Supportive Oncodermatology

Addressing dermatologic adverse events associated with oncologic therapies
Supportive oncodermatology is an emerging collaborative subspecialty between oncology and dermatology that aims to address dermatologic events associated with cancer therapy. An estimated 1.685 million new cancer diagnoses were made in 2016—many of these patients will require chemotherapy and/or radiotherapy and become part of the estimated 15.5 million living cancer survivors in the United States. With the rapid development and utilization of targeted therapies, a rise in both established and new cutaneous toxicities has been witnessed. Despite the frequency of dermatologic adverse events, efforts in supportive care in oncology have thus far been prioritized for gastrointestinal, hematopoietic, and constitutional toxicities based on data generated from epidemiological quality of life (QOL) studies.

The spectrum of dermatologic adverse events from cancer treatments has a profound impact on the physical, emotional, financial, and psychosocial well-being of patients. In a study by Gandhi et al., 379 cancer survivors were surveyed using a validated QOL tool to determine the impact of their dermatologic symptoms. Sixty-seven percent felt that their dermatologic toxicities were worse than what they had expected, 84 percent were not referred to a dermatologist, and 54 percent thought that they would have felt better had they been referred to a dermatologist. With the success of targeted anti-cancer therapies leading to a growing number of cancer survivors, we are also beginning to see long-term dermatologic effects of targeted therapies, many of which are underreported and overlooked. Knowledge of dermatologic toxicities is not only important for physicians so that prophylactic and reactive interventions can be instituted but also to provide realistic expectations to patients and prepare them for the potential and expected sequelae. Therefore, there is a clear need to establish communication between oncologists and dermatologists in order to effectively assess and manage dermatologic adverse events associated with cancer therapy—the core mission of the field of supportive oncodermatology.

Dermatologic Adverse Event Management

Over 50 distinct dermatologic toxicities have been reported in association with more than 30 anti-cancer agents. Here we will focus on the most common documented adverse events:

- Hand-foot skin reaction
- Nail changes
- Papulopustular eruptions (an acne-like rash)
- Pruritus (severe itching)
- Secondary malignancies
- New neoplasms
- Chemotherapy-induced alopecia (hair loss or spot baldness).

Hand-Foot Skin Reaction

Hand-foot skin reaction is one of the most common cutaneous side effects affecting 9 to 62 percent of patients on targeted cancer therapies. It is associated with multikinase inhibitors such as sorafenib, sunitinib, pazopanib, and bevacizumab that specifically...
target the vascular endothelial growth factor pathways implicated in angiogenesis, a process that provides the blood supply critical for development and invasive potential of many solid tumors, notably in advanced renal cell carcinoma and hepatocellular carcinoma.6-7 Hand-foot skin reaction clinically appears within six weeks of treatment initiation and most commonly within the first two to four weeks.8 It usually presents as tender, hyperkeratotic plaques surrounded by a peripheral halo of erythema and is sometimes accompanied by superficial blistering and callus formation (see photo, below). These lesions usually affect flexural surfaces subject to increased pressure and friction such as the digits, finger webs, palms, heels, soles, and periungual regions.9 The thickened lesions limit weight-bearing and range of motion, two impairments that have shown to limit activities of daily living and debilitate patient QOL. Additional symptoms of hand-foot skin reaction include paresthesia (abnormal sensation such as tingling, tickling, pricking, numbness or burning of a person’s skin with no apparent physical cause), burning, pain, and decreased tolerance to contact with hot objects.

Physicians must be able to distinguish between hand-foot skin reaction as described here and the hand-foot syndrome reported with conventional cytotoxic therapies such as cytarabine, doxorubicin, capecitabine, and 5-fluorouracil.10 Hand-foot syndrome presents as diffuse symmetric paresthesias, erythema (superficial reddening of the skin), and edema that localizes to flexural surfaces with associated pain and tenderness.8 Hand-foot skin reaction, in contrast, is characterized by the localized hyperkeratotic lesions with surrounding erythema and distinct histopathological features. The pathogenesis of hand-foot skin reaction is unknown, but a dual blockade of vascular endothelial growth factor and platelet-derived growth factor receptors may cause drug leakage from capillaries damaged by subclinical trauma and inhibit vascular repair pathways.11 This hypothesis is supported by the increased severity of hand-foot skin reaction with increased activity and friction.

Due to its negative impact on patient QOL, hand-foot skin reaction can result in dose reduction or interruption of therapy. For example, in Phase II studies, patients treated with sorafenib...
for prostate cancer and lung cancer experienced dose reductions due to hand-foot skin reaction toxicity (10 percent and 31 percent, respectively).12

Prevention involves prophylactic removal of hyperkeratotic (thickened outer layer of skin) areas on the palms and soles. Additionally, patients should be advised to make lifestyle modifications such as wearing soft, orthotic shoes to cushion calluses and cotton socks and avoiding tight-fitting soles, running, or any exercise that creates unnecessary friction in the palms and soles.13

Recently, researchers have attempted to identify prophylactic therapies to prevent hand-foot skin reaction. A randomized trial using a prophylactic urea-based cream in patients with hepatocellular carcinoma treated with sorafenib found that those treated had universally decreased grades of hand-foot skin reaction from 73.6 percent to 56 percent and delayed onset of hand-foot skin reaction from 34 days to 84 days.14

Treatment recommendations for each stage of hand-foot skin reaction are shown in Table 1, page 68. These recommendations address the different stages of hand-foot skin reaction that the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE Version 4.0)16 uses to grade severity of this adverse event.

**Nail Changes**

Nail changes are a distressing and frequently underreported chemotherapy side effect that can cause considerable cosmetic concern, pain, infection, and impact to QOL. The clinical presentation of nail toxicities varies, and classification schemes from the NCI are used to grade severity (see Table 2, page 68).15

Onycholysis (painless separation of the nail from the nail bed) occurs as acute damage to the nail bed epithelium and is common with taxanes such as docetaxel and paclitaxel, first- or second-line chemotherapy agents used against breast cancer. Taxane-induced onycholysis occurs in up to 44 percent of patients, with docetaxel as the more commonly offending agent (see photo on page 69). Additional taxane-related nail changes include17:

- Dark pigmentation
- Beau’s lines (deep grooved lines that run from side to side on the fingernail or the toenail)
- Subungual hemorrhage
- Transverse loss of the nail plate
- Thinning and ridging of the nail plate
- Subungual hyperkeratosis (abnormal thickening of the outer layer of the skin)
- Acute painful, paronychia (an infection of the skin around a fingernail or toenail)
- Discoloration.

The integrity of peripheral nerves may be necessary for the development of nail abnormalities and two mechanisms have been proposed: taxanes may activate nociceptive C-fibers that release neuropeptides and trigger neurogenic inflammation or release prostaglandins from sympathetic postganglionic terminals.18 Current management of taxane-induced nail changes includes hand protection with gloves and moisturizers. Although there are no approved treatments, research has explored the application of regional cooling via frozen glove and sock therapy. Scott et al. reported that the incidence of nail changes decreased from 51 percent to 11 percent in the hands and 21 percent to 0 percent in the feet with the use of frozen gloves and socks.19

Other chemotherapeutic agents can also cause nail alterations. The anthracyclines, such as doxorubicin, daunorubicin, and idarubicin, cause diffuse and banded patterns of nail pigmentation that resolve with discontinuation of therapy and subsequent nail growth.20 Multikinase inhibitors and epidermal growth factor receptor inhibitors (EGFRIs) can cause paronychia, fissures, slow nail growth, subungual splinter hemorrhages, and onycholysis.21 The most commonly seen nail changes associated with targeted therapy include paronychia and periungual pyogenic granuloma-like lesions. These nail changes typically occur one to six months after therapy initiation and most commonly affect the big toe and thumbs. These alterations can persist for months despite treatment interruption and are often complicated by secondary infections.

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Unfortunately, there are no approved treatments for targeted therapy-associated nail changes. As such, management strategies should be aimed at minimizing periungual trauma, decreasing periungual inflammation, preventing secondary infection, and eliminating excessive granulation tissue.

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Unfortunately, there are no approved treatments for targeted therapy-associated nail changes. As such, management strategies should be aimed at minimizing periungual trauma, decreasing periungual inflammation, preventing secondary infection, and eliminating excessive granulation tissue.22 Physicians can help minimize periungual trauma by instructing patients to wear comfortable shoes with wide toe boxes, wear gloves while cleaning, and trim their nails. Topical corticosteroids and anti-inflammatory dose tetracyclines are recommended to combat periungual inflammation and antimicrobial vinegar soaks are recommended to prevent secondary infection. Additionally, silver nitrate, electrocautery, and nail avulsion are recommended to eliminate excessive granulation tissue.23,24 For fissures, many patients have found success with thick moisturizers, bleach soaks to prevent infection, liquid glues, propylene glycol, salicylic acid, and topical steroids for red itchy areas.25

(continued on page 69)
### Table 1. Treatment Recommendations for NCI-CTCAE Version 4.0 Grades of Hand-Foot Skin Reaction

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Recommendation</th>
<th>Change in Dose</th>
</tr>
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| 1     | Minimal skin changes or dermatitis with no pain (erythema, edema, or hyperkeratosis) | • Avoid hot water  
• Moisturizing creams  
• Thick cotton gloves and/or socks  
• Lifestyle modifications | No change; maintain current dose of multikinase inhibitor |
| 2     | Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental activities of daily living | • Continue with grade 1 care  
• Urea 20%-40% cream  
• Tazarotene 0.1% cream  
• Fluorouracil 5% cream  
• Clobetasol propionate 0.05% ointment  
• 2% Lidocaine for pain  
• Nonsteroidal anti-inflammatory drugs, codeine, pregabalin for pain | 50 percent dose reduction for 7 to 28 days |
| 3     | Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting self-care activities of daily living | • Local intervention indicated  
• Intravenous antibiotic, antifungal, or antiviral intervention indicated  
• Radiologic or operative intervention indicated | 50 percent dose reduction or interrupt treatment until symptoms improve to Grade 0 or 1 |

### Table 2. NCI Criteria (Common Terminology Criteria for Adverse Events, Version 4.0) for Classification of Nail Changes

<table>
<thead>
<tr>
<th>CTCAE Version 4 Toxicty</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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| Nail discoloration      | • Asymptomatic; clinical or diagnostic observations only  
• Intervention not indicated | • Symptomatic separation of nail bed from nail plate  
• Nail loss | • Intravenous antibiotic, antifungal, or antiviral intervention indicated  
• Radiologic or operative intervention indicated |
| Nail loss               | • Asymptomatic separation of nail bed from nail plate  
• Nail loss | • Symptomatic separation of nail bed from nail plate  
• Nail loss  
• Limits activities of daily living |                                                                                         |
| Nail ridging            | • Asymptomatic; clinical or diagnostic observations only  
• Intervention not indicated |                                                                                         |                                                                                         |
| Nail infection          | • Localized  
• Local intervention indicated | • Oral intervention indicated (e.g., antibiotic, antifungal, antiviral) |                                                                                         |
| Paronychia              | • Nailfold edema or erythema  
• Disruption of cuticle | • Localized intervention indicated  
• Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)  
• Nailfold edema or erythema with pain  
• Associated with discharge or nail plate separation  
• Limits activities of daily living | • Surgical intervention or intravenous antibiotics indicated  
• Limits self-care activities of daily living |
Papulopustular Eruptions

Papulopustular eruptions are the most clinically significant dermatologic toxicities that have been reported with use of virtually all targeted cancer therapies. Of note, this adverse event most commonly occurs with EGFRIs and HER2 inhibitors. EGFRIs are used in the treatment of several malignancies including colorectal, head and neck, non-small cell lung, and breast cancers. Among patients treated with EGFRIs, up to 90 percent have experienced papulopustular eruptions.

The rash usually develops during the first two to four weeks after initiation of therapy as pruritic and tender erythematous papules and pustules in skin with a high density of sebaceous glands such as the scalp, face, neck, chest, and back (see photo on page 70). Mechanistically, the inhibition of EGFR-mediated signaling pathways affects keratinocytes by inducing growth rest and apoptosis, increasing cell attachment that inhibits cell migration and maturation, and stimulating inflammation. Interestingly, there is a relationship between the development of the papulopustular rash and response to chemotherapy and consequent survival, making the eruption a potential marker of response and/or survival. Multiple studies with erlotinib and cetuximab have reported a positive correlation between therapy-induced rash and clinical outcome. Though a herald of positive treatment outcomes, it is noteworthy for its impact on psychosocial well-being and can have negative effects on dose intensity.

Patients experiencing papulopustular rashes while on EGFRIs have higher median scores than patients on other targeted therapies in the symptom, emotion, and function subdomains (37.5, 50.0, and 16.7, respectively) of the Skindex-16 assessment, a patient-reported QOL measure used in dermatology. As such, these data suggest that the psychosocial burden associated with EGFRI sequelae is more severe than with other anticancer therapies. Moreover, a survey of oncologists revealed that 32 percent of providers discontinued therapy and 76 percent modified the dose when the rash was severe.

Because the eruption predictably occurs within the first month of therapy, preventive management is recommended: a prophylactic therapeutic cocktail of hydrocortisone 1 percent combined with moisturizer, sunscreen, and doxycycline 100 mg bid during the first six weeks of treatment has been found to delay the first occurrence of skin toxicity in a randomized controlled study. Reactive recommendations include the use of medium- to high-potency topical corticosteroids. Several case reports and studies have demonstrated successful treatment of EGFRI-induced rash with low-dose isotretinoin without chemotherapy dose reduc-
The promising use of isotretinoin is further supported by patient reports of improved quality of life.

Papulopustular rashes occur less frequently and are milder with the multikinase inhibitors sorafenib and sunitinib, HER2 inhibitor pertuzumab, and dual EGFR and HER2 inhibitor lapatinib. Recent case reports have paradoxically reported more severe papulopustular eruptions with the HER2 inhibitor trastuzumab. There are no approved treatments for HER2 inhibitor- and multikinase inhibitor-induced rashes. Nevertheless, guidelines of prevention and treatment of EGFR-induced papulopustular rash may be applicable.

**Pruritus**

Pruritus is a common adverse event associated with EGFRIs. Its incidence is 22.7 percent, with the highest occurrence associated with panitumumab (54.9 percent). Though the pathophysiology of pruritus remains unclear, targeted agents such as EGFRIs may inhibit the EGFR of basal keratinocytes, perturbing normal epidermal physiology. Additionally, EGFR-induced pruritus may be associated with an increased number of dermal mast cells surrounding adnexal structures. These mast cells may recruit mediators that activate sensory nerves, which trigger itch.

Current management options for pruritus require a tailored approach of stabilized hypochlorous acid 0.045 percent, pramoxine 1 to 2.5 percent, strontium 4 percent, capsaicin 0.1 to 8 percent, and menthol 1 to 2 percent for mild to moderate pruritus. Severe pruritus warrants the use of high dose antiepileptics, antidepressants, and anti-psychotics. Additionally, a therapeutic cocktail of ketamine 5 to 10 percent, lidocaine 5 percent, and amitryptiline 5 percent in a lipoderm base that targets ion channels has found success in itch management. Patients should be counseled on how to break the itch-scratch cycle by:

- Keeping fingernails short
- Wearing loose clothing
- Using a humidifier
- Restricting bath and shower time and using lukewarm water
- Avoiding cleansers with a high pH or containing alcohol.

**Secondary Skin Cancers**

The overall five-year survival rate for children with cancer now exceeds 80 percent, resulting in more than 360,000 living survivors in the United States. With this success comes a heightened recognition of the need to address treatment-related sequelae that may affect QOL. One such adverse event is anti-cancer therapy-associated secondary malignancies; these malignancies can be divided into two distinct groups: chemotherapy-related myelodysplasia and radiation-related solid second malignant neoplasm. Chemotherapy-related myelodysplasias are sequelae...
that appear within three years from the primary cancer and are more commonly associated with alkylating agents or topoisomerase II inhibitors. Radiation-related solid second cancers account for the largest burden of secondary malignancies (about 80 percent) and appear more than 10 years after the primary cancer. The most common radiation-associated solid tumor is non-melanoma skin cancer, particularly basal cell carcinoma, and the most well-established primary cancers that lead to radiation-related secondary malignancies include breast, lung, and thyroid cancers and brain tumors, sarcomas, and basal cell carcinomas. These secondary cancers are leading causes of non-relapse late mortality and serious morbidity. As such, the Children’s Oncology Group recommends that cancer survivors receive annual full-body skin checks after radiation treatment, especially of irradiated fields. However, such frequent medical evaluation and potential biopsies can add to emotional and financial distress among cancer survivors, leading to a gap and possible omission of necessary care. One such example is seen in a study conducted by Nathan et al., where 26.6 percent of surveyed cancer survivors reported never having had a skin examination of irradiated areas.

The problem, however, is not simply due to a patient lack of interest or adherence. In fact, cancer survivors are more likely to report an indicated skin examination if they receive follow-up care at a cancer center or are enrolled in a long-term follow-up program. However, few survivors (12.4 percent in the Nathan et al. cohort) continue to receive regular care at a cancer center or have access to specialized survivorship clinics once they reach adulthood. Thus, assessment and management of secondary malignancies must be aimed at initiating early and maintaining regular surveillance screenings. Physicians across all specialties should pay careful attention to dermatologic changes in cancer survivors and equip patients with knowledge of their cancer therapy to encourage them to seek care focused on secondary malignancy detection.

**Epidermal Neoplasms**

Epidermal neoplasms are adverse skin reactions frequently associated with BRAF gene inhibitor therapy (vemurafenib, dabrafenib) used to treat metastatic melanoma. The characteristic keratinocyte proliferation found in all BRAF inhibitor-induced skin toxicities drives the formation of lesions such as squamous cell carcinoma, keratoacanthoma, and verrucous keratosis. The mechanism behind BRAFI-induced squamous cell carcinoma is unknown, yet biochemical studies have shown that RAF blockade in wild-type BRAF cells, particularly in the presence of oncogenic RAS mutations caused by sun damage to keratinocytes, can lead to paradoxical mitogen-activated protein kinase (MAPK) pathway activation via dimerization of RAF isomers. To support this theory, studies have shown a high prevalence of RAS gene mutations in cutaneous squamous cell carcinomas developing in patients treated with RAF inhibitors (see photo on page 72). Therefore, the RAF inhibitor-driven activation of MAPK may unmask the oncogenic events in keratinocytes harboring preexisting RAS mutations caused by sun damage.

Squamous cell carcinomas sometimes appear in an eruptive fashion within the first week after initiation of a BRAF inhibitor and generally regress after treatment is discontinued. Management includes surgical excision if the squamous cell carcinoma is solitary or paucisional and intralesional 5-fluorouracil, systemic retinoids, and electrodessication and curettage if the carcinomas are multiple or eruptive. Patients should be closely monitored with visits every four to six weeks.

Verrucous keratoses are the most commonly encountered squamo-proliferative lesions induced by RAF inhibitors. The lesions tend to present in older patients between the first 6 to 12 weeks of RAF inhibitor therapy. They appear as verruciform white keratotic papules that occur in a widespread distribution in photoexposed and non-photoexposed skin (see photo on page 73). Pathologically, the lesions exhibit minimal to mild atypia, papillomatosis, acanthosis, hypergranulosis, and hyperkeratosis of the epidermis. Though verrucous keratoses are not malignant in nature, the variation of epidermal dysplasia and occasional presence of acantholysis suggest that these lesions may potentially be premalignancies. As such, patients with verrucous keratoses should be monitored closely for squamous cell carcinoma transformation; early cryotherapy can be very effective against these keratoses.

**Chemotherapy-Induced Alopecia**

Chemotherapy-induced alopecia is one of the most common and distressing adverse events in patients with cancer. Sixty-five percent of patients with cancer overall experience chemotherapy-induced alopecia, 47 percent consider it the worst side effect of chemotherapy, and 8 percent of women decline chemotherapy due to fear of hair loss. Chemotherapy-induced alopecia has a large psychosocial impact on patients by serving as a visual reminder and public statement of their cancer. It additionally leads to impairments such as decreased self-esteem, decreased sensuality and sexuality, and negatively affected social interactions.

There are two major types of chemotherapy-induced alopecia: telogen effluvium and anagen effluvium. Telogen effluvium rarely involves more than 50 percent of scalp hair and consequently produces a level of hair thinning. This type of hair loss occurs when a larger than normal proportion of anagen hairs on the scalp moves into the telogen phase of the hair cycle. This premature shift in the hair cycle terminates as hair shedding that is most profound three to four months after chemotherapy exposure. Anti-cancer agents that frequently lead to telogen effluvium include methotrexate, 5-fluorouracil, and retinoids.

In anagen effluvium, the second major type of chemotherapy-induced alopecia, chemotherapy targets the rapidly growing inner root sheath cells, which leads the hair to either fall out with mild pressure or break off when it reaches the scalp surface. The hair then remains in the resting telogen phase for the rest of the treatment duration. The most notable chemotherapy-induced alopecia chemotherapeutics include cyclophosphamide, etoposide, topotecan, and paclitaxel. Though hair does regrow, the new hair often presents with a different color and/or texture.
Scalp cooling is applied concurrently with chemotherapy. It is hypothesized to prevent chemotherapy-induced alopecia by either slowing down scalp cellular metabolism or by reducing blood perfusion and subsequently chemotherapy delivery to the scalp. Overall, scalp cooling has a good safety profile with no reported cases of systemic reactions. Common adverse events include cold intolerance; heavy cap weight; mild, transient headache; anxiety; nausea; dizziness; and chest pain. Patient tolerance to scalp cooling is unpredictable and highly variable. Discomfort and side effects can contribute to early discontinuation of scalp cooling, with studies finding that patient dropout occurs mostly in the first cycles and rarely later in treatment. Concerns about and limited data on scalp metastases have hindered physicians from recommending scalp cooling to patients. In 2009 Lemieux et al. followed 640 patients with breast cancer for approximately 5.5 years; 553 received scalp cooling and 87 did not receive scalp cooling. The study did not yield a significant difference in scalp metastases between the two groups; 6 patients (1.1 percent) in the scalp cooling group of 553 and 1 patient (1.2 percent) in the control group of 87.

The publication of multiple articles that show no increased risk for scalp metastases in breast cancer patients who used scalp cooling has bolstered the recent reconsideration of scalp cooling in American oncology clinics. The U.S. Food and Drug Admin-
crucial that oncologists and dermatologists communicate clearly with each other to address these often overlooked side effects. Supportive oncodermatology can bridge this gap in care by raising awareness of dermatologic adverse events, improving QOL in cancer patients, and ultimately maximizing the efficacy of anti-cancer therapies.

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References


