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Dermatologic Reactions to Cancer Therapies

Edited by
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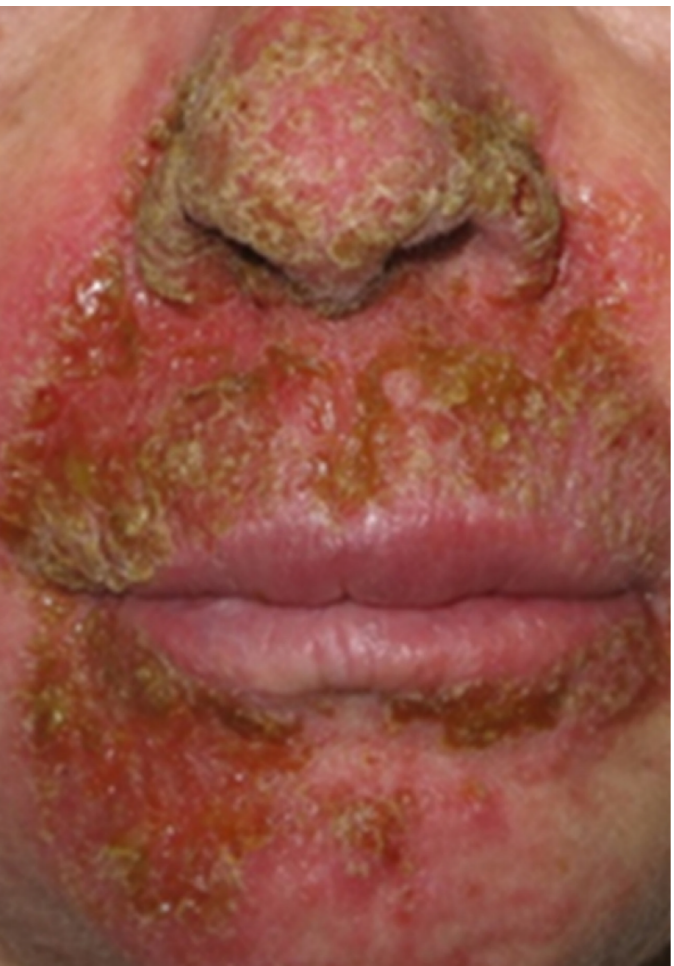

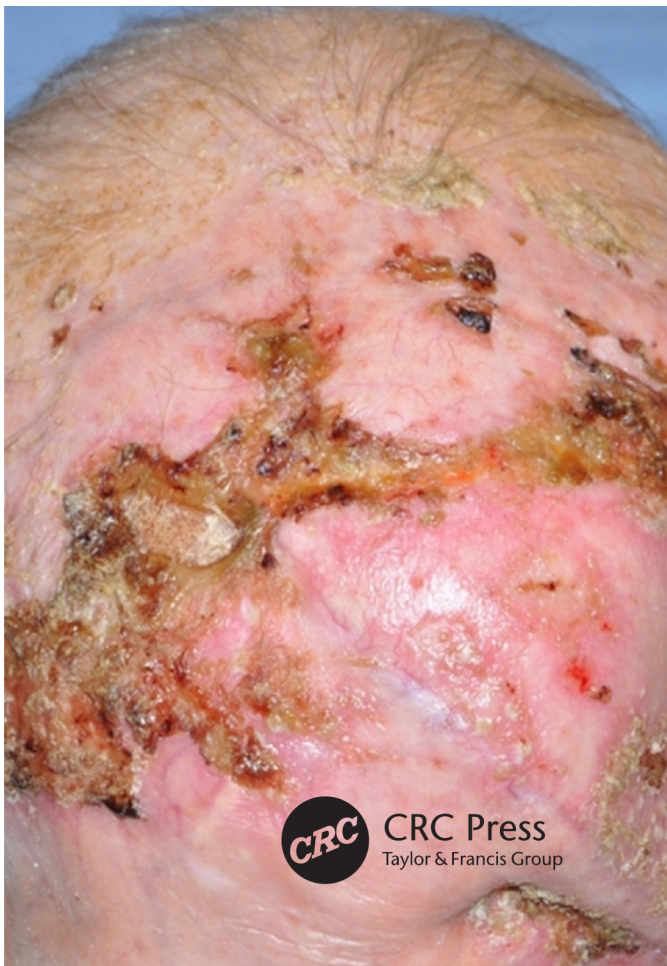

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Dermatologic Reactions to Cancer Therapies

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Gabriella Fabbrocini, Mario E. Lacouture and Antonella Tosti

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Dermatologic Reactions to Cancer Therapies

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Introduction to Anticancer Therapies

Jennifer Wu and Mario E. Lacouture

Overview: Cancer Incidence and Types of Systemic Anticancer Therapies

Cancer treatments have revolutionized during the past decades with many new anticancer therapies being developed and approved for a broad variety of cancer types every year (1). More than 10 million people were diagnosed with cancer every year according to World Health Organization (WHO), and 8 million cancer-related deaths and 30 million cancer survivors were reported (2). Accompanied by increased incidence and death, cancer prevention and treatments have become a major issue to public health. Yet the incidences of adverse events to anticancer therapies have also increased in parallel to the rapid emergence of novel treatment modalities, new regimens of combination therapies, and prolonged survival. Different anticancer treatment modalities such as cytotoxic chemotherapy, targeted therapy, immune checkpoint blockade agents, radiation therapy, adoptive T lymphocyte therapy, and hematopoietic stem cell transplantation have distinct spectrums of dermatologic adverse events (AEs), which can involve the skin, hair, nail, and mucous membranes. Dermatologic AEs can not only impair patient's physical function and quality of life but result in dose reduction, regimen modification, and discontinuation of anticancer treatment, which can eventually cause negative impacts on cancer outcomes and even lift-threatening conditions (3). Understanding the epidemiology and clinical manifestations of anticancer therapy–related dermatologic AEs in order to facilitate early recognition, and timely and proper management are important to continue treatments, optimize outcomes, and maintain quality of life. Patient counseling regarding potential dermatologic AEs and strategies for prevention and management before initiation of anticancer therapy is therefore highly recommended. This chapter aims to give a brief introduction on anticancer therapies and their associated dermatologic AEs (Figure 1.1; also see Tables 1.1 and 1.2). The main subjects of each dermatologic manifestation will be discussed in the following chapters.

Anticancer Therapies and Their Associated Dermatologic Adverse Events

Cytotoxic Chemotherapy

Toxic Erythema of Chemotherapy

Toxic erythema of chemotherapy (TEC) describes the overlapping features of skin toxicity induced by chemotherapy through a reproducible nonimmune mediated effect. The clinical characteristics of TEC are erythematous patches or plaques on the axillae and groins, hands, and feet, and, less often, the elbows, knees, and ears, associated with pain, burning, paresthesia, and pruritus. TEC usually appears within days to 3 weeks following the administration of chemotherapeutic agents but may occur late at 2–10 months in patients receiving lower-dose, continuous infusions of 5-fluorouracil (5-FU), or oral agents. Bullae and erosions within the affected area may be seen. The lesions are often self-limited but may recur with readministration of the same agents (4). Hand-foot syndrome (HFS) is a subtype of TEC involving mainly palms and soles (4,5). Chemotherapeutic agents more commonly associated with TEC include cytarabine (AraC), anthracyclines, doxorubicin and pegylated liposomal doxorubicin (PLD), 5-FU, capecitabine

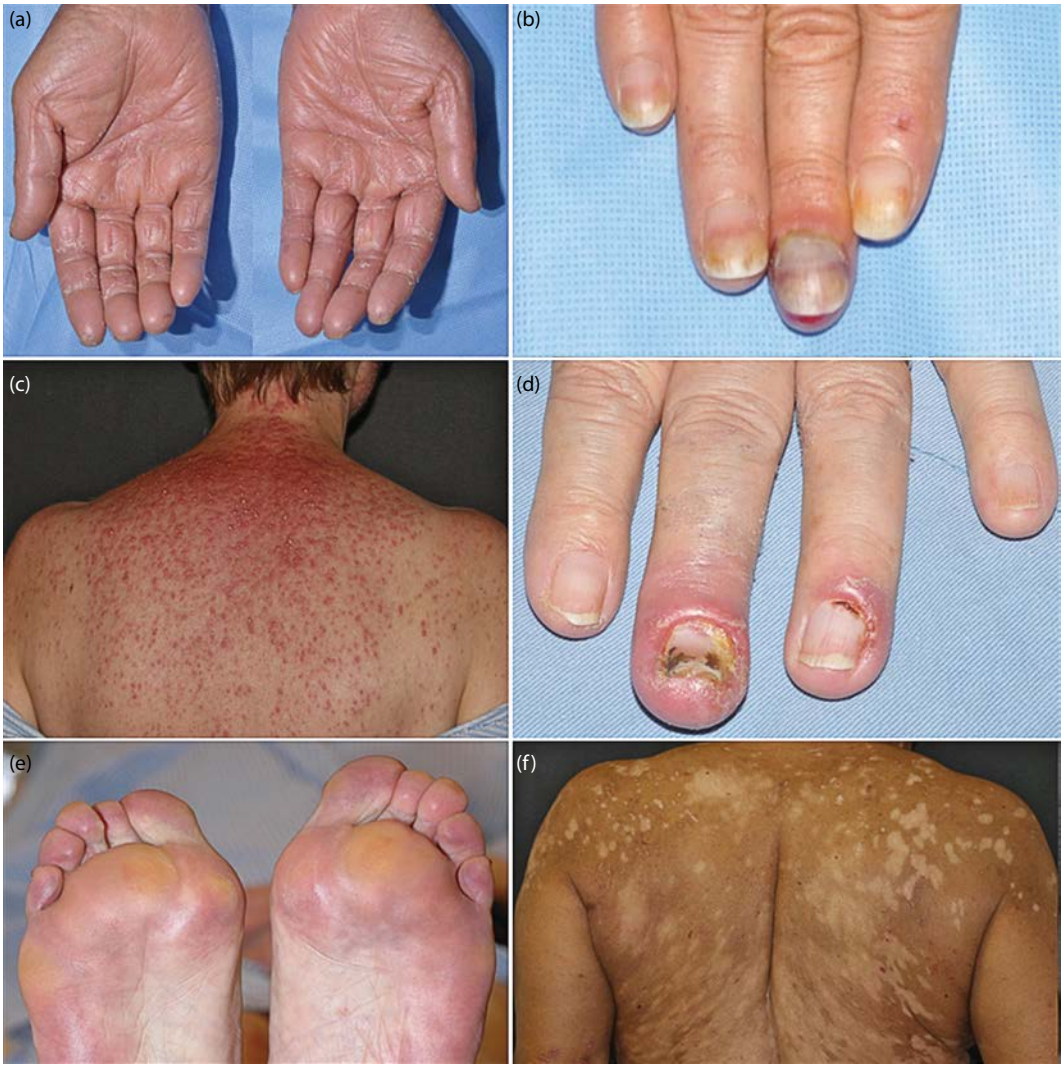

FIGURE 1.1 Dermatologic adverse events to anticancer therapies. (a) Hand-foot syndrome induced by capecitabine (b) swelling of fingertips, subungual hemorrhage, and onycholysis related to docetaxel. (c) Papulopustular eruption related to EGFRI. (d) Paronychia related to EGFRI. (e) Hand-foot skin reaction related to MKI. (f) Vitiligo-like lesions induced by ICIs.

(5-FU prodrug), taxanes (docetaxel and paclitaxel), and methotrexate. Bleomycin, busulfan, carmustine, lomustine, cisplatin, carboplatin, clofarabine, cyclophosphamide, ifosfamide, etoposide, gemcitabine, hydroxyurea, melphalan, 6-mercaptopurine, mitoxantrone, tyrosine kinase inhibitors (imatinib, sunitinib), tegafur, thiotepa, and vinorelbine have also been related to TEC.

Hand-Foot Syndrome

Hand-foot syndrome (HFS), previously named palmar-plantar erythrodysesthesia, is a well-described dermatologic AE induced by certain chemotherapeutic agents (4,5), most commonly capecitabine, 5-FU cytarabine, taxanes, doxorubicin, and PLD (6–10). HFS manifests as dysesthesia and subsequently symmetrical painful erythema and edema of palms and soles. The lesions may progress to blisters, crusts, or ulcerations (10,11). The pathophysiology is not fully understood but believed to be associated with the

TABLE 1.1

Summary of Anticancer Therapies and Their Associated Dermatologic Adverse Events

Types of Systemic Anticancer Therapies	Dermatologic Adverse Events	Common Culprits (Incidence %)
	Hand-foot syndrome (HFS) (palmar-plantar erythrodysesthesia)	Capecitabine (43–63%), continuously infused 5-fluorouracil, cytarabine, docetaxel (5–10%), doxorubicin, and pegylated liposomal doxorubicin (PLD) (45%)
	Immediate hypersensitivity reactions (IHSRs)	Taxanes (30% if without premedication); platinum-based regimens (12–24%) (21)
	Extravasation reactions	Irritants: Platinum-based alkylating agents, taxanes, and topoisomerase inhibitors Vesicants: Anthracyclines, vinca alkaloids, and nitrogen mustards; incidence: 0.1–6% (17,22)
	Pigmentary changes	Busulfan, cyclophosphamide, ifosfamide, bleomycin, 5-FU, vinorelbine, fotemustine, docetaxel, etc.
	Onychodystrophy	Beau's lines: Bleomycin, cisplatin, docetaxel, doxorubicin, melphalan, and vincristine. Onycholysis: Mitoxantrone, docetaxel, anthracyclines, and paclitaxel
	Chemotherapy-induced alopecia (CIA)	
	Chemotherapy-induced acute reversible alopecia	Taxanes are one of the top CIA-inducing drugs (33,34)
	Chemotherapy-induced persistent alopecia (CIPAL)	Busulfan, thiotepa, fluorouracil/epirubicin/ cyclophosphamide (FEC) and taxanes
	Radiation recall	Doxorubicin, taxanes, 5-FU, gemcitabine and capecitabine were most commonly reported (44)
EGFR inhibitors (EGFRIs)	Papulopustular eruption (PPE) or acneiform eruption	EGFR inhibitors are used to treat advanced or metastatic non-small cell lung cancer (afatinib, erlotinib, gefitinib, necitumumab), pancreatic cancer (erlotinib), breast cancer (lapatinib, neratinib), colon cancer (cetuximab, panitumumab), head and neck cancer (cetuximab), and in even broader clinical settings based on individual mutations of the tumor (23,49,54)
	Pigmentary changes	
	Changes in hair texture, nonscarring and scarring alopecia, facial hypertrichosis, and eyelash trichomegaly	
	Paronychia	
	Nasal vestibulitis (NV)	
Multitargeted kinase inhibitors (MKIs)	Hand-foot skin reaction (FHSR)	Sorafenib (Nexavar), and sunitinib (Sutent) (9–62% patients exposed to sorafenib and sunitinib, regorafenib, axitinib, pazopanib
BRAF inhibitors (BRAFIs)	Nonmalignant hyperkeratotic skin eruptions	Vemurafenib and dabrafenib
	Cutaneous squamous cell carcinomas (SCCs)	
	Photosensitivity	
	Maculopapular rash (MPR), papulopustular eruption (PPE), or folliculocentric rashes with or without pruritus (53), keratosis pilaris (KP)–like skin eruption on the proximal limbs, trunk, and face (5–9%) (79), and HFSR (80)	
MEK inhibitors		Trametinib, cobimetinib
BRAF inhibitors plus MEK inhibitors		

(*Continued*)

TABLE 1.1 (*Continued*)

Summary of Anticancer Therapies and Their Associated Dermatologic Adverse Events

Types of Systemic Anticancer Therapies	Dermatologic Adverse Events	Common Culprits (Incidence %)
Hedgehog inhibitors	Alopecia, follicular dermatitis, hypersensitivity reaction, KAs and cutaneous SCCs	Vismodegib, sonidegib
Immune checkpoint inhibitors	Rash, pruritus, vitiligo	Immune checkpoints inhibitors: Anti-CTLA4, anti-PD1, anti-PD-L1
	Autoimmune bullous dermatosis	Anti-PD1 and anti-PD-L1
	Severe cutaneous adverse reactions (SCARs)	Anti-CTLA4, anti-PD1 and anti-PD-L1
Chimeric antigen receptor modified T lymphocytes (CAR-T cell) therapy	Rash (cytokine releasing syndrome [CRS])	CAR-T cell therapy
Radiation therapy	Radiation dermatitis (RD)	Ionized radiation
Hematopoietic stem cell transplantation (HSCT)	Cutaneous graft-versus-host disease (GVHD)	HSCT
Other cutaneous adverse reactions from cancer treatment	Skin infections associated with anticancer treatment (63)	
	Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	SJS: Bendamustine TEN: Bendamustine, busulfan, chlorambucil, fludarabine, lomustine, and procarbazine (Food and Drug Administration Adverse Event Reporting System [FAERS])

apoptosis of keratinocytes induced by cytotoxic chemotherapeutic agents or accumulation of metabolites, which may be enhanced on palms and soles through the transport of sweat (12–14). The involvement of an inflammatory process mediated by the overexpression of cyclooxygenase 2 (COX-2) was also reported (15). HFS can significantly affect the patient's quality of life, limit daily activities, and often necessitates dose modification or even discontinuation of chemotherapy (16).

Acute Hypersensitivity Reactions

Immediate hypersensitivity reactions (IHSRs) usually occur during or shortly after infusion of the first two cycles of chemotherapy with a rapid onset, within minutes (17). The clinical manifestations vary, including nonspecific maculopapular rash, urticaria, angioedema, flushing, and pruritus, with or without constitutional symptoms and signs such as hypotension, dyspnea, or chills (17,18). IHSRs can present as life-threatening anaphylaxis, which requires clinical precautions.

Taxanes (docetaxel and paclitaxel) are most commonly associated with IHSRs with an incidence of 30%, if without premedication. Taxanes have been approved and frequently prescribed for the treatment of metastatic or locally advanced breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancer, and ovarian cancers (1,17–19). The underlying mechanism is suggested to be related to a hypersensitivity reaction to the solvent for paclitaxel (Cremophor EL®, castor oil vehicle), whereas the solvent for docetaxel (Tween 80, polyoxyethylene-20-sorbitan monooleate) is less frequently implicated (20). Platinum-based agent-induced IHSRs are also observed in 12–24% of patients (21).

Extravasation Reactions

Extravasation reactions occur in 0.1–6% of patients receiving chemotherapy. The severity varies by the volume, concentration, and type of chemotherapeutic agent. The causative agents include irritants (such as platinum-based alkylating agents, taxanes, and topoisomerase inhibitors) and vesicants (such as anthracyclines, vinca alkaloids, and nitrogen mustards) (17,22). Irritants usually cause milder

TABLE 1.2

CTCAE Grading of Dermatologic Adverse Events Associated with Anticancer Therapies

Grading and Treatment Algorithms for Dermatologic AEs from Cancer Treatments					
	Grading				
Adverse Events	**1**	**2**	**3**	**4**	**5**
Severity	Mild	Moderate	Severe or medically significant but not immediately life-threatening	Life-threatening consequences	Death
Description	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]	Urgent intervention indicated	Death related to AE
Hand-foot syndrome (HFS) (palmar-plantar erythrodysesthesia syndrome): A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL		
Rash acneiform (PPE): A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest, and back	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Rash maculopapular: A disorder characterized by the presence of macules (flat) and papules (elevated); also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL		

(*Continued*)

TABLE 1.2 (*Continued*)

CTCAE Grading of Dermatologic Adverse Events Associated with Anticancer Therapies

Grading and Treatment Algorithms for Dermatologic AEs from Cancer Treatments					
	Grading				
Adverse Events	**1**	**2**	**3**	**4**	**5**
Pruritus: A disorder characterized by an intense itching sensation	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated		
Dry skin: A disorder characterized by flaky and dull skin; the pores are generally fine; the texture is a papery thin texture	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		
Photosensitivity: A disorder characterized by an increase in sensitivity of the skin to light	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10–30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Alopecia: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact			

(*Continued*)

TABLE 1.2 (*Continued*)

CTCAE Grading of Dermatologic Adverse Events Associated with Anticancer Therapies

Grading and Treatment Algorithms for Dermatologic AEs from Cancer Treatments					
	Grading				
Adverse Events	**1**	**2**	**3**	**4**	**5**
Hand-foot skin reaction (HFSR): A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	—	—
Radiation dermatitis	Faint erythema or dry desquamation (55)	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema (55)	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion (55)	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site (55)	

Source: Adapted from the Common Terminology Criteria for Adverse Events (CTCAE) grading scale: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Note: A long dash (—) indicates a grade is not available. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection. Grade 5 (death) is not appropriate for some AEs, and therefore, is not an option. ADL, activities of daily living. BSA, body surface area.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

inflammatory reaction with the presentation of erythema, edema, and pain. Vesicants can lead to a more severe effect including blister formation, ulceration, and tissue necrosis (23).

Pigmentary Changes

Alkylating agents such as nitrogen mustards (cyclophosphamide, ifosfamide), alkyl sulfonate (busulfan), and nitrosoureas (fotemustine) are commonly reported to result in mucocutaneous hyperpigmentation. Bleomycin, 5-FU, vinorelbine, and docetaxel are also known to cause hyperpigmentation. These skin conditions usually resolve spontaneously and discontinuation of chemotherapy may not be needed (24). Cyclophosphamide and ifosfamide may cause localized hyperpigmentation of the nails, palms, and soles (25,26), whereas busulfan may induce an Addison-like generalized skin hyperpigmentation. Characteristic flagellate hyperpigmentation occurs in 20% of patients treated with bleomycin (27,28). Serpentine supravenous hyperpigmentation is associated with 5-FU, vinorelbine, fotemustine, and docetaxel (29,30).

Hair and Nail Changes

Nail Toxicities

Overall incidence of skin, nail, and hair side effects to chemotherapeutic agents, including taxanes (46%), PLD (7%), other anthracyclines (19%), topotecan (14%), and other agents (14%), is reported to be 86.8%, and among them 23.1% developed nail changes (6). Cytotoxic chemotherapeutic agents can damage the nail matrix and cause transverse ridges across the nail plate, that is, Beau's lines, which are usually self-limited (31). Onycholysis occurs when the nail bed is involved. Pain, paronychia, granulation tissue growth, nail loss, and secondary bacterial infection with abscess formation may complicate onycholysis which can affect the patient's activities of daily living and quality of life (32). Common nail changes related to chemotherapy also include brittle nails, discoloration, splinter hemorrhage, subungual hematoma, and hyperpigmentation (32).

Chemotherapy-Induced Alopecia

Sixty-five percent of patients receiving chemotherapy are estimated to have chemotherapy-induced alopecia (CIA). CIA has been considered the most traumatic impact of chemotherapy by 47% of female patients (33). Taxanes including docetaxel and paclitaxel and anthracyclines are among the most common CIA-inducing agents (33–36). Risk factors include prolonged treatment, higher doses, or multiple exposures (33,37).

Chemotherapy-Induced Reversible Alopecia

Anagen effluvium is a common cause of chemotherapy-induced acute reversible alopecia and typically occurs after the first 4 treatment cycles (37). Any hair-bearing areas including scalp hair, eyelashes, eyebrows, beard, axillae, pubic, and body hair can be involved. Regrowth of hair may be seen 3–6 months after the completion of chemotherapy; however, one-third of patients may experience a decreased amount of hair regrowth and texture and color changes (35).

Persistent Chemotherapy-Induced Alopecia

Persistent chemotherapy-induced alopecia (pCIA) is used to describe the incomplete or absence of hair regrowth lasting longer than 6 months after the cessation of chemotherapy (34). pCIA usually manifests as diffuse hair loss or hair thinning, which tends to be accentuated in vertex areas with clinical features similar to androgenetic alopecia (35,38–42). Eyelashes, eyebrows, axillae, pubic, and body hair can also be affected (39,40,43). Busulfan, thiotepa, fluorouracil/epirubicin/cyclophosphamide (FEC), and taxanes have been reported to cause pCIA (39,40,42). The incidence of pCIA in patients treated with docetaxel was estimated to be around 2% by Kluger et al. but was believed to be underestimated (39). The pathomechanism of pCIA is unclear. A separation of the matrix cells from the dermal papilla and a direct cytotoxic action of taxanes on hair matrix keratinocytes or hair bulge stem cells has been hypothesized (34,39,40).

Radiation Recall

Radiation recall is an acute inflammatory reaction confined to previously irradiated areas triggered by chemotherapy. Doxorubicin, taxanes, 5-FU, gemcitabine, and capecitabine were most commonly reported to be associated with radiation recall phenomenon (44). The incidences are drug dependent and vary from 1.8% to 11.5% (23,45,46). The latency period for radiation recall ranges from several months to years (45,46). Although the pathogenesis remains unclear, a cytotoxic chemotherapy-induced, memory cell–mediated hypersensitivity reaction may play a role (44,47).

Targeted Anticancer Therapy

Targeted therapies achieve anticancer effects through inhibition of specific signaling pathways that play a central role in tumor growth; these include the epidermal growth factor receptor (EGFR) and the intracellular mitogen-activated protein kinase (MAPK) or RAS-RAF-MEK-MAPK pathway (48,49). The emerging profile of dermatologic AEs to targeted anticancer therapies differs from that of cytotoxic chemotherapy. However, the potential to cause dose reduction, discontinuation of anticancer therapy, and impairment of quality of life remain, and may compromise clinical outcomes (50). Therefore, a comprehensive knowledge of prevention, diagnosis, and management of these dermatologic AEs is of paramount importance. Dermatologic AEs have been well characterized for tyrosine kinase inhibitors (TKIs) targeting the EGFR or vascular endothelial growth factor receptor (VEGFR) pathways with various incidences and severity depending on specific targeted therapies and different doses (23,51–54). Common dermatologic AEs related to targeted therapies include acneiform rash, hand-foot skin reaction, xerosis, pruritus, mucositis, alopecia, skin tumors, pigmentary change, and hair and nail disorders (50).

EGFR Inhibitors

EGFR inhibitors (EGFRIs) have been used in broad clinical settings based on individual mutations of the tumor, including advanced or metastatic non-small cell lung cancer (gefitinib, erlotinib, afatinib, osimertinib, necitumumab), pancreatic cancer (erlotinib), breast cancer (lapatinib, neratinib), colon cancer (cetuximab, panitumumab), and head and neck cancer (cetuximab) (23,49,54). Skin toxicities are the most common EGFRI-related AEs, and can manifest as papulopustular eruption (PPE; acneiform rash), xerosis, pruritus, hair, nail, and periungual abnormalities (23,51,52,55). These dermatologic AEs may be painful and debilitating, and may negatively impact treatment intensity, patients' activities of daily living and quality of life (56).

Papulopustular Eruption or Acneiform Eruption

An acneiform rash is the most common dermatologic AE of EGFRI treatment, affecting up to 90% of patients (55). EGFRIs not only inhibit specific signaling pathways on cancer cells but also interfere with signal transduction in normal tissues such as epidermal keratinocytes, sebaceous glands, hair follicle epithelium, and periungual tissues, leading to dermatologic toxicities (23,51,54).

PPE manifests as acneiform follicular and perifollicular papules and sterile pustules on mainly seborrheic areas (face, scalp, and upper trunk), often associated with xerosis and pruritus or even pain (57,58). Skin eruptions are usually transient, appearing in the first few weeks; however, xerosis, pruritus, postinflammatory erythema or hyperpigmentation may persist even after cessation of treatment (56,59).

The development of skin toxicity to EGFRIs was reported to be associated with a favorable cancer prognosis (60). A meta-analysis showed that the presence of rash is associated with a 60% decrease in mortality and a 55% decrease in risk of disease progression in patients with non-small cell lung cancer (60,61).

Pigmentary Changes

A systematic review showed the overall incidences of targeted therapy-induced pigmentary changes of skin and hair were 17.7% and 21.5%, respectively. EGFRI and imatinib were reported to be the most common culprits (62).

Hair and Nail Changes

Paronychia, that is periungual erythema, swelling, pain, with or without periungual pyogenic granuloma-like lesions can develop 2–3 months after the initiation of EGFRI therapy with an incidence varying with different EGFRIs between 12% and 58% (52,63). The lesion is initially sterile but can become superinfected (23). The hypothesized mechanism is periungual inflammation induced by keratinocyte damage and cytokine dysregulation, an effect that may be aggravated by ingrown nails and local trauma (23). Changes in hair texture and color, nonscarring and scarring alopecia, facial hypertrichosis, and eyelash trichomegaly may be seen.

Mammalian Target of Rapamycin Inhibitors

The phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signaling pathway is upregulated in multiple malignancies. Dermatologic AEs to mTOR inhibitors, such as temsirolimus and everolimus, are common and include stomatitis, eruptions, and nail changes, including paronychia. mTOR inhibitor–related stomatitis has been reported in 44% of patients and differs from that associated with chemotherapy by presenting as discrete aphthae on nonkeratinizing epithelium (64). Skin eruptions can be seen in one-third of the patients and usually present a maculopapular or papulopustular rash similar to EGFRI-induced PPE (64), which are thought to be related to the inhibition of the PI3K-Akt-mTOR signaling, one of the downstream effector pathways of the EGFR (50).

Multitargeted Kinase Inhibitors

The multitargeted kinase inhibitors (MKIs) such as imatinib, sorafenib, sunitinib, regorafenib, axitinib, and pazopanib achieve their anticancer effects by interfering with molecular signaling pathways involved in cell growth and angiogenesis (65). Dermatologic AEs are most commonly reported in patients receiving MKIs and share overlapping features due to the commonalities among these targeted signaling pathways (23,66,67).

Hand-Foot Skin Reaction

Hand-foot skin reaction (HFSR) is one of the most common dermatologic AEs occuring in 9–62% of patients receiving MKIs such as sorafenib, sunitinib, regorafenib, axitinib, and pazopanib (48,65,68–75). Symmetrical acral erythema associated with desquamation and fissures, followed by hyperkeratosis (presenting as yellowish painful plaques surrounded by an erythematous/edematous halo on pressure areas of the sole) with occasional blister formation is a characteristic feature of HFSR (68).

The proposed mechanism of HFSR include direct pressure and friction to the palms and soles causing the blistering and capillary endothelial damage; disruption of endothelial healing by inhibition of VEGFR and PDGFR; and direct cytotoxic effect to keratinocytes related to dysregulation of the Fas/FasL signaling pathway (48,65,71).

BRAF Inhibitors

BRAF is a serine–threonine protein kinase functioning in the RAS-RAF-MEK-MAPK signaling pathway that regulates cellular proliferation, differentiation, migration, survival, and apoptosis (48,53,76,77). BRAF is mutated in approximately 40–60% of cutaneous melanomas and one of the most frequently mutated protein kinases found in human cancers including hairy cell leukemia, papillary thyroid, serous ovarian, colorectal, and prostate cancers (64).

Dermatologic AEs are one of the most significant and frequent AEs associated with the use of vemurafenib and dabrafenib, occurring in up to 95% of patients (77,78) with a distinct profile including maculopapular rash, photosensitivity, hyperkeratotic lesions, or skin tumors (53). Paradoxical activation of wild-type BRAF cells or cells that harbor a RAS mutation that potentiates the activity of the MAPK pathway results in subsequent keratinocyte proliferation or tumor formation (53,76,77).

Skin Rashes

Rashes are the most common dermatologic AEs, affecting 64–75% of patients treated with BRAFIs, more commonly with vemurafenib than with dabrafenib. A variety of skin rashes can be seen in patients receiving BRAFIs including maculopapular rash (MPR), papulopustular eruption (PPE), or keratosis pilaris (KP)-like skin eruption on the proximal limbs, trunk, and face (5–9%) (79); folliculocentric rashes with or without pruritus (53), and HFSR (80). The occurrence of skin rashes is often within 2 weeks after initiation of treatment.

Photosensitivity

Photosensitivity is a well-known AE occurring in 30–52% of patients receiving vemurafenib, manifesting as acute-onset erythema, burning, and painful blistering with a predilection to sun-exposed areas (53).

Nonmalignant Hyperkeratotic Skin Eruptions

Squamoproliferative/keratinocytic lesions may affect 60–85% patients receiving BRAFIs. Verrucal keratosis is the most common presentation seen in >60% of patients and usually appears early within weeks in the treatment course (53,76,77). Other lesions include palmar/plantar hyperkeratosis over pressure or friction points (40%), skin papillomas, verruca vulgaris, seborrheic keratoses (SKs), warty dyskeratomas, inflamed actinic keratoses (AKs), and keratoacanthomas (KAs) (53).

Cutaneous Squamous Cell Carcinomas

Cutaneous squamous cell carcinomas (SCCs), usually KA type, presenting as rapid-growing, dome-shaped crateriform nodules on sun-exposed skin areas (4–36%) (53,76,77), usually appear early after initiation of BRAFIs such as vemurafenib, with a median onset of 8 weeks (53).

MEK Inhibitors

Upstream mutations at the level of EGFR, RAS, or BRAF can drive constitutive activation within the RAS-RAF-MEK-MAPK pathway, converging on MEK proteins leading to tumor growth (64). Dermatologic AEs of MEK inhibitors (MEKIs), such as trametinib and cobimetinib, share a similar spectrum with that of EGFRIs, including PPE, xerosis, pruritus, alopecia, paronychia, hyperpigmentation, trichomegaly of eyelashes, changes in hair texture, and hypertrichosis of face. PPE is the most common dermatologic AE of MEKIs occurring in 52–93% of treated patients. Secondary bacterial infection to the affected skin area is not uncommon (77,81).

BRAF Inhibitors plus MEK Inhibitors

Combination therapy of a BRAFI plus a MEKI seems to show an improved skin toxicity profile than a BRAFI alone due to the effect of downstream MEK inhibition on the paradoxical activation of the MAPK pathway by BRAF inhibitors (64). The combination of dabrafenib with trametinib showed a significant decrease of incidence of cutaneous SCCs (0% versus 26.1%), verrucal keratosis, and Grover's disease compared to that of dabrafenib alone, but a higher frequency of folliculitis (40% versus 6.7%) (76,77,82,83).

Hedgehog Pathway Inhibitors (Vismodegib, Sonidegib)

Abnormal activation of hedgehog pathway signaling is a key driver in the pathogenesis of basal cell carcinoma (BCC). Vismodegib and sonidegib, small molecule inhibitors of hedgehog pathway signaling, are approved for the treatment of adults who have metastatic BCC or locally advanced BCC in selected patients. Commonly observed AEs include muscle spasms, ageusia/dysgeusia, alopecia, weight loss, and fatigue (84).

Alopecia is a common dermatologic AE to hedgehog pathway inhibitors affecting 46–66% of treated patients and has a relatively delayed onset than that with cytotoxic chemotherapy, developing

after 2 months of treatment (84–87). The mechanism may be related to the important role that the hedgehog pathway plays in the normal hair follicle cycle. Follicle-based toxicities, such as alopecia and folliculitis, are hypothesized to be possible surrogate markers of tumor response (85). Follicular dermatitis, hypersensitivity reaction, KAs, and cutaneous SCCs have also been reported (84–91).

Immune Checkpoint Inhibitors

The cytotoxic T lymphocyte antigen-4 (CTLA-4) signaling pathway, and the programmed cell death receptor-1 (PD-1)/PD ligand-1 (PD-L1) signaling pathway are immune checkpoints of immunologic homeostasis and tumor-induced immune suppression (92). As immune checkpoint inhibitors (ICIs) restore antitumor immunity by interrupting the inhibitory signals and immune escape mechanisms induced by tumor cells, they may concurrently induce autoimmunity and inflammation of various organ systems, most commonly the skin, gastrointestinal tract, endocrine glands, and liver, referred to as immune-related adverse events (irAEs) (93–95).

The precise pathogenesis underlying dermatologic irAEs remains to be elucidated. Possible mechanisms include increasing T-cell activity against common antigens that are presented in both tumors and healthy tissue, for example, vitiligo; increasing levels of preexisting autoantibodies, for example, bullous pemphigoid; and increasing levels of inflammatory cytokines, for example, psoriasis and psoriasiform rash (95).

Pruritus, Rash, and Vitiligo

Immune-related dermatologic AEs are among the earliest and most common AEs of ICIs, which include pruritus, rash, and vitiligo. Vitiligo is more frequently seen in patients with melanoma (94,96–98). Autoimmune bullous dermatoses (99), lichenoid dermatitis/mucositis, exacerbated psoriasis, psoriasiform rash, alopecia areata/universalis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrosis (TEN) have been anecdotally reported (93,98,100–104). Increasing evidence suggest that vitiligo and/or rash developing during ICI treatments are correlated to favorable clinical outcomes (92,103,105–107).

Bullous Pemphigoid

Bullous pemphigoid (BP) may develop in patients receiving an anti-PD1/PD-L1 treatment and is thought to be mediated by both T-cell and B-cell immunity (99,108). BP associated with ICIs may occur accompanied or preceded by pruritus within months after the initiation of ICIs, and may persist after cessation of treatment. Skin biopsy, direct and indirect immunofluorescence study of skin and serum autoantibodies such as anti-BP180 and anti-BP230 may be helpful for diagnosis (99).

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs) are rare, but SJS, TEN, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome associated with ICIs were reported in the literature (109–111). A comprehensive review of clinical and drug history is necessary for accurate diagnosis and attribution of the culprit.

Chimeric Antigen Receptor-Modified T Lymphocytes Therapy

Adoptive cell therapy is a powerful and promising approach to cancer therapy. Cytokine release syndrome (CRS) can be observed shortly after administration of chimeric antigen receptor-modified T lymphocytes (CAR-T cell) therapy (92). Autoimmunity induced by administered T cells may occur when a T-cell receptor (TCR) targeting a protein is expressed in normal tissue, for example, when proteins of melanocytic origin are targeted with TCRs against melanoma antigen recognized by T cells 1 (MART-1) and glycoprotein 100, cutaneous, ocular, and internal ear toxicities occur (92).

Radiation Therapy

Radiation Dermatitis

Radiation dermatitis often occurs approximately 2–3 weeks after the initiation of radiotherapy (112). Acute radiation dermatitis, usually manifesting as erythema, dry and moist desquamation, and ulceration,

is self-limiting and usually resolves after 2–3 months. Late toxicities usually occur later in the treatment course at greater than 90 days. Skin lesions include telangiectasia, atrophy, fibrosis, edema, and ulceration, which may persist and result in a prolonged negative impact on a patient's quality of life (55,112,113).

Hematopoietic Stem Cell Transplantation

Cutaneous Graft-versus-Host Disease

Graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients with an incidence of 40–60%, and accounts for 15% of treatment-related deaths (114,115). Cutaneous GVHD is the most common to appear, affecting 60–80% of patients, which can result in long-term complications such as cosmetic, functional, and even life-threatening sequelae (114,115). Characteristic manifestations of cutaneous GVHD are poikiloderma, lichen planus–like eruptions, lichen sclerosus–like lesions, morphea-like sclerosis, and deep sclerosis or fasciitis (114).

Conclusion

Maintaining patients on an anticancer treatment is critical for cancer survival. The rapid development of novel therapies brings promising anticancer efficacy along with a wide variety of undesirable AEs. Dermatologic AEs are among the most frequently observed and may seriously impair patients' quality of life. Increasing evidence suggests that these dermatologic AEs are preventable and manageable by comprehensive pretreatment counseling, preemptive treatment, early diagnosis, and proper management. Dermatologists play a critical role in minimizing the impact of dermatologic AEs. Early and prompt dermatology referral and a multidiscipline team including dermatologists are beneficial for optimal cancer care.

REFERENCES

1. Giavina-Bianchi P, Patil SU, Banerji A. Immediate hypersensitivity reaction to chemotherapeutic agents. *J Allergy Clin Immunol Pract* 2017;5(3):593–9.
2. Santoni M et al. Risk of pruritus in cancer patients treated with biological therapies: A systematic review and meta-analysis of clinical trials. *Crit Rev Oncol Hematol* 2015;96(2):206–19.
3. Lacouture ME. Management of dermatologic toxicities. *JNCCN* 2015;13(5 Suppl):686–9.
4. Bolognia JL, Cooper DL, Glusac EJ. Toxic erythema of chemotherapy: A useful clinical term. *J Am Acad Dermatol* 2008;59(3):524–9.
5. Parker TL, Cooper DL, Seropian SE, Bolognia JL. Toxic erythema of chemotherapy following i.v. BU plus fludarabine for allogeneic PBSC transplant. *Bone Marrow Transplant* 2013;48(5):646–50.
6. Hackbarth M, Haas N, Fotopoulou C, Lichtenegger W, Sehouli J. Chemotherapy-induced dermatological toxicity: Frequencies and impact on quality of life in women's cancers. Results of a prospective study. *Support Care Cancer* 2008;16(3):267–73.
7. Saif MW, Katirtzoglou NA, Syrigos KN. Capecitabine: An overview of the side effects and their management. *Anti-Cancer Drugs* 2008;19(5):447–64.
8. Chew L, Chuen VS. Cutaneous reaction associated with weekly docetaxel administration. *J Oncol Pharm Pract: ISOPP* 2009;15(1):29–34.
9. Balagula Y, Rosen ST, Lacouture ME. The emergence of supportive oncodermatology: The study of dermatologic adverse events to cancer therapies. *J Am Acad Dermatol* 2011;65(3):624–35.
10. Lorusso D, Di Stefano A, Carone V, Fagotti A, Pisconti S, Scambia G. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). *Ann Oncol: ESMO* 2007;18(7):1159–64.
11. von Moos R et al. Pegylated liposomal doxorubicin-associated hand-foot syndrome: Recommendations of an international panel of experts. *Eur J Cancer* 2008;44(6):781–90.
12. Chen M et al. The contribution of keratinocytes in capecitabine-stimulated hand-foot-syndrome. *Environ Toxicol Pharmacol* 2017;49:81–8.
13. Yang J et al. The role of the ATM/Chk/P53 pathway in mediating DNA damage in hand-foot syndrome induced by PLD. *Toxicol Lett* 2017;265:131–9.

14. Lou Y et al. Possible pathways of capecitabine-induced hand-foot syndrome. *Chem Res Toxicol* 2016;29(10):1591–601.
15. Zhang RX et al. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: Result of a single-center, prospective randomized phase III trial. *Ann Oncol: ESMO* 2012;23(5):1348–53.
16. Nikolaou V, Syrigos K, Saif MW. Incidence and implications of chemotherapy related hand-foot syndrome. *Expert Opin Drug Saf* 2016;15(12):1625–33.
17. Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP. Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. *Curr Opin Oncol* 2016;28(4):254–63.
18. Syrigou E et al. Hypersensitivity reactions to docetaxel: Retrospective evaluation and development of a desensitization protocol. *Int Arch Allergy Immunol* 2011;156(3):320–4.
19. Aoyama T et al. Is there any predictor for hypersensitivity reactions in gynecologic cancer patients treated with paclitaxel-based therapy? *Cancer Chemother Pharmacol* 2017;80(1):65–9.
20. Gelmon K. The taxoids: Paclitaxel and docetaxel. *Lancet* 1994;344(8932):1267–72.
21. Park HJ et al. A new practical desensitization protocol for oxaliplatin-induced immediate hypersensitivity reactions: A necessary and useful approach. *J Investig Allergol Clin Immunol* 2016;26(3):168–76.
22. Langer SW. Extravasation of chemotherapy. *Curr Oncol Rep* 2010;12(4):242–6.
23. Kyllo R, Anadkat M. Dermatologic adverse events to chemotherapeutic agents, Part 1: Cytotoxic agents, epidermal growth factor inhibitors, multikinase inhibitors, and proteasome inhibitors. *Semin Cutan Med Surg* 2014;33(1):28–39.
24. Jain V, Bhandary S, Prasad GN, Shenoi SD. Serpentine supravenous streaks induced by 5-fluorouracil. *J Am Acad Dermatol* 2005;53(3):529–30.
25. Teresi ME, Murry DJ, Cornelius AS. Ifosfamide-induced hyperpigmentation. *Cancer* 1993;71(9): 2873–5.
26. Chittari K, Tagboto S, Tan BB. Cyclophosphamide-induced nail discoloration and skin hyperpigmentation: A rare presentation. *Clin Exp Dermatol* 2009;34(3):405–6.
27. Abess A, Keel DM, Graham BS. Flagellate hyperpigmentation following intralesional bleomycin treatment of verruca plantaris. *Arch Dermatol* 2003;139(3):337–9.
28. Vuerstaek JD, Frank J, Poblete-Gutierrez P. Bleomycin-induced flagellate dermatitis. *Int J Dermatol* 2007(46 Suppl 3):3–5.
29. Huang V, Anadkat M. Dermatologic manifestations of cytotoxic therapy. *Dermatol Ther* 2011;24(4): 401–10.
30. Suvirya S, Agrawal A, Parihar A. 5-Fluorouracil-induced bilateral persistent serpentine supravenous hyperpigmented eruption, bilateral mottling of palms and diffuse hyperpigmentation of soles. *BMJ Case Reports* 2014;2014.
31. Kyllo RL, Anadkat MJ. Dermatologic adverse events to chemotherapeutic agents, part 1: Cytotoxics, epidermal growth factor receptors, multikinase inhibitors, and proteasome inhibitors. *Semin Cutan Med Surg* 2014;33(1):28–39.
32. Capriotti K et al. The risk of nail changes with taxane chemotherapy: A systematic review of the literature and meta-analysis. *Br J Dermatol* 2015;173(3):842–5.
33. Trueb RM. Chemotherapy-induced hair loss. *Skin Therapy Lett* 2010;15(7):5–7.
34. Tallon B, Blanchard E, Goldberg LJ. Permanent chemotherapy-induced alopecia: Case report and review of the literature. *J Am Acad Dermatol* 2010;63(2):333–6.
35. Lindner J et al. Hair shaft abnormalities after chemotherapy and tamoxifen therapy in patients with breast cancer evaluated by optical coherence tomography. *Br J Dermatol* 2012;167(6):1272–8.
36. Nangia J et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: The SCALP randomized clinical trial. *JAMA* 2017;317(6):596–605.
37. Trueb RM. Chemotherapy-induced anagen effluvium: Diffuse or patterned? *Dermatology* 2007; 215(1):1–2.
38. Fonia A, Cota C, Setterfield JF, Goldberg LJ, Fenton DA, Stefanato CM. Permanent alopecia in patients with breast cancer after taxane chemotherapy and adjuvant hormonal therapy: Clinicopathologic findings in a cohort of 10 patients. *J Am Acad Dermatol* 2017;76(5):948–57.
39. Kluger N et al. Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: A prospective study of 20 patients. *Ann Oncol: ESMO* 2012;23(11):2879–84.

40. Miteva M, Misciali C, Fanti PA, Vincenzi C, Romanelli P, Tosti A. Permanent alopecia after systemic chemotherapy: A clinicopathological study of 10 cases. *Am J Dermatopathol* 2011;33(4):345–50.
41. Asz-Sigall D, Gonzalez-de-Cossio-Hernandez AC, Rodriguez-Lobato E, Ortega-Springall MF, Vega-Memije ME, Arenas Guzman R. Differential diagnosis of female-pattern hair loss. *Skin Appendage Disord* 2016;2(1–2):18–21.
42. Palamaras I, Misciali C, Vincenzi C, Robles WS, Tosti A. Permanent chemotherapy-induced alopecia: A review. *J Am Acad Dermatol* 2011;64(3):604–6.
43. Prevezas C, Matard B, Pinquier L, Reygagne P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009;160(4):883–5.
44. Burris HA, 3rd, Hurtig J. Radiation recall with anticancer agents. *Oncologist* 2010;15(11):1227–37.
45. Sanborn RE, Sauer DA. Cutaneous reactions to chemotherapy: Commonly seen, less described, little understood. *Dermatol Clin* 2008;26(1):103–19, ix.
46. Wyatt AJ, Leonard GD, Sachs DL. Cutaneous reactions to chemotherapy and their management. *Am J Clin Dermatol* 2006;7(1):45–63.
47. Korman AM, Tyler KH, Kaffenberger BH. Radiation recall dermatitis associated with nivolumab for metastatic malignant melanoma. *Int J Dermatol* 2017;56(4):e75–7.
48. Belum VR, Fontanilla Patel H, Lacouture ME, Rodeck U. Skin toxicity of targeted cancer agents: Mechanisms and intervention. *Future Oncol* 2013;9(8):1161–70.
49. Tang N, Ratner D. Managing cutaneous side effects from targeted molecular inhibitors for melanoma and nonmelanoma skin cancer. *Dermatol Surg* 2016;42(Suppl 1):S40–8.
50. Belum VR, Washington C, Pratilas CA, Sibaud V, Boralevi F, Lacouture ME. Dermatologic adverse events in pediatric patients receiving targeted anticancer therapies: A pooled analysis. *Pediatr Blood Cancer* 2015;62(5):798–806.
51. Lacouture ME, Ciccolini K, Kloos RT, Agulnik M. Overview and management of dermatologic events associated with targeted therapies for medullary thyroid cancer. *Thyroid* 2014;24(9):1329–40.
52. Lacouture ME et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer* 2011;19(8):1079–95.
53. Belum VR, Fischer A, Choi JN, Lacouture ME. Dermatological adverse events from BRAF inhibitors: A growing problem. *Curr Oncol Rep* 2013;15(3):249–59.
54. Tischer B, Huber R, Kraemer M, Lacouture ME. Dermatologic events from EGFR inhibitors: The issue of the missing patient voice. *Support Care Cancer* 2017;25(2):651–60.
55. Lacouture ME et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Support Care Cancer* 2010;18(4):509–22.
56. Hofheinz RD et al. Recommendations for the prophylactic management of skin reactions induced by epidermal growth factor receptor inhibitors in patients with solid tumors. *Oncologist* 2016;21(12):1483–91.
57. Hsiao YW, Lin YC, Hui RC, Yang CH. Fulminant acneiform eruptions after administration of dovitinib in a patient with renal cell carcinoma. *J Clin Oncol* 2011;29(12):e340–1.
58. Drilon A et al. Beyond the dose-limiting toxicity period: Dermatologic adverse events of patients on phase 1 trials of the cancer therapeutics evaluation program. *Cancer* 2016;122(8):1228–37.
59. Clabbers JMK et al. Xerosis and pruritus as major EGFRI-associated adverse events. *Support Care Cancer* 2016;24(2):513–21.
60. Liu HB et al. Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: A systematic review and meta-analysis. *PLoS One* 2013;8(1):e55128.
61. Lacouture ME 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):1351–7.
62. Dai J, Belum VR, Wu S, Sibaud V, Lacouture ME. Pigmentary changes in patients treated with targeted anticancer agents: A systematic review and meta-analysis. *J Am Acad Dermatol* 2017;77(5):902–10.e2.
63. Gandhi M, Brieva JC, Lacouture ME. Dermatologic infections in cancer patients. *Cancer Treat Res* 2014;161:299–317.
64. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol* 2015;72(2):221–36, quiz 37–8.
65. Lacouture ME et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist* 2008;13(9):1001–11.

66. Valentine J et al. Incidence and risk of xerosis with targeted anticancer therapies. *J Am Acad Dermatol* 2015;72(4):656–67.
67. Ensslin CJ, Rosen AC, Wu S, Lacouture ME. Pruritus in patients treated with targeted cancer therapies: Systematic review and meta-analysis. *J Am Acad Dermatol* 2013;69(5):708–20.
68. Gomez P, Lacouture ME. Clinical presentation and management of hand-foot skin reaction associated with sorafenib in combination with cytotoxic chemotherapy: Experience in breast cancer. *Oncologist* 2011;16(11):1508–19.
69. Lacouture ME, Reilly LM, Gerami P, Guitart J. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. *Ann Oncol: ESMO* 2008;19(11):1955–61.
70. Lacouture ME et al. Dermatologic adverse events associated with afatinib: An oral ErbB family blocker. *Expert Rev Anticancer Ther* 2013;13(6):721–8.
71. Yeh CN et al. Fas/Fas ligand mediates keratinocyte death in sunitinib-induced hand-foot skin reaction. *J Invest Dermatol* 2014;134(11):2768–75.
72. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: A meta-analysis. *Investig New Drugs* 2013;31(4):1078–86.
73. Fischer A, Wu S, Ho AL, Lacouture ME. The risk of hand-foot skin reaction to axitinib, a novel VEGF inhibitor: A systematic review of literature and meta-analysis. *Investig New Drugs* 2013;31(3):787–97.
74. McLellan B, Ciardiello F, Lacouture ME, Segaert S, Van Cutsem E. Regorafenib-associated hand-foot skin reaction: Practical advice on diagnosis, prevention, and management. *Ann Oncol: ESMO* 2015;26(10):2017–26.
75. Balagula Y, Wu S, Su X, Feldman DR, Lacouture ME. The risk of hand foot skin reaction to pazopanib, a novel multikinase inhibitor: A systematic review of literature and meta-analysis. *Investig New Drugs* 2012;30(4):1773–81.
76. Carlos G et al. Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma. *JAMA Dermatol* 2015;151(10):1103–9.
77. Choi JN. Dermatologic adverse events to chemotherapeutic agents, Part 2: BRAF inhibitors, MEK inhibitors, and ipilimumab. *Semin Cutan Med Surg* 2014;33(1):40–8.
78. Belum VR, Cercek A, Sanz-Motilva V, Lacouture ME. Dermatologic adverse events to targeted therapies in lower GI cancers: Clinical presentation and management. *Curr Treat Options Oncol* 2013;14(3):389–404.
79. Pugliese SB, Neal JW, Kwong BY. Management of dermatologic complications of lung cancer therapies. *Curr Treat Options Oncol* 2015;16(10):50.
80. Chandrakumar SF, Yeung J. Cutaneous adverse events during vemurafenib therapy. *J Cutan Med Surg* 2014;18(4):223–8.
81. Balagula Y, Barth Huston K, Busam KJ, Lacouture ME, Chapman PB, Myskowski PL. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). *Investig New Drugs* 2011;29(5):1114–21.
82. Dreno B et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. *Ann Oncol: ESMO* 2017;28(5):1137–44.
83. Keating GM. Cobimetinib plus vemurafenib: A review in BRAF (V600) mutation-positive unresectable or metastatic melanoma. *Drugs* 2016;76(5):605–15.
84. Lacouture ME et al. Characterization and management of hedgehog pathway inhibitor-related adverse events in patients with advanced basal cell carcinoma. *Oncologist* 2016;21(10):1218–29.
85. Kwong B, Danial C, Liu A, Chun KA, Chang AL. Reversible cutaneous side effects of vismodegib treatment. *Cutis* 2017;99(3):19–20.
86. LoRusso PM et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. *Clin Cancer Res* 2011;17(8):2502–11.
87. Sekulic A et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer* 2017;17(1):332.
88. Aasi S et al. New onset of keratoacanthomas after vismodegib treatment for locally advanced basal cell carcinomas: A report of 2 cases. *JAMA Dermatol* 2013;149(2):242–3.
89. Sekulic A et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012;366(23):2171–9.
90. U.S. Food and Drug Administration. Vismodegib. January 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203388lbl.pdf. Accessed June 26, 2017.

91. European Medicines Agency. European Public Assessment Report: Erivedge. October 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002602/WC500146821.pdf.
92. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol* 2015;33(18):2092–9.
93. Michot JM et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *Eur J Cancer* 2016;54:139–48.
94. Wolchok JD et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol* 2010;11(2):155–64.
95. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;378(2):158–68.
96. Larsabal M et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol* 2017;76(5):863–70.
97. Belum VR et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer* 2016;60:12–25.
98. Robert C et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015;372(26):2521–32.
99. Naidoo J et al. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res* 2016;4(5):383–9.
100. Damsky W, King BA. JAK inhibitors in dermatology: The promise of a new drug class. *J Am Acad Dermatol* 2017;76(4):736–44.
101. Shreberk-Hassidim R, Ramot Y, Zlotogorski A. Janus kinase inhibitors in dermatology: A systematic review. *J Am Acad Dermatol* 2017;76(4):745–53.e19.
102. Sibaud V et al. Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: Clinicopathological findings. *J Eur Acad Dermatol Venereol* 2017;31(10):e464–9.
103. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS, MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: Detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer* 2013;119(9):1675–82.
104. Curry JL et al. Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. *J Cutan Pathol* 2017;44(2):158–76.
105. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: Characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res* 2016;22(4):886–94.
106. Goldinger SM et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res* 2016;22(16):4023–9.
107. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30(21):2691–7.
108. Jour G et al. Autoimmune dermatologic toxicities from immune checkpoint blockade with anti-PD-1 antibody therapy: A report on bullous skin eruptions. *J Cutan Pathol* 2016;43(8):688–96.
109. Nayar N, Briscoe K, Fernandez Penas P. Toxic epidermal necrolysis-like reaction with severe satellite cell necrosis associated with nivolumab in a patient with ipilimumab refractory metastatic melanoma. *J Immunother* 2016;39(3):149–52.
110. Johnson DB et al. Severe cutaneous and neurologic toxicity in melanoma patients during vemurafenib administration following anti-PD-1 therapy. *Cancer Immunol Res* 2013;1(6):373–7.
111. Voskens CJ et al. The price of tumor control: An analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One* 2013;8(1):e53745.
112. Wong RK et al. Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC skin toxicity study group. *Support Care Cancer* 2013;21(10):2933–48.
113. Shaitelman SF et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: A randomized clinical trial. *JAMA Oncol* 2015;1(7):931–41.
114. Hymes SR, Alousi AM, Cowen EW. Graft-versus-host disease: Part I. Pathogenesis and clinical manifestations of graft-versus-host disease. *J Am Acad Dermatol* 2012;66(4):515.e1–18, quiz 33–4.
115. Villarreal CD, Alanis JC, Perez JC, Candiani JO. Cutaneous graft-versus-host disease after hematopoietic stem cell transplant: A review. *Anais Brasileiros de Dermatologia* 2016;91(3):336–43.