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USCOM IV Algorithm for the Prevention and Management of Targeted Therapy-Related Cutaneous Adverse Events

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ABSTRACT

Introduction: Targeted therapy has improved clinical outcomes for various types of cancer. However, their use is associated with dermatologic adverse events that impact quality of life and consistent therapies.
Objectives: The United States Cutaneous Oncodermatology Management (USCOM) multidisciplinary-guided algorithm for preventing and managing cutaneous targeted therapy-related adverse events provides practical recommendations for cancer patients and survivors.
Methods: The USCOM advisory board (panel) identified 6 commonly occurring cutaneous adverse events associated with targeted therapies. Practical recommendations for prevention and management were developed based on the results of a literature search, clinical expertise, and opinion.
Results: Acneiform rash, pruritus, xerosis, paronychia, hyperpigmentation, and hand-foot skin reaction were selected as common targeted therapy-related cutaneous adverse events. The panel provides practical steps for preventing and treating these cutaneous conditions.
Conclusions: The USCOM multidisciplinary-guided algorithm is for healthcare providers treating oncology patients receiving targeted therapies. Cutaneous targeted therapy-related adverse events necessitate prompt and accurate diagnosis and multidisciplinary management that includes a dermatologist and the oncologic team, limiting disruption of cancer treatment and optimizing quality of life and treatment outcomes.

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INTRODUCTION

In 2023, an estimated 1,958,310 Americans were diagnosed with cancer.[1] Although overall incidence continues to rise, ongoing advancements in anticancer therapy have improved survival. Some historically fatal malignancies are treated as chronic diseases, and progress in the discovery of new targets and drugs has exposed patients to a new spectrum of drug toxicities both from novel agents as well as the extended duration of use.[1-4]

Targeted therapy-related cutaneous adverse events (TTcAEs) frequently occur and vary in severity depending on the drug and patient population. In oncology, targeted therapy (TT) has revolutionized cancer treatment by specifically targeting molecules or pathways crucial for cancer cell growth and survival, distinct from the cytotoxic effects of traditional chemotherapy. TT inhibits specific receptors (eg, Epidermal Growth Factor Receptor (EGFR) inhibitors, Human EGFR receptor 2 (HER2) inhibitors, or intracellular kinases (eg, Proto-oncogene B-Raf (BRAF) inhibitors, mitogen-activated protein kinase kinase (MEK) inhibitors), disrupting signaling cascades essential for tumor proliferation or interfering with angiogenesis. TT offers enhanced efficacy with reduced systemic toxicity.[5-10] The overall percentage of cancers treated with TT increases as more agents are developed. TT is commonly used to treat certain types of cancer, including breast cancer (BC), especially HER-2 positive BC, non-small cell lung cancer (NSCLC), colorectal cancer, melanoma, chronic myeloid leukemia, lymphoma, and renal cell carcinoma.[5-10]

Multiple studies have found that patients treated with TT experience a greater number of cAEs compared to those receiving non-TT and experience a more significant impact on quality of life (QoL), including the physical and emotional domains.[11,12] Dermatologists remain important multidisciplinary care team members by managing TTcAEs and promoting preventative skin care practices. Cancer patients receiving dermatologic care are more likely to resume and continue their treatment with TT and, therefore, have better outcomes.[2-4,13,14]

METHODS

The United States Cutaneous Oncodermatology Management (USCOM) project offers tools for preventing and managing cAEs related to cancer therapy to improve cancer patients' and survivors' QoL.[2-4] The USCOM panel has previously published 3 foundational algorithms for skin management in people with cancer to support healthcare providers treating oncology patients.[2-4]

The panel used the AGREE II instrument following the modified Delphi method to develop the USCOM practical algorithm for treating TTcAEs.[15,16] The modified Delphi method is a communication technique for interactive decision-making for medical projects.[16]

During a face-to-face meeting on September 16, 2023, the panel discussed the results of a systematic literature review, which generated evidence to develop a practical treatment algorithm for TTcAEs. Working with a draft algorithm, the panel discussed the assembled evidence and coupled it with the panel's experience and opinion. An online process was used to fine-tune the algorithm, reach a consensus, and prepare and review the publication.

Literature Review

The systematic literature review included guidelines, consensus papers, and clinical research publications on the prevention and management of TTcAEs published in English from January 2010 to May 2023. Articles were excluded if they were irrelevant to TTcAEs or the publication language was other than English.

Two physicians (AA and TE) conducted the literature searches in May 2023, utilizing PubMed as the primary search engine and Google Scholar as the secondary source. The following criteria were used: Tyrosine kinase inhibitors (TKIs) OR Multikinase inhibitors (MKIs) OR Epidermal growth factor (EGFR) inhibitor OR Vascular endothelial growth factor (VEGF) inhibitor OR Fibroblast growth factor inhibitor (FGFRi) OR MEKi OR BRAF inhibitor OR Inhibitor agonists modulator antagonists (PanRAF) inhibitor OR Philadelphia chromosome breakpoint cluster region – Abelson murine leukemia (BCR-abl) inhibitor OR osimertinib OR afatanib OR dacomitinib OR erlotinib OR gefitinib OR getfitinib OR erlotinib OR lapatinib OR cetuximab OR panitumumab OR sunitinib OR bevacizumab OR lenvatinib OR vandetinib OR regorafenib OR sorafenib OR axitinib OR pazopanib OR erdafitinib OR pemigatinib OR trametinib OR cobimetinib OR dabrafenib OR vemurafenib OR belvarafenib OR Proto-oncogene receptor tyrosine kinase (KIT) OR Platelet-derived growth factor receptor (PDGFR) OR imatinib OR dasatinib OR nilotinib AND cutaneous adverse event for Group 1 and paronychia OR hand foot skin reaction OR papulopustular eruption OR xerosis OR pruritus OR skin toxicities AND targeted therapy prescription medication OR skin care OR treatment OR quality of life OR adjunctive OR adherence OR safety OR tolerability AND cutaneous adverse event AND targeted therapy for Group 2.

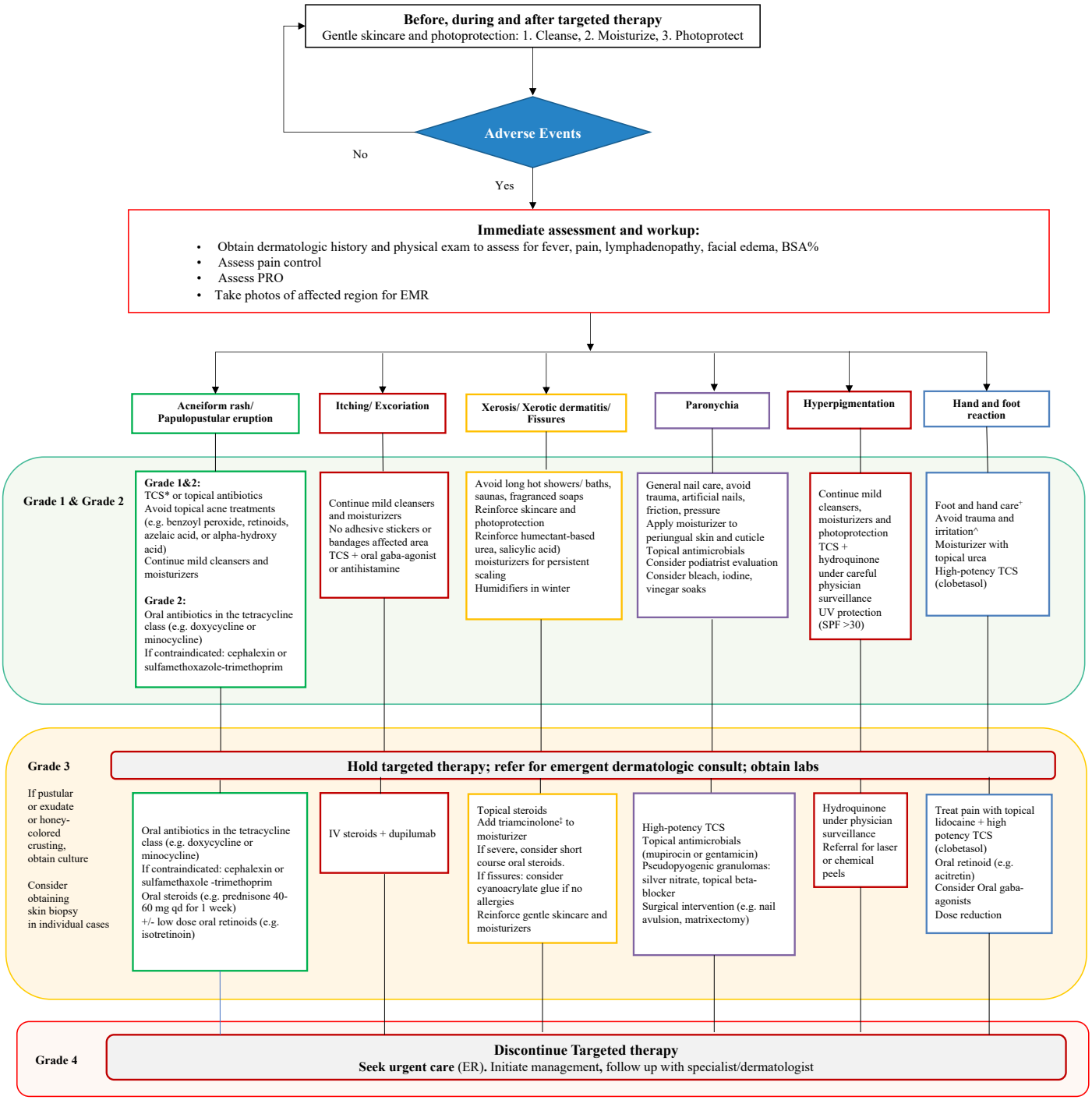
The search yielded 422 papers, of which 297 were included: 114 reviews, 27 systematic reviews, 3 guidelines, 12 consensus publications, 141 clinical trials, 13 case series, and 22 retrospective chart reviews. The second search yielded 34 papers, of which 4 were included: 2 reviews and 2 clinical trials, totaling 301 publications.

Type of Cancers Treated With Targeted Therapy

TT can be classified by the molecules they inhibit. Table 1 illustrates the selected classes of TT discussed in this article, including EGFR inhibitors, MKIs, selective VEGF inhibitors, mTOR inhibitors, BRAF inhibitors, and MEK inhibitors. Multiple drugs exist within each class and are used in different types of malignancies.[2,5-10,17-22]

EGFR inhibitors block the EGFR signaling pathway, preventing activation of other mainstream signaling pathways like phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (AKT) and RAS/RAF/MEK/ extracellular signal-regulated kinase (ERK) inhibitor. EGFR inhibitors include cetuximab, panitumumab, amivantamab, erlotinib, afatinib, and osimertinib, amongst others, and are used for NSCLC, colorectal cancer, advanced pancreatic cancer, and HER-2 positive BC.[17-22] Multikinase inhibitors simultaneously block multiple kinase enzymes involved in the growth of cancer cells, eg, platelet-derived growth factor (PDGF), VEGF, and c-KIT.[17-22] These include sorafenib, cabozantinib, sunitinib, and pazopanib and are mainly used for renal cell carcinoma, soft tissue sarcomas, gastrointestinal stromal tumors, medullary thyroid cancer, hepatocellular carcinoma, and pancreatic neuroendocrine tumors.

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



VEGF inhibitors block an essential pathway for angiogenesis, reducing the blood supply to tumors.[19] These include bevacizumab and ramucirumab and are used for several gynecological tumors, renal cell carcinoma, glioblastoma, NSCLC, and non-oncologic conditions like age-related macular degeneration. mTOR inhibitors block a growth and proliferation pathway, reducing protein synthesis. This category includes everolimus, temsirolimus, and sirolimus, which are used for renal cell carcinoma, HER-2 positive breast cancer, neuroendocrine tumors, and non-oncologic conditions like tuberous sclerosis complex (TSC), and transplant recipients.

BRAF is a protein kinase in the RAS/RAF/MEK/ERK pathway.[17] BRAF inhibitors target mutated forms of this protein, specifically the V600E mutation, which drives cancer cell proliferation.[17] BRAF inhibitors include vemurafenib and dabrafenib, which treat melanoma and colorectal cancer. Lastly, MEK inhibitors block the activity of MEK, which prevents the activation of ERK, leading to cell death. These are typically used in combination with BRAF inhibitors, with examples including trametinib and cobimetinib, which are used for melanoma, NSCLC, and anaplastic thyroid cancer.[22]

The Algorithm for Management of Targeted Therapy-Related Cutaneous Adverse Events

The algorithm for preventing and managing TTcAEs used systematic literature review results and the panel members' expertise (Figure 1). As with the USCOM Algorithm II for the prevention and management of acute radiation dermatitis[3] and the USCOM III Algorithm for the prevention and management of cutaneous immunotherapy-related adverse events,[4] the USCOM IV TTcAEs algorithm expanded on the USCOM I algorithm for cancer-treatment-related cAEs[2] which utilizes the CTCAE grading system v.5 (Table 2).[23]

The algorithm has 3 steps: 1) general measures before, during, and after TT using skincare with gentle cleansers and moisturizers and photoprotection, 2) TTcAEs identifying the severity and risk and the need for an immediate dermatology consult, 3) selected TTcAEs, grading and recommendations for prevention and treatment.

The panel included the following common TTcAEs in the practical algorithm: Acneiform rash/ Papulopustular eruption, Itching/Excoriation, Xerosis/ Xerotic dermatitis/ Fissures, Paronychia, Hyperpigmentation, Hand-foot skin reaction (HFSR). Exanthem and mucositis are not in the algorithm but are discussed in the text (Table 3).

Step 1: General measures before, during, and after TT

The general measures before, during, and after TT are discussed in step 3 for the specific TTcAEs.

Step 2: TTcAEs identifying severity and risk

Early identification of severe TTcAEs, which may be detected by signs and symptoms including fever, skin pain, epidermal changes, high body surface area involvement, or laboratory abnormalities, is an important step. Irrespective of the etiology of the cutaneous reaction, the patient should obtain immediate evaluation by a dermatologist and often inpatient or ICU-level care. In the absence of severe symptoms, recommendations are based on the severity and grade of the TTcAE (Table 1).[23]

Step 3: Selected TTcAEs

Papulopustular Eruptions

Papulopustular eruptions occur in approximately 57% of all patients treated with TT, most commonly with EGFR and MEK inhibitors.[17] EGFR inhibitors are a common culprit due to EGFR being expressed and activated in basal keratinocytes and the outer root of hair follicles.[20] When this growth is arrested, hyperkeratosis and follicular plugging ensue, as well as changes in skin microflora due to altered leukocyte chemotaxis leading to inflammatory reactions.[20-22]

The lesions manifest as inflammatory papules and pustules that predominantly occur in a seborrheic dermatitis-like pattern on the scalp, face, chest, and back (Figure 2).[20] Pruritus and lack of comedones are often associated, distinguishing the eruption from classical acne. In addition, secondary infection with *staphylococcus aureus* commonly occurs in high-grade presentations or late-onset eruptions after months of therapy.[20] Treatment of papulopustular eruptions is based on severity. For prevention and grade 1 reaction, skincare combined with photoprotection, topical hydrocortisone 1%, and oral antibiotics in the tetracycline class may be considered.[20,24-28] Patients should minimize

FIGURE 2. Acneiform/papulopustular eruptions.

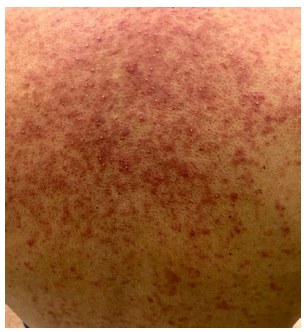


Photo courtesy of J Leventhal.

TABLE 1.

Select Targeted Therapy Classes, Molecules, and Indications

Drug Class	Name	Oncologic Indications*
Epidermal Growth Factor Receptor (EGFR) inhibitors	Cetuximab Panitumumab Erlotinib Gefitinib Lapatinib Neratinib Afatinib Osimertinib Amivantamab Dacomitinib Mobocertinib Canertinib	Metastatic colorectal cancer Head and neck squamous cell carcinoma Advanced pancreatic cancer
HER2 inhibitors	Pertuzumab Trastuzumab	HER-2 positive breast cancer
Multikinase inhibitors	Sorafenib Sunitinib Regorafenib Pazopanib Cabozantinib Axitinib Vandetanib	Renal cell carcinoma Soft tissue sarcomas Gastrointestinal stromal tumors Pancreatic neuroendocrine tumors Hepatocellular carcinoma Medullary thyroid cancer
Selective VEGF inhibitors	Bevacizumab Ranibizumab	Colorectal cancer NSCLC Glioblastoma Renal cell carcinoma Cervical cancer Ovarian cancer Other nononcologic uses: Age-related macular degeneration Diabetic macular edema Retinal vein occlusion Myopic choroidal neovascularization
Mammalian target of Rapamycin (mTOR) inhibitors	Everolimus Sirolimus Temsirolimus	Renal cell carcinoma HER-2 positive breast cancer Neuroendocrine tumors Other non-oncologic conditions: Tuberous sclerosis complex Transplant recipients
BRAF inhibitors	Dabrafenib Vemurafenib Encorafenib	Melanoma NSCLC Anaplastic thyroid cancer Colorectal cancer Erdheim-Chester Disease (rare non-Langerhans cell histiocytosis)
MEK inhibitors	Trametinib Cobimetinib Binimetinib	Melanoma Non-Small Cell Lung Cancer (NSCLC) Colorectal Cancer Medullary thyroid cancer. Ovarian Cancer Pancreatic Cancer Acute Myeloid Leukemia

*Oncologic indications for the listed organ are non-all-encompassing. Each agent has specific FDA-approved indications for subvarieties of each type of cancer based on biology and/or behavior.

Padma VV. An overview of targeted cancer therapy. *Biomedicine (Taipei).* 2015;5(4)12:19. doi: 10.7603/s40681-015-0019-4

TABLE 2.

Common Terminology Criteria for Adverse Events (CTCAE v.5) Grading Of Cutaneous Adverse Events					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acneiform rash/ Papulopustular eruption	Papules and/or pustules covering <10% BSA (with or without pruritus/tenderness)	Papules and/or pustules covering 10-30% BSA, with or without pruritus/tenderness, associated psychosocial impact	Papules and or pustules covering 30% BSA with moderate to severe symptoms associated with superinfection	Life-threatening consequences, urgent intervention needed	Death related to adverse event
Itching/ Excoriation	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental AD	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	--	--
Xerosis/ Xerotic dermatitis/ Fissures	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self-care ADL	--	--
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL	--	--
Hyper pigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	--	--	--
Hand-foot skin reaction	Minimal skin changes or dermatitis (erythema, edema, hyperkeratosis), without pain	Skin changes (Peeling, blisters, fissures, edema, or hyperkeratosis) with pain, limiting instrumental ADL	Severe skin changes with pain, limiting self-care ADL	--	--

Body surface area (BSA), Activity of daily living (ADL)

TABLE 3.

Prevention and treatment of TTcAEs			
Acneiform Rash/ Papulopustular Eruption			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prevention and/or treatment: • Emollients and gentle skin care using a fragrance-free cleanser • Avoid mechanical, physical, and chemical skin irritation, sun exposure, and occlusive makeup • Mild to moderate potency topical corticosteroids, (hydrocortisone 1% or 2.5% cream) on the face and trunk BID for the first 6 weeks of treatment • Topical antibiotics (clindamycin, dapsone) • Topical antiseptic wash	• Continue gentle skin care and sun protection • Oral antibiotics in the tetracycline class (eg, doxycycline or minocycline) for at least 6 weeks, and a longer period if needed • If contraindicated: cephalexin or sulfamethoxazole-trimethoprim • If the acneiform eruption is atypical, proceed to bacterial culture and viral swab to rule out bacterial or herpetic infection. • Culture-driven oral antibiotic or oral antiviral if there is a proven infection	• Short course of systemic steroids (prednisone 40-60 mg daily for 1 week • Interruption of the targeted therapy then consider dose reduction • Can be restarted when back to grade 0-1 • Oral dapsone • Low-dose oral isotretinoin (0.2-0.3 mg/kg or 20-30 mg once daily) or acitretin 10-25 mg daily after discontinuing oral tetracycline	• Stop medication • Hospitalization • Intravenous antibiotics for secondary infection • Oral or intravenous corticosteroids • Supportive care
Itching/Excoriation			
Grade 1	**Grade 2**	**Grades 3 and 4**	
• Limited shower time, avoid hot showers, hot baths, and saunas • Emollient applied within fifteen minutes following shower or bath for better absorption • Gentle skin care using a fragrance-free cleanser with pH close to that of the skin (pH 5.5) • Emollients containing a humectant like urea or lactic acid • Use loose-fitting clothing, cool ambient, avoid heat exposure • Keep nails short • Treat underlying xerosis • Moderate-to-high potency topical steroids • Topical calcineurin inhibitors • Cold compresses or wet dressing for a cooling effect • Other topical agents (eg, lidocaine, pramoxine, menthol, camphor, doxepin 5%, capsaicin)	• Continue gentle skin care and emollients • Medium-potency topical corticosteroids • Topical calcineurin inhibitors • First-generation oral anti-H1 at night • Gabapentin or pregabalin	• Continue gentle skin care and emollients • High potency corticosteroids • Oral antihistamines • Oral doxepin • Oral gabapentinoids, mirtazapine • Oral aprepitant • Oral systemic steroids • For Grade 3: Interruption of TT, consider dose reduction	

TABLE 3. (CONTINUED)

Prevention and treatment of TTcAEs

Xerosis/ Xerotic Dermatitis/ Fissures

Grade 1	Grade 2	Grades 3 and 4
• Gentle skin care comprising gentle cleansers and emollients containing humectants like 5% urea or lipids like ceramides • Limited bathing time • Avoid irritants such as soap and perfume • Avoid stress to the skin (mechanical, extreme temperature, humidity, occlusion) • Photoprotection • Low-moderate potency topical corticosteroids	• Moderate-high potency topical corticosteroids • Liquid cyanoacrylate for fissures	• Systemic steroids • Consider dupilumab (recalcitrant dermatitis)

Paronychia

Grade 1	Grade 2	Grades 3 and 4
• Avoid trauma, including aggressive manicure and pedicure, artificial nails, friction, excessive pressure, or biting nails • Apply an emollient to periungual skin and cuticle to create a waterproof layer • Avoid prolonged contact with water • Wear well-fitting shoes or wide, open-toed shoes • Wear cotton socks • Correction of nail curvature by a podiatrist if needed • Topical antiseptics • Antiseptic soaks to prevent nail fold infection (dilute bleach or dilute white vinegar soaks) • Topical antibiotics (eg, mupirocin, gentamicin) • High-potency topical corticosteroids if there is no local infection • Topical calcineurin inhibitor	• Continue topical treatments with antiseptics (eg, povidone-iodine 2%), antibiotics, and steroids • Combination of topical steroid and topical antibiotic • Oral tetracyclines • If infection is suspected, culture-driven topical and systemic antibiotics and antifungals • Incision and drainage if abscess • For periungueal pseudopyogenic granuloma: • Silver nitrate once or twice a week can be done by the patient if instructed how to do it • Topical beta-blocker (timolol gel) • Topical trichloroacetic acid Electrodesiccation • Cryotherapy • Shave or curettage and electrodesiccation	• Surgical approach should be done if medical treatments have failed • Partial matricectomy using phenol • Partial or full nail avulsion • IV antibiotics if severe infection

Hyperpigmentation

Grade 1	Grade 2	Grades 3 and 4
• Avoid UV exposure and irritating conditions • Sun protection • Topical corticosteroids, retinoids, azelaic acid, hydroquinone	• Continue Grade 1 therapy, add lasers and chemical peels	--

Hand-Foot Skin Reaction

Grade 1	Grade 2	Grade 3	Grade 4
• Limit traumatic activities • Topical keratolytic (salicylic acid 3-10%, lactic acid 5-8%, or urea 10-50%), topical retinoid • Low-moderate potency topical corticosteroids • Topical analgesics (lidocaine gel, lidocaine 5% patch, prilocaine cream or benzocaine gel) • Cold compresses, cooling packs, or cooling hand and foot baths to manage pain	• Emollients • Moderate-high potency topical corticosteroids • Keratolytics • Oral analgesics • Hydrocolloid dressing for erosion or bullae • Interruption of TT then dose reduction (recalcitrant cases)	• Emollients • High-potency topical corticosteroids • Keratolytics • Oral analgesics • Topical corticosteroids • Oral acitretin 10-25 mg daily • Hydrocolloid dressing for erosion or bullae • Interruption of TT then dose reduction	• Hospitalization • High-potency topical corticosteroids • Regular monitoring • Hydrocolloid dressing for erosion or bullae • Discontinuation of TT

Exanthem*

Grades 1 and 2	Grade 3	Grade 4
• Topical steroids • Oral antihistamines	• Check CBC, CMP, skin biopsy, assess for symptoms of SCAR* • Oral steroids • Oral antihistamines • Interruption of TT, consider dose reduction or alternative therapy	• Hospitalization • IV steroids • Discontinue TT

Stomatitis*

Grades 1 and 2	Grade 3	Grade 4
• Rule out HSV, Candida infection • Topical analgesia (eg, lidocaine, doxepin) • Oral hygiene, specify antiseptics, artificial saliva • Topical steroids (gel, oral rinses) • Oral tacrolimus (ointment, rinse) • Oral analgesia and nutritional support (recalcitrant)	• Check CBC, CMP, mucosal biopsy, assess for symptoms of SCAR* • Continue topical management, analgesia, and nutritional support • Oral steroids • If persistent, rule out other etiologies (eg, possible nutritional deficiencies) • Interruption of TT, consider dose reduction	• Discontinue TT • Hospitalization • IV steroids or IV antibiotics as indicated • Continued pain control, nutritional support, and supportive care

*Not included in the algorithm but discussed in the text, twice daily (BID)

dryness by bathing in tepid water and using alcohol-free emollients to mitigate the TTcAEs.[24] Other prevention measures include photoprotection with various measures and sunscreen with a sun protection factor (SPF) of 50+, topical hydrocortisone 1%, and oral antibiotics in the tetracycline class.[24-29] Phototoxicity induced by tetracycline class antibiotics must be considered in patients receiving targeted therapy.[30]

For grade 2, oral antibiotics like minocycline and doxycycline may be used, and for grade 3 or higher, it is recommended to stop TT and consider oral corticosteroids (eg, prednisone 40-60 mg daily for 7 days) and antibiotics until inflammation has decreased.[24,29,31] Dapsone 5% gel has also been proven helpful in this reaction.[32] Isotretinoin has been used for refractory papulopustular eruptions due to EGFR inhibitors.[33,34] Wang et al proposed topical BRAFi therapy for treating and preventing papulopustular eruptions due to MAPK pathway inhibitors like EGFR and MEK inhibitors following observations that patients treated with a combination of BRAFi and MEKi experienced less skin toxicity.[35] To treat bacterial superinfection, bleach soaks, topical mupirocin, clindamycin lotion for Gram-positive bacteria, topical gentamicin for Gram-negative bacteria are recommended, and oral antibiotics if Grade 2 or higher.3[6] Care should be taken to rule out other concomitant cutaneous infections, such as herpes simplex virus or candidiasis, and should be treated if present. Because this reaction is photosensitive, patients are encouraged to use sunscreen with SPF 50+ at all times.[30] Studies have also supported using prophylactic topical corticosteroids, sunscreen, and oral tetracycline to reduce the severity of papulopustular eruption.[18-29]

Itching/Excoriation

TT-related pruritus is common, including 14% for BCR-ABL inhibitors, 9-19% for multikinase inhibitors, and 24% for mTOR inhibitors.[37-39] It can occur with or without visible skin changes and is almost always accompanied by xerosis (Figure 3).[37] For EGFR inhibitors, the pathogenesis involves inhibiting EGFR in keratinocytes and sebostasis.[37-40] Pruritus can sometimes be prevented with diligent skincare with creams and lotions containing 5-10% urea.[40-42] Exposure to UV radiation should be avoided.[40-42] Mild pruritus is managed mainly by using emollients containing humectants and loose-fitting clothing.[40-42] For severe pruritus, topical agents, including lidocaine, pramoxine, doxepin, capsaicin, menthol, and camphor can be used. As a second line, first-generation oral antihistamines and oral gabapentinoids, and as a third line, oral aprepitant, doxepin, and systemic steroids can be used.[43] Dupilumab has been anecdotally used in cancer patients experiencing pruritus and xerotic dermatitis.

FIGURE 3. Excoriation and xerotic dermatitis.

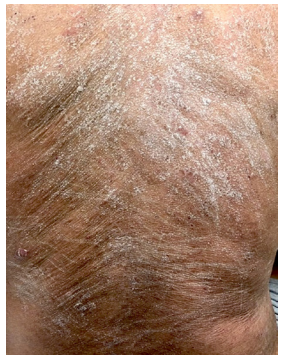


Photo courtesy of J Leventhal.

Xerosis/ Xerotic Dermatitis/ Fissures

Xerosis is a widespread adverse event associated with TT (Figure 4). Its incidence varies on the specific drug and patient population. For example, it can occur in 30-60% of patients treated with EGFRi, such as erlotinib, gefitinib, cetuximab, and panitumumab.[22,34,35] It occurs in 20%-40% of patients treated with TKi, 10%-30% in BRAFi and MEKi, and 10%-20% of patients treated with mTOR inhibitors.[22,34,35] A study found that within 6 weeks of treatment with an EGFRi, patients developed exfoliation leading to pruritus and that the moisture content of the stratum corneum decreased significantly while using the drug.[39,42] Supportive skin care measures enable patients to continue TT with minimal disruption when experiencing xerosis.[2,14,40,42] Daily liberal use of moisturizers is encouraged while limiting bath time, avoiding hot temperatures, using SPF, and choosing gentle, fragrance-free skin care to prevent xerosis.[2,14] Moisturizers containing petrolatum jelly, humectants, or lipids should be used at least twice daily, and as second-line topical steroids

FIGURE 4. Xerotic dermatitis/fissures.

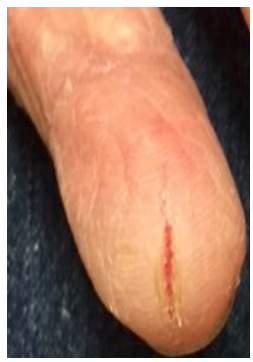


Photo courtesy of J Leventhal.

can be used, especially if coexisting dermatitis or fissures exist.[2,14] Liquid cyanoacrylate can also help promote the healing of painful fissures that occur during EGFRi therapy.[2,14]

Paronychia

Paronychia is initially characterized by edema, erythema, and nail fold tenderness with or without superimposed infection (Figure 5).[44-52] It can occur in 1 or several nail folds. The risk of nail changes is highest with EGFR inhibitors out of all TT, according to a 2011 systematic review and meta-analysis, and will usually appear after 2 or more months of drug exposure.[47] However, it can also occur due to MEK inhibitors. Its pathogenesis is based on the thinning of stratum corneum, decreased keratinocyte proliferation, and increased apoptosis of epidermal keratinocytes, which lead to the fragility of the nail plate secondary to EGFR inhibition.[44-52] Also, dysregulation of nail plate growth may result in ingrown nails and painful pseudopyogenic granulomas.[44-52] Patients often have positive cultures for bacteria or fungus. A strong and significant correlation exists between paronychia and quality of life.[37]

For Grade 0 reactions, instructions are given on using moisturizing creams and gentle skincare.[2] For Grade 1 reactions, the anticancer agent is continued at the current dose and monitored for change in severity. Together with skincare, topical antibiotics/antiseptics and vinegar soaks are used, and the reaction is reassessed after 2 weeks.[2,53] The same guide is used for Grade 2, but weekly silver nitrate or trichloroacetic acid application can be added weekly.[2] If there is no coexistent infection, topical steroids can help alleviate inflammation, pain, and hypergranulation tissue.[2,44] For Grade 3 reactions, the anticancer agent dose is modified, viral and bacterial cultures should be obtained if infection is suspected (if exudate is present), and oral antimicrobials are initiated in addition to continued topical and antiseptic therapy.[2,44] In recalcitrant cases, nail avulsion by a dermatologist or podiatrist is considered.[54]

Vinegar soaks may be considered using a solution of white vinegar in water in a 1:4 ratio for 15 minutes daily.[2] Other topical treatments that can be used for pseudo-pyogenic granulomas include timolol 0.5% gel or propranolol cream, while povidone-iodine solution or locacorten-vioform ear drops twice daily function as antiseptics.[2,55] Trauma should be avoided, including aggressive manicures and pedicures, artificial nails, friction, excessive pressure, and nail-biting, and adhering to gentle nail care consisting of trimming once a week for fingernails and once a month for toenails, not too short.[2] It is recommended that an emollient be applied to the periungual skin and cuticle to create a waterproof layer.[2] Additionally, patients should avoid prolonged contact with water and use absorbent cotton socks to avoid excessive moisture. If periungual pseudo-pyogenic granuloma is present, silver nitrate can be used as well as topical trichloroacetic acid, intralesional corticosteroid, electrodesiccation, cryotherapy, and surgical intervention with nail avulsion as last-line treatment.[2,55]

Hyperpigmentation

Up to 20% of patients treated with EGFRi[40] may present hyperpigmentation,[48] 15% of patients treated with TKIs, especially imatinib, in which melasma-type hyperpigmentation has been reported,[49,52] 5%-10% of patients treated with MEKi, and less common in patients treated with BRAFi.[50,51] Its pathogenesis involves several mechanisms that alter melanin production, including generalized inflammation, which leads to increased melanin production and postinflammatory hyperpigmentation (PIH), oxidative stress, which affects melanocyte function, and direct effect on melanocytes (Figure 6).[56]

FIGURE 5. Paronychia.

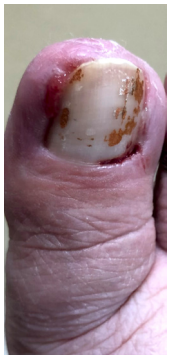


Photo courtesy of J Leventhal.

FIGURE 6. Hyperpigmentation.

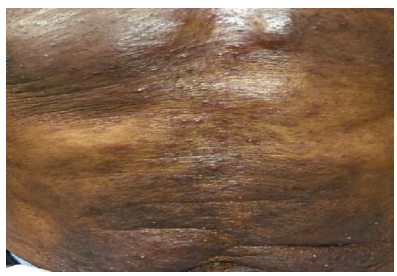


Photo courtesy of J Leventhal.

For TKIs, c-KIT is crucial for melanocyte development and function, as its inhibition leads to changes in pigmentation.56 Hyperpigmentation may result from a compensatory increase in melanin production in certain areas.[56] MEKi and BRAFi disrupt pathways involved in cell proliferation as well.5[6] The mainstay of treatment for hyperpigmentation from TKIs includes sun protection using SPF 30 or higher, UV protectant clothing, and avoidance of topical irritants like alcohol and fragrances.[56] In addition to these preventative measures, topical treatments have been proposed, like hydroquinone, retinoids, azelaic acid, kojic acid, and vitamin C.[2,57] Laser therapy and chemical peels administered by dermatologists can aid in the physical appearance. Understanding the pathogenic mechanisms helps healthcare providers to anticipate and manage these TTcAEs.

Hand-Foot Skin Reaction (HFSR)

HFSR is a common TTcAE characterized by painful, erythematous, palmoplantar lesions with callus-like hyperkeratosis and more pronounced scaling in areas with increased friction (Figure 7). It is often associated with painful dysesthesia. It is proposed that this is due to impaired vascular repair of epidermal injury. It occurs most commonly in patients on MKIs that block VEGF and PDGF, including sorafenib, sunitinib, cabozantinib, and pazopanib.[42] Its incidence can vary widely depending on the drug and dose but can range from 10%-60%.[42]

There are 2 types of HFSR proposed: Type 1 HFSR typically presents with painful bullous erythema, edema, and desquamation, and type 2 HFSR presents as callus-like hyperkeratosis or bullae with an erythematous halo.[44-53] The highest frequency of HFSR occurs with sorafenib (48%) and sunitinib (36%). Patients are advised to apply urea-containing lotions and creams at least twice daily and reduce physical stress on the skin, such as friction and pressure.[44-53] Of note, the incidence rate of about 30% with vemurafenib or dabrafenib is decreased to 6%-10% upon the addition of a MEKI.[44-53]

Generally, it is recommended that patients avoid friction, pressure, hot water, extremes of temperature, and traumatic activities that induce stress on the extremities, like long walks, jogging, and running.[2] Wearing thick cotton gloves, socks, and well-fitting shoes is advised to avoid constriction and friction.[2] For grade 1 HFSR, keratolytics and emollients like urea cream and salicylic acid could be recommended used, avoiding exacerbating factors such as heat and trauma, well-fitting footwear, seamless thick socks, and moisturization prior to activities.[2,53] For grade 2 HFSR, high-potency topical corticosteroids like clobetasol and halobetasol are used under occlusion, as well as topical or systemic analgesics such as lidocaine, gabapentin or pregabalin, NSAIDS and/or narcotics.[2,44] Oral retinoids such as acitretin may help reduce hyperkeratosis due to the histopathologic similarity of HFSR to psoriasis.[57] For grade 3 HFSR, a dose reduction of the offending agent or dose interruption is advised, which typically results in improvement within several days of drug discontinuation.[37]

Maculopapular Rash

Drug-induced exanthem is a maculopapular or morbilliform eruption, which presents as erythematous macules and papules that coalesce into patches and plaques that are most confluent on the trunk (Figure 8) Exanthem is perhaps the most commonly reported drug reaction by any type of drug, including antibiotics and NSAIDs, and can occur in > 75% of patients treated with EGFRi, (58), >40% of TKIs[40], and 50% of BRAFis.[51] Overall, exanthem occurs in ~40-90% of patients treated with TT and is especially frequent in patients <50 years of age and associated with cetuximab and panitumumab treatment.[42] The exanthem is dose-dependent and can be aggravated by UV light, and when severe, can be accompanied by fever and chills. The treatment is based on the severity of the presentation. For grade 1, moisturizers and low to moderate-potency TCS could be sufficient with anti-histamines, but high-potency topical steroids are added for grades 2 to 3.[2,26] For grade 3,

FIGURE 7. Hand-foot-skin reaction.

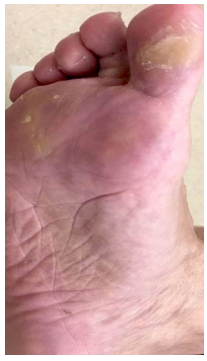
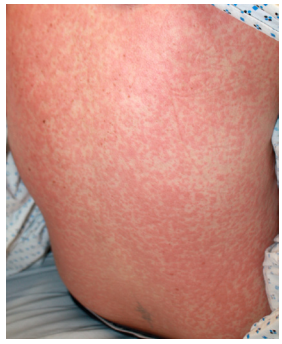


Photo courtesy of J Leventhal.

FIGURE 8. Maculopapular rash.



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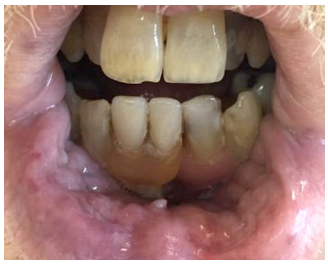
TT dose interruptions and systemic corticosteroids might be needed.[2,26] Close monitoring to ensure there is no concern for severe cAEs such as drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (grade 4) is warranted.[2]

Stomatitis

Stomatitis is less commonly associated with TT but can occur with several classes of drugs, particularly mTOR inhibitors like everolimus and temsirolimus (occurring in around 40%-60%).[37] It may also occur in patients on EGFRi (20%) and in 5%-15 of patients on other TKIs.[37] Oral mucositis is characterized by ulceration and irritation of the mucous membranes in the mouth, which is secondary to DNA damage and proinflammatory cytokines and enzymes.[37] Mucositis manifests as dysgeusia, aphthous lesions, mucosal bleeding, xerostomia, and gingival hyperplasia and is often debilitating (Figure 9).[37] Superimposed infections, when present, should be treated promptly. Prevention of mucositis includes optimizing oral hygiene and dentition by using soft toothbrushes, avoiding irritants like hot and spicy foods, tobacco, and alcohol, and using antiseptic mouthwashes or rinses.[2,37] For analgesia treatment, doxepin 5% solution or topical lidocaine can decrease pain.[2,37] In addition, TCS rinses may provide symptomatic relief. Evaluation and treatment of secondary infection, including herpes simplex virus or candidal thrush, are necessary, and pain control and nutritional support are indicated in severe presentations.[2,37]

FIGURE 9. Mucositis/stomatitis.



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CONCLUSION

Given the widespread application of targeted therapies in treating malignancies, TTcAEs are common and necessitate prompt and accurate diagnosis and management to limit disruption of treatment and optimize QoL. By recognizing these common cutaneous reactions, clinicians who interface with cancer patients can expedite consultation and initiate therapy as suggested by the multidisciplinary physician-developed algorithm. Moderate-severe or recalcitrant cutaneous reactions are best managed collaboratively with a dermatologist and the oncologic team to optimize oncologic outcomes and patient QoL during and after treatments.

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REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2023. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf. Accessed July 2024.
2. Lacouture ME, Choi J, Ho A et al. US Cutaneous Oncodermatology Management (USCOM) I: a practical algorithm. *J Drugs Dermatol.* 2021;20:3ss-s19.
3. Leventhal J, Lacouture M, Andriessen A, et al. USCOM II: A multidisciplinary-guided algorithm for the prevention and management of acute radiation dermatitis in cancer patients. *J Drugs Dermatol.* 2022;21:SF3585693-SF35856914.
4. Deutsch A, Lacouture M, Andriessen A, et al. USCOM III Algorithm for the prevention and management of cutaneous immunotherapy-related adverse events. *J Drugs Dermatol.* 2023;22(11)SF389716s4:s3-s10.
5. Granito A, Marinelli S, Negrini G, et al. Prognostic significance of adverse events in patients with hepatocellular carcinoma treated with sorafenib. *Therap Adv Gastro.* 2016; 9(2):240-249.
6. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapy for cancer: Part II. Targeted therapy. *J Am Acad Dermatol.* 2014;71(2):e217-11.
7. Owczarek W, Słowińska M, Lesiak A, et al. The incidence and management of cutaneous adverse events of the epidermal growth factor receptor inhibitors. *Postepy Dermatol Alergol.* 2017;34(5):418-428.
8. Barton-Burke M, Ciccolini K, Mekas M, Burke S. Dermatologic Reactions to Targeted therapy: A focus on epidermal growth factor receptor inhibitors and nursing care. *Nurs Clin North Am.* 2017;52(1):83-113.
9. Robert C, Sibaud V, Mateus C et al. Nail toxicities induced by systemic anticancer treatments. *Lancet Oncol.* 2015;16(4):e181-189.
10. Jain L, Gardner ER, Figg WD, Chernick MS, Kong HH. Lack of association between excretion of sorafenib in sweat and hand-foot skin reaction. *Pharmacother.* 2010;30(1):52-56.
11. Rosen AC, Case EC, Dusza SW et al. Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. *Am J Clin Dermatol.* 2013;14(4):327-333.
12. Chan JC, Lee YH, Liu CY, et al. A correlational study of skin toxicity and quality of life in patients with advanced lung cancer receiving targeted therapy. *J Nurs Res.* 2019;27(6):e51.
13. Sauder MB, Addona M, Andriessen A et al. The role of skin care in oncology patients. *Skin Therapy Lett.* 2020;S Oct10:1-12.
14. Sauder MB, Andriessen A, Claveau J, et al. Canadian skin management in oncology (CaSMO) algorithm for patients with oncology treatment-related skin toxicities. *Skin Therapy Lett.* 2021;S March 21:1-10.
15. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting, and evaluation in health care. Prev Med. 2010;51:421-4.
16. Trevelyan EG, Robinson, N. Delphi methodology in health research: how to do it? *Eur J Integrat Med.* 2015;7:423-8.
17. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 2014;371(20):1877-88.
18. Scarpato L, Festino L, Vanella V, et al. Dermatologic adverse events associated with targeted therapies for melanoma. *Expert Opin Drug Saf.* 2021;21(3):385–395.
19. Moret E, Ambresin A, Gianniou C, et al. Non-immediate drug hypersensitivity reactions secondary to intravitreal anti-vascular endothelial growth factors. *Graefes Arch Clin Exp Ophthalmol.* 2022;260(3):1005-1014.
20. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer.* 2006;6(10):803-812.
21. Sanmartin O. Skin manifestations of targeted antineoplastic therapy. *Curr Probl Dermatol.* 2018;53:93-104.
22. Espinosa ML, Abad C, Kurtzman Y, et al. Dermatologic Toxicities of targeted therapy and immunotherapy in head and neck cancers. *Front Oncol.* 2021;11:605941.
23. U.S. Department of Health and Human Services, National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
24. Varvaresou A, Iakovou K, Mellou F, et al. Targeted therapy in oncology patients and skin: Pharmaceutical and dermocosmetic management. *J Cosmet Dermatol.* 2020;19(4):782-788.
25. Liu RC, Consuegra G, Fernandez-Penas P. Management of the cutaneous adverse effects of antimelanoma therapy. *Melanoma Manag.* 2017;(4):187-202.
26. Lacouture ME, Sibaud V, Gerber PA, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2021 Feb;32(2):157-170.
27. Gravalos C, Sanmartin O, Gurpide A, et al. Clinical management of cutaneous adverse events in patients on targeted anticancer therapies and immunotherapies: a national consensus statement by the Spanish Academy of Dermatology and Venereology and the Spanish Society of Medical Oncology. *Clin Transl Oncol.* 2019;21(5):556-571.
28. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010;28(8):1351-1357.
29. Deplanque G, Chavaillon J, Vergnenegre A, et al. CYTAR: a randomized clinical trial evaluating the preventive effect of doxycycline on erlotinib-induced folliculitis in non-small cell lung cancer patients. 2010 ASCO Annual Meeting. *J Clin Oncol.* 2010;28(15suppl):9019-9019.
30. Jatoi A, Thrower A, Sloan JA, et al. Does sunscreen prevent epidermal growth factor receptor (EGFR) inhibitor-induced rash? Results of a placebo-controlled trial from the North Central Cancer Treatment Group (N05C4). *Oncologist.* 2010;15(9):1016-22.
31. Ouwerkerk J, Boers-Doets C. Best practices in the management of toxicities related to anti-EGFR agents for metastatic colorectal cancer. *Eur J Oncol Nurs.* 2010;14(4):337-49.
32. Belum VR, Marchetti MA, Dusza SW, et al. A prospective, randomized, double-blinded, split-face/chest study of prophylactic topical dapsone 5% gel versus moisturizer for the prevention of cetuximab-induced acneiform rash. *J Am Acad Dermatol.* 2017;77(3):577-579.
33. Caruana M, Hatami A, Marcoux D, et al. Isotretinoin for the treatment of severe acneiform eruptions associated with the MEK inhibitor trametinib. *JAAD Case Rep.* 2020;6(10):1056-1058.
34. Chiang HC, Anadkat MJ. Isotretinoin for high-grade or refractory EGFR-related acneiform papulopustular eruptions. *J Am Acad Dermatol.* 2013;69(4):657-8.
35. Wang CJ, Brownell I. BRAF Inhibitors for the treatment of papulopustular eruptions from MAPK pathway inhibitors. Am J Clin Dermatol. 2020;21(6):759-764.
36. Nikolaou V, Strimpakos AS, Stratigos A, et al. Azithromycin pulses for the treatment of epidermal growth factor receptor inhibitor-related papulopustular eruption: an effective and convenient alternative to tetracyclines. *Dermatology.* 2012;224(4):315-319.
37. Lacouture M, Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. *Am J Clin Dermatol.* 2018;19(Suppl 1):31-39.
38. Albanell J, Rojo F, Averbuch S, et al. Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. *J Clin Oncol.* 2002;20(1):110-24.
39. Chanprapaph K, Vachiramon V, Rattanakaemakorn P. Epidermal growth factor receptor inhibitors: a review of cutaneous adverse events and management. *Dermatol Res Pract.* 2014;2014:734249.
40. Melosky B, Anderson H, Burkes RL, et al. Pan Canadian Rash Trial: A randomized phase III trial evaluating the impact of a prophylactic skin treatment regimen on epidermal growth factor receptor-tyrosine kinase inhibitor-induced skin toxicities in patients with metastatic lung cancer. *J Clin Oncol.* 2016;34(8):810-815.
41. Salzmann M, Marmé F, Hassel JC. Prophylaxis and management of skin toxicities. *Breast Care (Basel).* 2019;14(2):72-77.
42. Watanabe S, Nakamura M, Takahashi H, et al. Dermopathy associated with cetuximab and panitumumab: investigation of the usefulness of moisturizers in its management. *Clin Cosmet Investig Dermatol.* 2017;10:353-361.
43. Santini D, Vincenzi B, Guida FM, et al. Aprepitant for management of severe pruritus related to biological cancer treatments: a pilot study. *Lancet Oncol.* 2012;13(10):1020-4.
44. Chanprapaph K, Rutnin S, Vachiramon V. Multikinase inhibitor-induced hand-foot skin reaction: A review of clinical presentation, pathogenesis, and management. *Am J Clin Dermatol.* 2016;17(4):387-402.
45. Rzepecki AK, Franco L, McLellan BN. PATEO syndrome: periarticular thenar erythema with onycholysis. *Acta Oncol.* 2018;57(7):991-992.
46. Rodriguez-Lomba E, Molina-Lopez I, Suarez-Fernandez R, et al. Periarticular thenar erythema and onycholysis syndrome: A manifestation of taxane-induced cutaneous toxicity. *Actas Dermosifiliogr.* 2017;108(6):595-597.
47. Garden BC, Wu S, Lacouture ME. The risk of nail changes with epidermal growth factor receptor inhibitors: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol.* 2012;67(3):400-408.
48. Chang GC, Yang TY, Chen KC et al. Complications of therapy in cancer patients: Case 1. Paronychia and skin hyperpigmentation induced by gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol.* 2004;22(22):4646-4648.
49. Subhadarshani S, Abhishek GN. Imatinib-induced Melasma-like Pigmentation. *Indian J Dermatol.* 2019;64(2):158-159.
50. Anforth RM, Blumetti TC, Kefford RF. Cutaneous toxicities of RAF inhibitors. *The Lancet Oncology.* 2012;13(10): e375-e382.
51. Yip D, Karapetis, C. Hyperpigmentation secondary to the use of imatinib mesylate. *Anticancer Drugs.* 2006;17(1):101-103.
52. Strumia M, Perrin ML, Patras de Compaigno E, et al. Dermatological adverse drug reactions of anticancer drugs: International data of pharmacovigilance: VigiBase®. Therapie. 2022;77(2):219-227.
53. Ren Z, Zhu K, Kang H, et al. Randomized controlled trial of the prophylactic effect of urea-based cream on sorafenib-associated hand-foot skin reactions in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2015;33(8):894-900.
54. Hanania HL, Pacha O, Heberton M, et al. Surgical intervention for paronychia induced by targeted anticancer therapies. *Dermatol Surg.* 2021;47(6):775-779.
55. Sibaud V, Casassa E, D'Andrea M. Are topical beta-blockers really effective "in real life" for targeted therapy-induced paronychia. *Support Care Cancer.* 2019;27(7):2341-2343.
56. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol.* 2005;16(9):1425-1433.
57. Said JT, Singer S, Iannattone L et al. Outcomes of acitretin treatment for refractory multikinase inhibitor-induced hand-foot skin **reaction.** *JAMA Dermatol.* 2022;158(7):824-826.

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