and periungual tissues. It plays an essential role in skin physiology and differentiation and proliferation of these tissues. EGFR blockage induces upregulation of IL-1 and TNF-alpha and increases synthesis of other inflammatory chemokines and cytokines, leading to an inflammatory response.[6] Apoptosis of normal keratinocytes, abnormal keratinization, and the subsequent inflammatory response could explain the occurrence of papulopustular eruption. EGFR inhibitor-induced xerosis results from abnormal keratinocyte proliferation and differentiation, leading to a deteriorated stratum corneum and a decrease in moisture retention.[7, 8] Paronychia pathogenesis is unclear. It could be secondary to skin fragility, leading to onychocryptosis and subsequent paronychial inflammation.[9] EGFR inhibitors induce an inflammatory response which could result in paronychia.[10] EGFR inhibition-induced abnormal keratinocyte differentiation and proliferation lead to periungual stratum corneum thinning and fragility, resulting in piercing of paronychium and granulation tissue formation.[11] EGFR is also involved in the normal healing process, so EGFR blockage leads to abnormal healing which could contribute to excessive periungual granulation tissue.[11] Infection does not appear to

play a consistent role in the pathogenesis of paronychia.[9] HFSR pathophysiology is even less understood. In contrast to hand-foot syndrome induced by chemotherapy agents excreted in sweat, a study on sorafenib showed that this targeted therapy is not excreted through eccrine glands.[12]

In an era in which there is a growing number of targeted therapy indications and use, it is essential that dermatologists, oncologists, and other physicians know how to manage these common CAEs to enable patients to continue receiving these survival-prolonging therapies and improve their outcomes.

This review article discusses the management of four common CAEs induced by targeted therapy: papulopustular eruption, xerosis, paronychia, and HFSR.

Scope

The CaSMO project aims to improve the quality of life for cancer patients and survivors by offering tools to prevent and manage CAEs.[13-16] A general management algorithm to reduce the incidence of all CAEs and maintain healthy skin using general measures and skin care,[14] an algorithm to reduce and treat acute radiation dermatitis,[15] and an algorithm for the management of hormonal therapy-related CAEs[16] were previously published. These algorithms aim to support all health care providers (HCPs) treating oncology patients, including physicians, nurses, pharmacists, and advanced providers. A practical primer followed on prevention, identification, and treatment, including skin care for immune-related CAEs, focusing on isolated pruritus, psoriasiform eruptions, lichenoid eruptions, eczematous eruptions, and bullous pemphigoid.[17] The next step in the project was to develop practical guidance for the management of four common CAEs (papulopustular eruption, xerosis, paronychia, and HFSR) in oncology patients receiving targeted therapies.

Methods

The CaSMO advisors convened for a meeting to develop practical guidance for targeted therapy-related CAEs. The advisors used a modified Delphi approach following the AGREE II instrument.[18-20]

Literature Review

Searches included literature describing current best-practice in improving comfort during targeted therapy, reducing/treating CAEs, and promoting healing of affected skin. Selected literature is clinically relevant to the practical guidance and included guidelines, consensus papers, reviews, and publications describing current best-practice in CAEs-related targeted therapy in the English language from January 2010 to May 2022. Excluded were articles with no original data (unless a review was deemed relevant), articles not dealing with prescription treatment, skincare for cAEs-related to targeted therapy, and publication language other than English.

A dermatologist and physician/scientist conducted searches on PubMed and Google Scholar for English-language literature on May 20 and 21, 2022, using the following AND OR search terms:

A dermatologist and a physician/scientist conducted the searches on September 16 and 17, 2019 on PubMed and Google Scholar of the English-language literature using the terms:

Group 1: TKIs OR MKIs OR tyrosine kinase inhibitors OR multikinase inhibitors OR EGFR inhibitor OR VEGF inhibitor OR FGFR inhibitor OR MEK inhibitor OR BRAF inhibitor OR PanRAF inhibitor OR BCR-abl inhibitor OR osimertinib OR afatinib OR dacomitinib OR erlotinib OR gefitinib OR lapatinib OR cetuximab OR panitumumab OR sunitinib OR bevacizumab OR Lenvatinib OR vandetanib OR regorafenib OR sorafenib OR axitinib OR pazopanib OR erdafitinib OR pemigatinib OR trametinib OR cobimetinib OR dabrafenib OR vemurafenib OR belvarafenib OR KIT OR PDGFR OR imatinib OR dasatinib OR nilotinib AND cutaneous adverse event

Group 2: paronychia OR hand-foot skin reaction OR papulopustular rash OR acneiform rash OR xerosis OR pruritus OR rash OR skin toxicities AND targeted therapy

Group 3: prescription medication OR skincare OR topical OR prevention OR treatment OR maintenance OR QOL OR quality of life OR adjunctive OR education OR communication OR communication strategies OR adherence OR concordance OR efficacy OR safety OR tolerability OR skin irritation AND cutaneous adverse event AND targeted therapy

Two reviewers independently evaluated the results of the literature search. The abstracts of 422 articles were reviewed after which 116 were excluded for duplication or poor quality. After a review of the articles in full, 297 remained (Figure 1).

General Management Principles for Skin Toxicities of Anti-Cancer Treatment (Stats), Including Caes Induced by Targeted Therapy

A recently published article by the CaSMO working group reviewed in details general skincare measures to prevent STATs, including CAEs induced by targeted therapies.[14] Their preventive algorithm is mainly based on three major behaviors: cleanse, moisturize, and protect. (Tables from the previous publication).

Papulopustular Eruption

EGFR inhibitors and mTOR inhibitors can induce a papulopustular eruption. MEK inhibitor monotherapy is also a common cause whereas BRAF inhibitors rarely induce this toxicity. Combining a BRAF inhibitor to MEK inhibitors significantly decreases the incidence and severity of MEK inhibitor induced papulopustular eruption.[21] Papulopustular eruption is the most common toxicity of EGFR inhibitors, affecting 50-100% of patients, depending on the agent.[22] Cancer response and survival have a positive correlation with the incidence and severity of the papulopustular eruption in patients receiving EGFR inhibitors.[4]

Papulopustular eruption, also sometimes referred as acneiform eruption or folliculitis, classically occurs early after the initiation of targeted therapy, in the first 7 to 10 days of treatment. It peaks after two to four weeks, then stabilizes and decreases in intensity after six to eight weeks. A mild papulopustular eruption often persists over months or the eruption may sometimes self-relieve despite continuing targeted therapy. It affects seborrheic and UV-exposed areas, mainly the scalp, face, neck, upper chest, and back. The eruption is characterized by monomorphous inflammatory papules and pustules. Pruritus

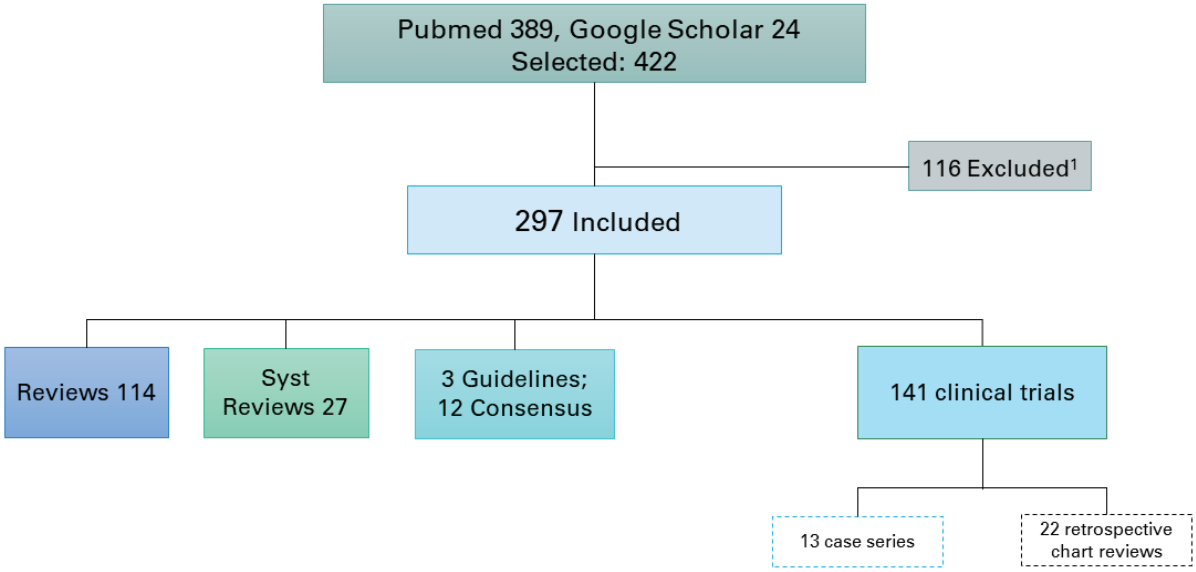

Figure 1: Systematic literature search results

[1]Excluded were: Poor quality paper, duplications (in case of an update on a review article the latest version was used).

Papulopustular Eruption
General principles and prevention • Gentle skin care using a fragrance-free cleanser close to skin pH (pH 5.5) • Emollient at least once a day (twice a day is preferable) • Photoprotection (sunscreen with SPF 50+ and other methods)[1] • Consider topical hydrocortisone 1% • Consider oral antibiotics in tetracycline class[2] (if contraindicated: erythromycin, clarithromycin, or azithromycin) • Consider the combination of an emollient, photoprotection, topical hydrocortisone 1%, and oral antibiotics in tetracycline class[3]
First-line treatment • Continue preventive measures • Oral antibiotics in tetracycline class (if contraindicated: erythromycin, clarithromycin, or azithromycin[4]) • Topical steroids (low-to-medium potency on face, medium-to-high potency on body) • Avoid topical acne treatments (e.g. benzoyl peroxide, retinoids, azelaic acid, or alpha-hydroxy acid)
Second-line treatment • Bacterial/viral cultures; treat accordingly (including topical and/or systemic antibiotics and antivirals) • Topical dapsone • Low-dose oral isotretinoin
Third-line treatment • Systemic steroids • Acitretin • Oral dapsone • Dose reduction or intermittent interruption of targeted therapy

Table 2: Prevention and treatment recommendations for targeted therapy-induced papulopustular eruption

[1]Photoprotection must be reinforced if patients are on doxycycline or isotretinoin with the increased risk of phototoxicity.
[2]Either doxycycline 100 once daily to BID, minocycline 50-100 mg BID, or tetracycline 500 mg BID.
[3]STEPP trial regimen should be considered in patients being treated with EGFR inhibitors or MEK inhibitors.[25]
[4]There is evidence to support the use of pulse azithromycin 500 mg daily for 3 consecutive days per week.[34]

is a common associated symptom. As opposed to classic acne, it lacks typical comedones and cysts. Papulopustular eruption is dose dependent.

Atypical acneiform eruption warrants bacterial culture and viral swab to exclude bacterial and herpetic infection. It can either be a primary cutaneous infection or a superinfection developing on a pre-existing papulopustular eruption. Infection should be considered when papulopustular eruption is widespread and involves non-seborrheic areas such as upper extremities, lower extremities, abdomen, and buttocks, does not involve the face, lasts longer than eight weeks, appears late after more than 12 weeks of targeted therapy, or is recalcitrant to appropriate treatment.[23, 24] Other signs of infection include the presence of vesicles, yellow crusts, discharge, or painful lesions.[23, 24]

Some trials have studied preventive tools to decrease the incidence and severity of papulopustular eruption (Table 2). A phase II randomized controlled trial (STEPP trial) evaluated a pre-emptive regimen in patients receiving panitumumab, an EGFR inhibitor, for metastatic adenocarcinoma of the colon or rectum.[25] Patients were randomized into two groups. One group received a pre-emptive treatment beginning day -1 of panitumumab and continued through weeks 1 to 6 and it consisted of a combination of skin moisturizer daily in the morning, sunscreen before going outdoors, hydrocortisone 1% cream at night, and oral doxycycline 100 mg twice a day. The other group received only reactive treatment deemed necessary by the investigator to manage emergent skin toxicity. The incidence of protocol-specified grade 2 or higher skin toxicities during the 6-week skin treatment period was 29% and 62% for the pre-emptive and reactive groups, respectively. These protocol-specified skin toxicities included pruritus, acneiform dermatitis, skin desquamation, exfoliative dermatitis, paronychia, nail disorder, skin fissures, skin laceration, pruritus, rash, pustular rash, skin infection, skin ulceration, and local infections. Papulopustular eruption was reported less frequently with pre-emptive treatment (77%) comparing to reactive treatment (85%). This preventive regimen should be initiated in patient receiving EGFR inhibitors and MEK inhibitors which are targeted therapies with a higher risk of papulopustular eruption. Another randomized controlled trial evaluated the preventive use of doxycycline to prevent erlotinib-induced acneiform eruption.[26] Incidence was comparable between patients receiving doxycycline and the ones receiving the placebo, but doxycycline decreased the eruption severity.

Photoprotection is likely an important preventive tool even though some studies did not show any benefits.[27] Patients must avoid using tanning bed. A physical/inorganic sunscreen should be favored instead of chemical/organic sunscreen that can irritate the skin.[28]

Treatment lines are detailed in Table 2. Typical over the counter and prescribed topical acne treatments such as benzoyl peroxide, retinoid, azelaic acid, and alpha-hydroxy acid should be avoided. These therapies are typically drying and irritating, which may worsen the papulopustular eruption. Topical tazarotene was studied in a cohort of patients on cetuximab.[29] Patients applied it on one side of the face and the other side was used as control. Most patients did not experience any improvement with the use of topical tazarotene. Furthermore, the rash was assessed as more severe on the tazarotene side for some patients.

Phototoxicity induced by tetracycline class antibiotics must be taken into consideration in patients receiving targeted therapy. Doxycycline has an overall better tolerance and safety profile than minocycline but comes with a risk of phototoxicity which could potentially worsen the papulopustular eruption. Photoprotection must be reinforced in this setting. Minocycline is another option that does not lead to phototoxicity but has potential serious side effects including autoimmune hepatitis and drug-induced systemic lupus. In patients who cannot commit to strong photoprotective measures or who are living in areas with high ultraviolet index, minocycline may be a better option, but should be given for less than a year to decrease the risk of autoimmune side effects. For all other patients, doxycycline is a better option because of its safety profile. Especially for patients with renal insufficiency, doxycycline is the drug of choice.

Topical dapsone has been studied in patients receiving cetuximab.[30] They were randomized to apply dapsone 5% gel to one side of the face and chest twice daily, and a moisturizer to the contralateral side, used as control. All patients were also receiving oral minocycline. A statistically significant reduction in lesion count was observed on the dapsone-treated sides. Dapsone has anti-inflammatory and anti-bacterial properties without the risk of skin atrophy or microbial resistance potentially induced by the prolonged application of topical steroids and antibiotics, respectively.[30]

Isotretinoin is an effective treatment if tetracyclines or topical treatments fail. A low dose of 0.15-0.35 mg/kg is recommended.[31] Tetracyclines should be stopped before starting isotretinoin. Concomitant use of isotretinoin and tetracycline increases the risk of pseudotumor cerebri (idiopathic intracranial hypertension). Isotretinoin has overlapping side effects with targeted therapy such as xerosis and excessive granulation tissue. Isotretinoin-induced xerosis may exacerbate the papulopustular eruption, so the regular application of an emollient should be reinforced. Isotretinoin can also induce photosensitivity, which can worsen the acneiform eruption. Photoprotective measures must be reinforced in patients receiving isotretinoin.

Targeted therapy dosage sometimes needs to be reduced or the medication even needs to be temporarily stopped. If targeted therapy is stopped, it should be restarted when papulopustular eruption is back to a CTCAE severity grades 0 or 1 (papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness).[32] Some recommend restarting targeted therapy at 50% of the initial dosage.[33]

Xerosis

All targeted therapies can induce xerosis. This ttCAE is progressive and appears usually one to three months after the initiation of cancer treatment. Xerosis can potentially worsen papulopustular eruptions. It can also lead to pruritus, asteatotic eczema, and painful fissures, especially on the hands and feet.

Emollient containing humectant such as urea and lactic acid can be effective to manage xerosis. Fissures are challenging to treat. They can be symptomatic with a burning sensation and significant pain. Emollient and barrier cream are essential. Cyanoacrylate glue, more commonly known as liquid skin glue or liquid bandage, can be applied directly in the fissures to decrease the healing time. Hydrocolloid dressing is another treatment option.

Pruritus induced by targeted therapy is challenging to manage and can be multifactorial. A detailed discussion about pruritus is beyond the scope of this article.

Xerosis
General principles and prevention • Gentle skin care regimen using a fragrance-free cleanser close to skin pH (pH 5.5), such as a syndet • Limited shower time: avoid hot showers, hot baths, saunas, and other irritants • Regular use of an emollient (cream, balm, or ointment are preferred)
First-line treatment • Continue preventive measures • Ensure patient is using an appropriate emollient in adequate amount and frequency
Second-line treatment • Topical steroids if associated dermatitis • Cyanoacrylate glue for fissures

Table 3: Prevention and treatment recommendations for targeted therapy-induced xerosis

Paronychia

Paronychia is a late CAE that can be induced by EGFR inhibitors, MEK inhibitors, mTOR inhibitors, multikinase inhibitors, and VEGF inhibitors. It usually appears after one to two months of targeted therapy with painful periungual inflammation characterized by erythema and swelling. The first digit and first toe are most affected. Paronychia is highly morbid with severe pain and functional limitation. It can lead to the formation of excessive friable granulation tissue, onychocryptosis/ingrown nail, and periungual abscess. It is a common cause of targeted therapy dose reduction or discontinuation. Bacterial and fungal superinfections represent a common complication. If a superinfection is suspected, a bacterial and fungal culture must be done, and the infection treated accordingly.

A few trials have evaluated paronychia treatment. In a retrospective cohort study evaluating the topical use of timolol 0.5% gel twice daily under occlusion to treat targeted therapy-induced paronychia and/or periungueal pyogenic granuloma, 15% of patients were considered in complete response (2/13 patients), 46% in partial response (6/13) and 39% in failure (5/13).[35]

Surgical interventions may be needed for severe or refractory cases. In a retrospective case series, partial matricectomy, nail avulsion, debridement/clipping, and incision and drainage were performed with resolution rates of 100% (11/11), 38.5% (5/13), 12.5% (1/8), and 0% (0/4), respectively.[36]

Paronychia
General principles and prevention • Gentle nail care. Avoid trauma such as cutting nails too short, aggressive manicure and pedicure, artificial nails, friction, excessive pressure, or biting nails • Apply a moisturizer to periungual skin and cuticle to create water-proof layer • Consider podiatrist evaluation

First-line treatment
• Continue preventive measures
• Antiseptic soaks (dilute bleach/dilute white vinegar soaks) or topical povidone iodine 2%
• High-potency topical steroids (if there is no local infection)
• Topical antibiotics (mupirocin, fusidic acid, or gentamycin ophthalmic drops)
• Consider combination of topical steroids and antibiotics +/- antifungal
• If infection is suspected, culture-driven topical and systemic antibiotics and antifungals
• For periungual hypergranulation:
  • High potency topical steroids
  • Topical beta-blockers using timolol 0.5% gel twice a day under occlusion

Second-line treatment
• Incision, drainage, and culture if abscess
• Culture-driven antibiotics
• For periungual hypergranulation:
  • Silver nitrate
  • Shave or curettage and eletrodessication
  • Cryotherapy
  • Topical trichloroacetic acid (TCA)

Third-line treatment
• Further surgical procedures may be necessary:
  • Partial or full nail avulsion
  • Partial matricectomy using phenol

Table 4: Prevention and treatment recommendations for targeted therapy-induced paronychia and periungual hypergranulation

Hand Foot Skin Reaction

HFSR can be induced by multikinase inhibitors, VEGF inhibitors, BRAF inhibitors, and one specific EGFR inhibitor (lapatinib). It usually appears after one-to-six weeks of treatment and has three overlapping clinical phases. It first presents with an inflammatory phase described as symmetrical well-defined erythema over palms and soles with occasional painful tense blisters. Then, it evolves to painful yellowish plaques with surrounding erythema. This is followed by hyperkeratotic plaques more pronounced over pressure points and friction-prone areas on both hands and feet. Soles are more commonly involved than palms. HFSR is most severe with first cycles of treatment and tends to decrease in severity and incidence with subsequent cycles.[37] HFSR is another highly morbid toxicity

with significant tenderness and functional impairment. It may lead to dose reduction, temporary interruption, or even permanent discontinuation of targeted therapy, compromising cancer outcomes.

HFSR, also referred as acquired palmoplantar keratoderma in few articles, must be differentiated from hand foot syndrome and periarticular thenar erythema with onycholysis (PATEO) that are also STATs involving hands and feet, but with different clinical presentations and causal medications (Table 5).

HFSR preventive and management tools are described in Table 6. One multicenter randomized controlled trial evaluated the preventive application of 10% urea three times a day on hands and feet in patients receiving sorafenib for advanced hepatocellular carcinoma.40 Incidence of any grade HFSR within twelve weeks of starting sorafenib was significantly lower in the urea group compared to the group with best supportive care alone excluding the use of any cream. Incidence of grades 2 and 3 HFSR was also lower in the urea group. Pre-emptive visits to a podiatrist should be considered, especially for patients starting a targeted therapy associated with a high risk of HFSR (vemurafenib for example).

HFSR has two main components, hyperkeratosis and inflammation, and they guide treatments. Hyperkeratosis is treated with topical keratolytics or retinoids. Inflammation is treated with high potency topical steroids. Oral acitretin has been described in a retrospective study for the treatment of refractory HFSR induced by multikinase inhibitors.[41] It was effective in seven out of eight patients.

Combining a BRAF inhibitor with a MEK inhibitor decreases the incidence and severity HFSR induced by BRAF inhibitor.[42] Approved combinations of BRAF inhibitors and MEK inhibitors are dabrafenib with trametinib, vemurafenib with cobimetinib, and encorafenib and binimetinib. These combinations are used in the adjuvant or active settings for stage III and stage IV melanoma harboring a BRAF V600 mutation.

Conclusion

Cancer treatments are constantly evolving, and targeted molecular therapy indications are increasing. Targeted therapies are safer than conventional chemotherapies, but they come with a high risk of CAEs that can lead to poor quality-of-life and cancer treatment dose reduction or even discontinuation, compromising cancer outcomes. This article aims to provide physicians information on frequent skin toxicities associated with targeted cancer therapies, including preventing and treating these CAEs. With this knowledge, dermatologists, medical oncologists, and other physicians can manage ttCAEs with confidence, thereby improving quality of life, treatment adherence, and cancer outcomes.

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	HFSR	Hand Foot Syndrome	PATEO[38, 39]
Triggering medications	Multikinase inhibitors, BRAF inhibitors	Traditional cytotoxic chemotherapies including cytarabine, capecitabine, anthracyclines, fluoropyrimidines, and taxanes	Traditional cytotoxic chemotherapies, specifically paclitaxel and docetaxel
Onset after drug initiation	Early (1-6 weeks)	Delayed (weeks to months)	Days to months
Clinical presentation	Erythema, hyperkeratosis, bullae, and pain in a symmetrical pattern and localized to palmoplantar areas prone to friction and trauma. Feet > hands	Dysesthesia, erythema, edema, desquamation, and scaling in a symmetrical and diffuse pattern. Hands > feet	Palmar erythema mainly over the thenar and hypothenar eminences, violaceous coloration predominantly of the dorsum of the hands, especially over the joints of the hands and around the Achilles tendon and perimaleolar area, and nail changes such as subungual hemorrhages, Beau lines, onycholysis, and onychomadesis
Histopathology findings	Dyskeratotic keratinocytes, epidermal acanthosis, papillomatosis, and parakeratosis	Damage of the eccrine gland and varying degrees of epidermal necrosis	Hyperkeratosis, acanthosis, necrotic keratinocytes, focal vacuolar degeneration of the basal layer, and lichenoid inflammatory infiltrate

Table 5: Description of hand foot skin reaction (HFSR), hand foot syndrome, and periarticular thenar erythema with onycholysis (PATEO)

Hand Foot Skin Reaction

General principles and prevention

- Cream with urea 10% 3 times a day on both hands and feet
- Avoid trauma:
  - activities that stress the extremities (e.g. long walks, running, aerobics, heavy carrying without gloves)
  - friction, pressure, hot water, extremes of temperature
- Avoid irritation: skin irritants such as solvents and disinfectants, normal soap
- Foot and hand care:
  - well-fitting shoes
  - orthopedic shoes/inserts, gel insoles
  - prophylactic removal of pre-existing hyperkeratotic lesions on hands and feet

First-line treatment

- Increase the concentration of topical keratolytic (salicylic acid 3-10%, lactic acid 5-8%, or urea 10-50%)
- Topical retinoid
- For erythematous component: high-potency topical steroid
- If blisters: drain as required

Second-line treatment

- Oral retinoid (e.g. acitretin, alitretinoin if available)
- Hydrocolloid dressing for erosion or bullae

Third-line treatment

- Systemic steroids
- Dose reduction or interruption of targeted therapy

Table 6: Prevention and treatment recommendations for targeted therapy-induced hand foot skin reaction

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