



## Review

Dermatologic conditions in women receiving systemic cancer therapy<sup>☆</sup>Michelle N. Ferreira, BA<sup>1</sup>, Julie Y. Ramseier, BS<sup>1</sup>, Jonathan S. Leventhal, MD<sup>\*</sup>

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## ABSTRACT

As advances in cancer therapies have improved cancer-related survival, novel therapeutics have also introduced a variety of dermatologic toxicities, and an increased number of patients are living with these sequelae. Women with cancer in particular experience a spectrum of dermatologic conditions that affect their skin, hair, nail, and mucosal surfaces. Studies have shown that these toxic effects can significantly affect quality of life and alter a woman's self-image, cultural identity, femininity, sexuality, and mental health. In severe instances, dermatologic toxicities may even disrupt cancer therapy and can therefore affect overall survival and treatment response. In this article, we review the dermatologic adverse effects from traditional chemotherapy, targeted therapy, immune checkpoint inhibitors, and endocrine therapy that disproportionately affect women. The timely diagnosis and management of these dermatologic conditions is crucial in the multidisciplinary care of women with cancer.

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## Introduction

Over the past several decades, advances in oncologic therapies have revolutionized the management of patients with cancer. As a result, there has been a significant increase in cancer-related survival. In 1975, an estimated 3.6 million cancer survivors were living in the United States; in 2016, the number of cancer survivors increased to 15.5 million (Shapiro, 2018). With regard to patient sex, an estimated 878,980 female patients and 856,370 male patients were diagnosed with cancer in the United States in 2018; however, there were only an estimated 268,010 female cancer-related deaths compared with 323,630 male cancer-related deaths (Siegel et al., 2018a,b). Globally, this pattern of increased female survival has also been observed (Clocchiatti et al., 2016).

Patients with cancer undergo a variety of oncologic treatments, including surgery, radiation, traditional chemotherapy, targeted immune checkpoint inhibitor (ICPI) and endocrine therapies, and stem cell transplantation. Many of the pathways targeted by anticancer therapies are also important for skin, hair, mucosal, and nail homeostasis; therefore, dermatologic toxicities are among the most frequently encountered adverse effects. When severe, these conditions may result in interruption of cancer therapy, and late or persistent complications can arise. According to quality-of-life studies, women are affected to a greater degree than men by the toxic dermatologic effects of cancer therapy (Gandhi et al., 2010; Hackbarth et al., 2008; Lee et al., 2018; Ra et al., 2013), and these toxicities can affect a woman's self-image, cultural identity, femininity, sexuality, and mental health (Choi et al., 2014; Munstedt et al., 1997; Rosman, 2004). Recognition and management of these conditions in women demands increased attention.

In this review, we discuss the most common dermatologic toxicities associated with traditional chemotherapy, targeted therapy, ICPIs, and endocrine therapies (Table 1), with a special focus on malignancies and dermatologic conditions that predominantly affect women. We highlight the dermatologic toxicities associated with particular classes of oncologic drugs (Table 2) and the grading criteria of such toxicities (Table 3), and we review management strategies for prevention and treatment (Table 4). With timely diagnosis and management, dermatolo-

gists can play a pivotal role in the multidisciplinary care of women with cancer.

## Traditional chemotherapy

Due to the aggressive nature of breast, ovarian, and other gynecologic cancers and their propensities to relapse, women with these malignancies often receive cytotoxic chemotherapy that put them at increased risk for toxic changes in the hair, mucosa, nails, and skin (Can et al., 2013; Kayl and Meyers, 2006). For example, ovarian cancer often requires multiple courses of chemotherapy to achieve and maintain remission (Kayl and Meyers, 2006). Even certain forms of early stage breast cancer are treated with adjuvant cytotoxic chemotherapy. The most commonly used agents for breast, ovarian, and uterine cancers are taxanes (e.g., docetaxel, anthracyclines such as pegylated-liposomal doxorubicin [PLD], and antimetabolites such as capecitabine). These agents, which generally target rapidly dividing cells, are associated with a myriad of mucocutaneous toxicities due to the high turnover rate of epithelial cells in the skin, mucosa, and hair shaft. The most commonly encountered chemotherapy-induced dermatologic toxicities of cytotoxic drugs will be discussed, including alopecia, hand-foot syndrome (HFS), mucositis, and nail changes.

### Chemotherapy-induced alopecia

Chemotherapy-induced (CIA), often the most common and visually striking toxicity after chemotherapy, is a significant source of morbidity in women with cancer. A wide range of chemotherapeutic agents cause alopecia, with an incidence of up to 100% with topoisomerase inhibitors, 80% with antimicrotubule agents (e.g., taxanes and vinca alkaloids), 60% with alkylating agents, and 50% with antimetabolites (Trüeb, 2009). CIA occurs due to the high sensitivity of the rapidly dividing matrix keratinocytes in the hair shafts to chemotherapy. The follicles in the anagen phase, where 90% of scalp hairs usually reside, are affected most, resulting in anagen effluvium (Rubio-Gonzalez et al., 2018; Susser et al., 1999).

Studies have shown that women more frequently experience total CIA compared with men and report a more negative body image as well as lower psychological, social, physical, emotional, and general wellbeing than women who do not experience CIA

**Table 1**  
Categories of anticancer drugs, associated class, and oncologic indication.

Drug class	Drug name	Oncologic indication
<b>Traditional chemotherapy</b>		
<i>Antimetabolites</i>		
	5-fluorouracil	Gastrointestinal, breast, pancreatic
	Capecitabine	Gastrointestinal, breast, pancreatic
	Gemcitabine	Bladder, pancreatic, ovarian, breast, non-small cell lung
	Cytarabine	AML, ALL, CML, non-Hodgkin's lymphoma
	Cladribine	Hairy cell leukemia, CLL
	Methotrexate	Breast, head and neck, leukemia, lymphoma, lung, osteosarcoma, bladder
	Hydroxyurea	CML, cervical, polycythemia vera
	Mercaptopurine	ALL, CML
<i>Taxanes</i>		
	Docetaxel	Breast, head and neck, stomach, prostate, non-small-cell lung
	Paclitaxel	Ovarian, breast, lung, Kaposi sarcoma, cervical, pancreatic
	Nanoparticle albumin-bound (nab)-paclitaxel	Breast, lung, pancreatic
<i>Vinca alkaloids</i>		
	Vincristine	ALL, AML, Hodgkin's disease, neuroblastoma, small cell lung
	Vinblastine	Hodgkin's disease, non-small cell lung, bladder, brain, melanoma, testicular
<i>Alkylating agents</i>		
	Cyclophosphamide	Lymphomas, multiple myeloma, leukemia, ovarian, breast, small cell lung, neuroblastoma, sarcoma
	Ifosfamide	Testicular, soft tissue sarcoma, osteosarcoma, bladder, small cell lung, cervical, ovarian
	Melphalan	Multiple myeloma, melanoma, ovarian
	Dacarbazine	Hodgkin's disease, melanoma
	Nitrosoureas	Brain
	Busulfan	Conditioning agent prior to stem cell transplantation
	Thiotepa	Breast, ovarian, bladder, Hodgkin's disease
<i>Platinum-based</i>		
	Cisplatin	Testicular, ovarian, breast, cervical, bladder, head and neck, esophageal, lung, mesothelioma, brain, neuroblastoma
	Carboplatin	Ovarian, lung
	Oxaliplatin	Colorectal
<i>Topoisomerase inhibitors</i>		
	Topotecan	Ovarian, cervical, lung
	Irinotecan	Colorectal, lung
	Etoposide	Testicular, lung, lymphoma, leukemia, neuroblastoma, ovarian
<i>Antibiotics</i>		
	Bleomycin	Hodgkin's disease, non-Hodgkin's lymphoma, testicular, ovarian, cervical
	Actinomycin D	Wilms tumor, rhabdomyosarcoma, Ewing's sarcoma, trophoblastic neoplasm, testicular, ovarian
<i>Anthracyclines</i>		
	Doxorubicin	Ovarian, AIDS-related Kaposi sarcoma, multiple myeloma, breast, ALL, AML, Wilms tumor, neuroblastoma, soft tissue and bone sarcomas, bladder, thyroid, gastric, Hodgkin disease, lymphoma, lung
	Pegylated liposomal doxorubicin	Ovarian, multiple myeloma, breast, cutaneous T-cell lymphoma, Hodgkin's disease, soft tissue sarcoma, uterine sarcoma
	Daunorubicin	AML, ALL, CML, Kaposi sarcoma
	Epirubicin	Breast, ovarian, gastric, lung, lymphomas
<b>Targeted therapy</b>		
<i>EGFR inhibitors/HER1 inhibitors</i>		
	Cetuximab	Head and neck, colorectal
	Panitumumab	Colorectal
	Erlotinib	Lung, pancreatic
	Gefitinib	Non-small cell lung
<i>HER2 inhibitors</i>		
	Trastuzumab	Breast
	Pertuzumab	Breast
<i>EGFR/HER2 inhibitors</i>		
	Lapatinib	Breast
	Afatinib	Non-small cell lung
<i>Bruton's tyrosine kinase inhibitor</i>		
	Ibrutinib	Mantle cell lymphoma, CLL, Waldenström's macroglobulinemia
<i>Multikinase inhibitors</i>		
	Sorafenib	Renal cell, liver, AML, thyroid
	Sunitinib	Renal cell, GIST
	Regorafenib	Colorectal, hepatocellular, GIST
	Pazopanib	Renal cell, soft tissue sarcoma
	Cabozantinib	Thyroid, renal cell
	Axitinib	Renal cell
	Vandetinib	Thyroid
	Dasatinib	CML, ALL
	Imatinib	CML, ALL, GIST, hypereosinophilic syndrome, chronic eosinophilic leukemia, systemic mastocytosis, myelodysplastic syndrome

(continued on next page)

**Table 1** (continued)

Drug class	Drug name	Oncologic indication
<i>MEK inhibitors</i>	Trametinib	Melanoma
	Cobimetinib	Melanoma
<i>B-Raf inhibitors</i>	Dabrafenib	Melanoma, lung
	Vemurafenib	Melanoma, Erdheim-Chester
<i>mTOR inhibitors</i>	Sirolimus	Lymphangioliomyomatosis, prevention of transplant rejection
	Everolimus	Renal cell, pancreatic, breast, neuroendocrine, prevention of transplant rejection
	Temsirolimus	Renal cell
<i>VEGFR inhibitors</i>	Bevacizumab	Colorectal, lung, renal cell, brain, ovarian
<i>Sonic hedgehog inhibitors</i>	Vismodegib	Basal cell
	Sonidegib	Basal cell
<b>ICPI therapy</b>		
<i>CTLA-4 inhibitors</i>	Ipilimumab	Melanoma, renal cell, colorectal
	Tremelimumab	Not FDA approved; orphan drug designation for mesothelioma
<i>PD-1 inhibitors</i>	Nivolumab	Melanoma, lung, head and neck, Hodgkin's disease, bladder, colorectal, hepatocellular, renal cell
	Pembrolizumab	Melanoma, lung, head and neck, Hodgkin's disease, primary mediastinal large B-cell lymphoma, bladder, colorectal, gastric, cervical, hepatocellular, Merkel cell, renal cell
	Cemiplimab	Squamous cell
<i>PD-L1 inhibitors</i>	Avelumab	Merkel cell, bladder, renal cell
	Atezolizumab	Bladder, lung, breast
	Durvalumab	Bladder, lung
<b>Endocrine (hormonal) therapy</b>		
<i>Aromatase inhibitors</i>	Anastrozole	Breast
	Exemestane	Breast
	Letrozole	Breast
<i>SERMs</i>	Raloxifene	Breast
	Tamoxifen	Breast
	Toremifene	Breast

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; HER, human epidermal growth factor receptor; ICPI, immune checkpoint inhibitor; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; SERMs, selective estrogen receptor modulators; VEGFR, vascular endothelial growth factor receptor.

(Can et al., 2013). The rapid or gradual loss of scalp hair after chemotherapy can cause significant distress, particularly for women, for whom hair often represents identity, personality, sexuality, and femininity. Studies have shown that 58% of patients consider CIA the worst chemotherapy-associated side effect, and 8% even consider declining treatment out of fear of it (Rubio-Gonzalez et al., 2018). Some women with breast cancer have reported that CIA is more difficult to cope with than removal of breast tissue (Browall et al., 2006). Furthermore, decreased self-esteem, depression, and anxiety are commonly reported (Choi et al., 2014; Rosman, 2004), and this may persist even after hair regrowth (Munstedt et al., 1997).

Importantly, proper counseling prior to hair loss may soften its impact, and dedicated education on the use of wigs or head coverings as well as referrals to support groups are effective (Burish et al., 1991; Haley et al., 2011; Harcourt and Frith, 2008; Nolte et al., 2006). Recently, a computer-imaging program, Help with Adjustment to Alopecia by Image Recovery (HAAIR), was developed to better prepare women for CIA by simulating baldness on digitalized headshots to allow women to virtually try on different wigs and headpieces. Women who used this intervention experienced significantly lower distress after losing their hair compared with women who were verbally counseled (McGarvey et al., 2009).

### Clinical presentation

Clinically, CIA manifests as diffuse, non-scarring alopecia (Fig. 1A; Rubio-Gonzalez et al., 2018) that usually occurs within 2 weeks of treatment and peaks around 1 to 2 months after therapy initiation. Most cases resolve with gradual hair regrowth 3 to 6 months after completion of therapy (Susser et al., 1999). CIA most typically affects the frontal and occipital hairlines of the scalp (Freites-Martinez et al., 2019; Rubio-Gonzalez et al., 2018). Table 3 shows the grading criteria.

Although usually reversible, cases of persistent alopecia, termed chemotherapy-induced persistent alopecia (CIPAL), may occur and can be a particularly devastating (Susser et al., 1999). This side effect is defined as a lack of hair regrowth more than 6 months after discontinuing chemotherapy (Sibaud et al., 2016) and typically manifests as diffuse alopecia, although an androgenetic-type of alopecia may also occur (Fig. 1B). The alkylating agents busulfan and thiotepea are linked to CIPAL in children, with 24% of children experiencing CIPAL with busulfan (Palamaras et al., 2011). Taxanes, cyclophosphamide, and doxorubicin are the most common offending agents in women's cancers, and some studies show a persistent lack of full hair regrowth or reduced hair volume within 6 months of taxane cessation in up to 30% of women (Freites-Martinez et al., 2019a,b; Kang et al., 2017; Palamaras

**Table 2**

Select dermatologic toxicities that may develop in women receiving systemic oncologic drugs with associated class of anticancer therapy.

Dermatologic toxicity	Associated class of anticancer therapy
Alopecia (reversible)	Alkylating agents, anthracyclines, antimetabolites, taxanes, topoisomerase inhibitors, vinca alkaloids MKIs, EGFR, SHH SERMs, aromatase inhibitors
Alopecia (permanent)	Alkylating agents, anthracyclines, taxanes
Bullous pemphigoid	Anti-PD-1/PD-L1 therapy
Flushing	SERMs, aromatase inhibitors
HFS (toxic erythema of chemotherapy)	Antimetabolites, anthracyclines, taxanes, topoisomerase inhibitors
HFSR	MKIs, BRAF, VEGFR
Lichenoid dermatitis	Anti-PD-1/PD-L1 therapy
Mucocutaneous hemorrhage	MKIs, VEGFR
Mucositis	Alkylating agents, anthracyclines, antimetabolites, antibiotics, taxanes, topoisomerase inhibitors mTOR anti-CTLA-4, PD-1/PD-L1 therapy
Nail changes (onycholysis, pigmentary alteration, brittle nails)	Antimetabolites, anthracyclines, taxanes MKIs, EGFR, MEK, HER2
Panniculitis	BRAF, MKIs
Papulopustular (acneiform) eruption	EGFR, MEK, HER2, MKIs, mTOR
Paronychia ( $\pm$ pyogenic granulomas)	EGFR, MEK, HER2, MKIs, mTOR Anthracyclines, taxanes
Phototoxicity	BRAF EGFR Antimetabolites
Trichomegaly, hirsutism	EGFR, MKIs, MEK, HER2
Vitiligo-like leukoderma	MKIs, anti-CTLA-4, PD-1/PD-L1 therapy
Vulvovaginal dryness/atrophy	SERMs, aromatase inhibitors

BRAF, B-Raf proto-oncogene, serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; HFS, hand-foot syndrome; HFSR, hand-foot skin reaction; MEK, mitogen-activated protein kinase; MKIs, multikinase inhibitors; mTOR, mammalian target of rapamycin; PD-1, programmed cell death 1; PD-L1, programmed death–ligand 1; SERMs, selective estrogen receptor modulators; SHH, sonic hedgehog; VEGFR, vascular endothelial growth factor receptor.

et al. 2011; Prevezas et al., 2009; Susser et al., 1999). Patients who were not warned of the risk of permanent hair loss successfully won lawsuits against pharmaceutical companies; thus, counseling women on the possibility of this devastating side effect prior to beginning treatment is important.

In addition to hair loss, permanent hair changes, including texture, quality, quantity, and color, may occur, even after full hair regrowth. One study suggests that 65% of patients who had undergone traditional cytotoxic chemotherapy noticed a change from straight to curly hair after completing treatment (Freites-Martinez et al., 2019a,b). Additional changes in hair texture are discussed in the targeted therapy section.

#### Prevention and treatment

Scalp cooling during chemotherapy infusions using manual cold caps (Fig. 1C) or machine caps has been widely studied as a way to prevent CIA. This form of localized cryotherapy works by vasoconstriction-induced reduction in the cytotoxic chemotherapeutic agents reaching hair follicles (Shin et al., 2015). The U.S. Food and Drug Administration approved two machine cap systems: DigniCap in 2015 and Paxman Cooler in 2017 (Shah et al., 2018). A large number of studies have investigated the prevention of CIA by scalp cooling with promising results.

The Dutch Scalp Cooling Registry, which looked retrospectively at 1411 women who received scalp cooling, found that scalp cooling resulted in a success rate (defined as the lack of wearing a head cover at end of the final scalp cooling session) of >50% (van den

Hurk et al., 2012). Two meta-analyses of randomized controlled trials (RCTs) of patients with breast cancer primarily receiving anthracyclines (Rugo and Voigt, 2018) and doxorubicin- or epirubicin-containing chemotherapy (Shin et al., 2015) showed that scalp cooling significantly reduced CIA risk. A more recent RCT investigated scalp cooling in neoadjuvant chemotherapy for early breast cancer and also supports the efficacy of scalp cooling to prevent hair loss (Smetanay et al., 2019).

Scalp cooling may be more effective for certain regimens, such as taxane-based chemotherapy (41–59% success rate), compared with anthracycline-based chemotherapy (16–36% success rate; Kruse and Abraham, 2018; Nangia et al., 2017). In one study, scalp cooling not only reduced rates of CIA but also helped mitigate decreases in patient-perceived physical attractiveness and quality-of-life metrics (Rugo et al., 2017). With an efficacy rate of roughly 50%, scalp cooling can help prevent CIA but still falls short in nearly half of patients who use this technique.

Although overall safe, scalp cooling may result in headache, chills, scalp pain, pruritus, nausea, sinus pain, and rare skin ulceration due to cold injury (Kruse and Abraham, 2018). Scalp cooling had no effect on the overall survival of patients with breast cancer in a retrospective cohort study performed in 2014 (Lemieux et al., 2015), and the incidence of scalp metastases in treated patients with solid tumors was <1% in a recent meta-analysis (Kruse and Abraham, 2018). Scalp cooling should be avoided in patients with cold agglutinin disease, cryoglobulinemia, cold-induced migraines, and posttraumatic cold injury and is contraindicated in patients with hematologic malignancies due to concerns about lower doses of chemotherapy reaching cancer cells circulating in the scalp, as well as central nervous system malignancies, head and neck cancer, and skin cancers (Kruse and Abraham, 2018; Rubio-Gonzalez et al., 2018).

Scalp cooling is estimated to cost between \$1500 and \$3000 per session (Rubio-Gonzalez et al., 2018), and although insurance companies often partially cover wigs and head coverings for patients undergoing chemotherapy, they do not currently cover the use of scalp cooling systems (Freites-Martinez et al., 2019a,b; Rubio-Gonzalez et al., 2018). Some nonprofit organizations, such as HairToStay, help offset these costs (Kruse and Abraham, 2018), but lack of insurance coverage remains a major barrier to the greater adoption of scalp cooling and a challenge that demands attention in the coming years.

Other treatments have been explored for CIA, albeit less extensively. Topical minoxidil, often used in androgenetic alopecia and alopecia areata, has been investigated for CIA in two RCTs with mixed results. In one trial, minoxidil did not prevent CIA, whereas in the other, minoxidil hastened hair regrowth and decreased the duration of CIA but failed to prevent it (Duvic et al., 1996; Granai et al., 1991; Rodriguez et al., 1994). Therefore, topical minoxidil may be offered to patients to promote a faster rate of hair regrowth after treatment. Another agent that has been investigated is topical bimatoprost 0.03%, a prostaglandin analogue that showed efficacy in treating chemotherapy-induced eyelash loss in an RCT of 130 patients (Glaser et al., 2015). In addition to medical management, camouflaging techniques, such as volumizers, hair extensions/weaves, crayons, tinted powder, scalp tattoo, and hairpieces, should be discussed with patients. Preventative measures and treatments are outlined in Table 4.

#### Hand-foot syndrome

HFS, also referred to as palmar-plantar erythrodysesthesia, chemotherapy-associated acral erythema, or toxic erythema of chemotherapy, is a common toxic eruption from pyrimidine analogues, doxorubicin, PLD, and taxanes (Degen et al., 2010; Qiao and Fang, 2012). It has an incidence as high as 42% with certain

**Table 3**  
Grading criteria for commonly encountered dermatologic toxicities of anticancer drugs adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<i>Chemotherapy</i>					
CIA	Hair loss of <50% of normal, obvious only on close inspection. May require use of a different hair style but not a wig or hair piece.	Hair loss of >50% of normal, readily apparent to others. A wig or hair piece is required to hide hair loss if desired. Causes psychosocial distress.			
HFS	Minimal skin changes, no pain.	Skin changes (including peeling, blisters, bleeding, fissures, edema, hyperkeratosis) accompanied by pain. Limits IADLs.	Severe skin changes with pain. Limits self-care ADLs.		
Mucositis	Mild discomfort without affecting oral intake.	Moderate pain altering oral intake. Analgesics indicated. Limits IADLs.	Severe pain, severely altering oral intake and swallowing. Medical intervention indicated.	Life-threatening airway compromise. Urgent intervention (tracheostomy, intubation) required.	Death
Nail infection	Infection is localized; only local intervention is indicated.	Oral intervention is indicated (antibiotics, antifungals, antivirals).	IV intervention is indicated (antibiotics, antifungals, antivirals). Invasive interventions may also be indicated.		
Nail loss	Separation of nail bed from nail plate without symptoms.	Separation of nail bed from nail plate with symptoms that limit IADLs.			
Paronychia	Nail fold edema, erythema with disruption of the cuticle.	Nail fold edema, erythema with pain. May be associated with discharge or nail plate separation. Local intervention is indicated. Oral intervention may also be indicated (antibiotics, antifungals, antivirals). Limits IADLs.	IV antibiotics indicated. Operative intervention indicated. Limits self-care ADLs.		
<i>Targeted therapy</i>					
Acneiform rash*	Papules and/or pustules that cover <10% BSA. May be associated with pruritus or tenderness.	Papules and/or pustules covering 10%–30% BSA. May be associated with pruritus or tenderness. Associated with psychosocial impact and limits IADLs. Alternatively, papules and/or pustules covering >30% BSA with or without mild symptoms.	Papules and/or pustules covering >30% BSA with moderate to severe symptoms. IV antibiotics indicated. Limits self-care ADLs.	Life-threatening consequences due to superinfection.	Death.
HFSR	Same as HFS				
<i>Endocrine Therapy</i>					
Flushing		Presence of flushing			
Alopecia	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			
Vulvovaginal atrophy/	dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	

ADLs, activities of daily living; BSA, body surface area; CIA, chemotherapy-induced alopecia; HFS, hand-foot syndrome; HFSR, hand-foot skin reaction; IADLs, instrumental activities of daily living; IV, intravenous. In general, other rashes from traditional chemotherapy or immune checkpoint inhibitor are similarly graded according to BSA involvement (<10%, 10%–30%, >30%) and impact on quality of life (IADLs, self-care ADLs).

agents (Susser et al., 1999). Women with breast and gynecologic cancers are at a greater risk of experiencing HFS due to the associated regimens used for these cancers (namely PLD and capecitabine; Gressett et al., 2006). PLD has a particularly high association because its liposomal formulation endows it with a long circulation time, enabling substantial deposits to develop in inflamed or irritated skin via the sweat glands in a dose-dependent fashion (Lotem et al., 2000).

HFS can be painful and may significantly affect women's quality of life due to its propensity to interfere with both manual activities and ambulation. The HFS-14 scale was developed specifically to

quantify HFS's impact on quality of life and demonstrated that higher grades of HFS were directly correlated with decreased quality of life when it was validated in a cohort of patients that consisted of almost 75% women (Sibaud et al., 2011). Furthermore, HFS has been associated with loss of dermatoglyphs, leading to problems with fingerprint verification for bank or government documents or international travel (Al-Ahwal, 2012; Chavarrri-Guerra and Soto-Perez-de-Celis, 2015; Wong et al., 2009). HFS's large impact on quality of life may lead to premature drug discontinuation or interruption of chemotherapy (Gressett et al., 2006).

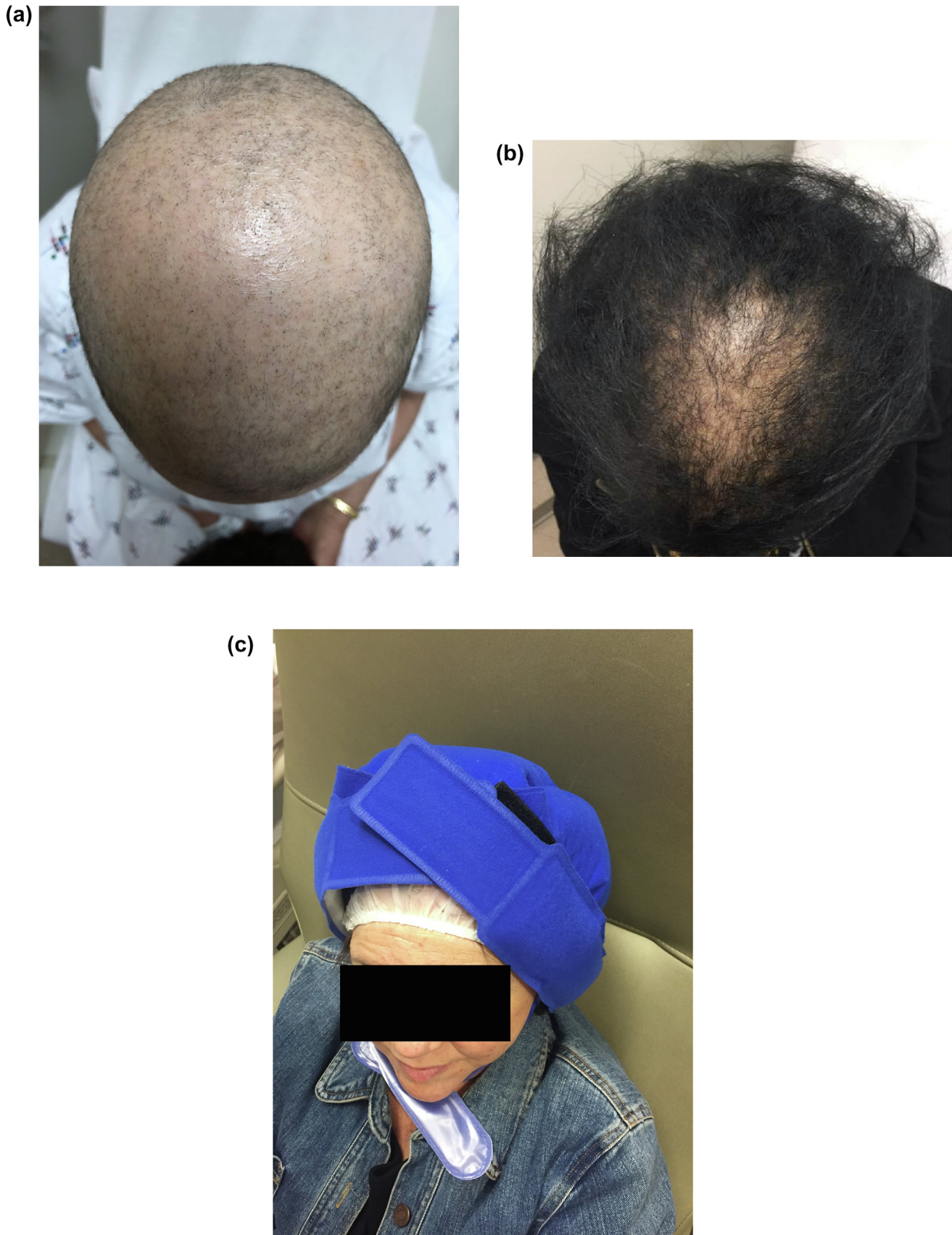
**Table 4**

Summary of prevention and treatment strategies for dermatologic toxicities to anticancer therapies, listing the most commonly employed and/or standard-of-care modalities (other investigational treatments or preventative measures with less evidence are discussed in the text).

Side effect	Prevention	Treatment
<i>Chemotherapy</i>		
CIA	Scalp cooling	Topical minoxidil Topical bimatoprost
HFS	Avoid extreme temperatures, irritants, and friction; topical emollients Regional cooling	Conservative measures (topical emollients, avoid irritants)  Topical corticosteroids under occlusion NSAIDs Ice packs/cold compresses Dose reduction or treatment interruption for high grade/recalcitrant presentation
Oral mucositis	Oral hygiene/soft toothbrushes/baking soda rinses Oral cooling	Pain control via saline rinses, baking soda rinses, topical anesthetics (e.g. lidocaine, doxepin) or sucralfate; ice chips Topical dexamethasone suspension Systemic opioids if higher grade toxicity Liquid diets or gastrostomy tubes if poor nutritional intake Antifungal, antibacterial mouthwashes; treat bacterial/viral/fungal superinfection
Chemotherapy-induced nail toxicities	Avoid activities that can damage the nails through irritation or friction Regional cooling (frozen gloves and socks)	Topical or oral antibiotics for acute paronychia infection (obtain wound culture); topical corticosteroids/antifungal agents for chronic paronychia Antiseptic washes in dilute white vinegar or peroxide
<i>Targeted therapy</i>		
Papulopustular eruption	Sunscreen and sun avoidance Hydrating skin (emollients, avoiding long hot showers and irritating soaps) Prophylactic oral tetracyclines	Topical antibiotics (clindamycin, dapson, erythromycin) Low potency topical corticosteroids for low grade; mid-high potency topical corticosteroids for higher grade Oral tetracyclines and/systemic corticosteroids for higher grade Dose reduction for grade 3; discontinuation and hospitalization for grade 4 Consider isotretinoin for recalcitrant rash Long-term nasal mupirocin ointment, bleach baths for recurrent staphylococcal infection
Paronychia	Nail care (e.g., regular nail trimming, avoidance of trauma, wearing properly fitting shoes)	Topical antibiotics for acute bacterial infection (obtain wound culture); oral tetracyclines or cephalosporins for more severe infections; antiseptic washes (dilute vinegar, peroxide) Topical corticosteroids for chronic paronychia Silver nitrate, electrodesiccation, intralesional triamcinolone, topical propranolol/timolol for pyogenic granuloma-like lesions Nail plate avulsion or surgical debridement for painful ingrown nails
HFSR	Gentle skin care (e.g., emollients, avoid friction/hot water, properly fitting shoes, orthopedic shoe inserts)	Emollients for low grade and topical keratolytics (urea, salicylic acid, tazarotene) High potency topical corticosteroids for higher-grade presentations Dose reduction if grade 3 or higher; podiatric evaluation
<i>ICPI therapy</i>		
Rash (e.g., lichenoid, eczema, exanthem, psoriasiform, granulomatous, bullous pemphigoid)		Topical corticosteroids for low grade 1/2*  Oral/IV corticosteroids for high grade 3/4* Treatment interruption, hospitalization, adjunct immunosuppressive agents for recalcitrant grade 3/4 rash (e.g., IVIG, anti-TNF-alpha, cyclosporine for SJS/TEN; rituximab for bullous pemphigoid) Anti-pruritics: topical camphor-menthol, antihistamines, gabapentin/pregabalin, aprepitant, systemic corticosteroids (for intractable pruritus)
<i>Endocrine therapy</i>		
Endocrine-therapy induced alopecia		Topical minoxidil Consider spironolactone for refractory cases after discussion with oncologist
Flushing	Avoiding common triggers (e.g. heat, stress, hot beverages and food, alcohol).	SSRIs (non-cytochrome P450 2D6 pathway inhibitors)  SSNRIs Gabapentin Cognitive behavioral therapy
Vulvovaginal atrophy		Vaginal lubricants Vaginal moisturizers Vaginal dilators and pelvic floor physical therapy Consider vaginal estrogen therapy after discussion with oncologist

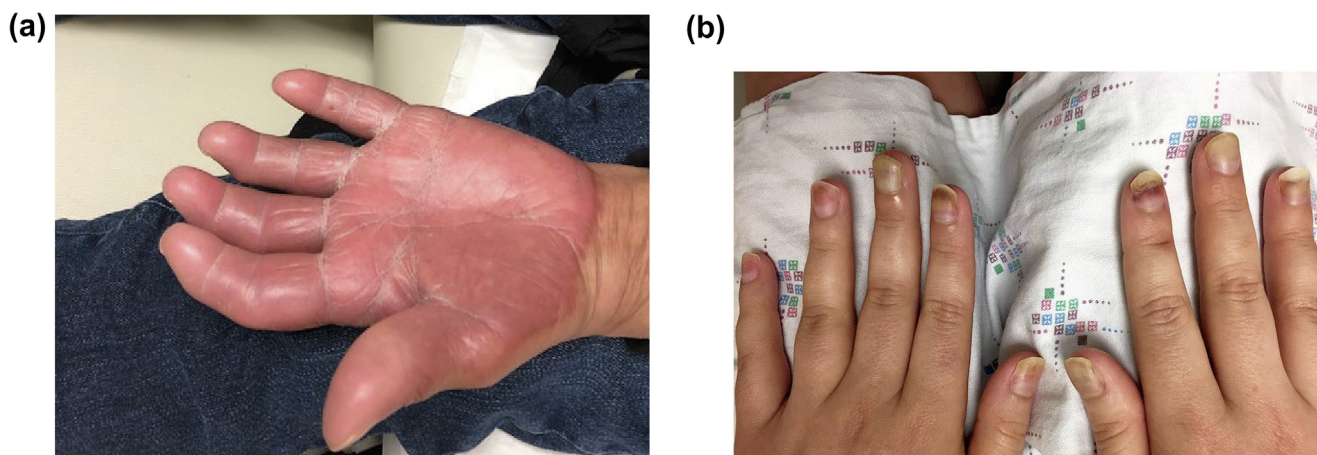
CIA, chemotherapy-induced alopecia; HFS, hand-foot syndrome. HFSR, hand-foot skin reaction; ICPI, immune checkpoint inhibitor; IVIG, intravenous immune globulin; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS/TEN, Steven-Johnson syndrome/toxic epidermal necrolysis; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; TNF, tumor necrosis factor.

For ICPI rashes, consider skin-directed treatments depending on the particular rash (e.g., phototherapy or acitretin for lichenoid, eczematous, or psoriasiform presentations; doxycycline/niacinamide, omalizumab, rituximab for bullous pemphigoid; hydroxychloroquine, minocycline for granulomatous presentations).



**Fig. 1.** (A) Diffuse, nonscarring alopecia of the scalp as a result of taxane chemotherapy-induced anagen effluvium in a patient with breast cancer; (B) chemotherapy-induced permanent alopecia of the mid-scalp and crown after taxane chemotherapy for breast cancer; (C) scalp cooling during chemotherapy infusion with a manual cold cap to prevent chemotherapy-induced alopecia.





**Fig. 2.** (A) Well-demarcated palmar erythema and edema consistent with hand-foot syndrome or toxic erythema of chemotherapy from capecitabine treatment for breast cancer; (B) subungual hemorrhage with distal onycholysis of the nails during taxane chemotherapy.

### Clinical presentation

HFS usually occurs within 2 weeks after exposure to the offending agent, although it can occur months after starting therapy (Degen et al., 2010). HFS typically presents on the palms and soles as a prodrome of tingling or burning with well-demarcated areas of erythema and often edema that may progress to blistering or desquamation (Fig. 2A; Qiao and Fang, 2012). Patients can also have eruptions involving intertriginous zones (i.e., malignant intertrigo), with erythematous patches or plaques that may desquamate (Smith et al., 2016). HFS is theorized to occur primarily on the palms and soles due to the relatively higher proportion of eccrine sweat glands, where cytotoxic drugs tend to be deposited (Jacobi et al., 2005). Traditional chemotherapy-induced HFS has a predilection for the hands over the soles and may be distinguished from hand-foot skin reaction (HFSR) induced by the multikinase inhibitors sorafenib and sunitinib, which will be discussed later (Degen et al., 2010).

Patients on taxanes may develop a particular type of toxicity referred to as periarticular thenar erythema and onycholysis (PATEO), which generally involves the dorsal hands and feet, the extensor surfaces of the arms, and the lateral aspect of the legs (Sibaud et al., 2016). Pain, burning, and tingling are common symptoms of PATEO (Sibaud et al., 2016). Nails can be involved, and 27% of patients with PATEO may have permanent nail dystrophy. PATEO occurs more commonly with docetaxel compared with paclitaxel and occurs much less frequently with nanoparticle-albumin-bound paclitaxel, a solvent-free version of paclitaxel that may be less predisposing to toxicity development (Dow et al., 2015; Sibaud et al., 2016).

### Treatment and prevention

Treatment of HFS largely depends on the grade of the rash. The National Cancer Institute's Common Terminology Criteria for Adverse Events grading scale is widely used to grade toxicities from anticancer drugs, taking into account the severity of the reaction type and impact on activities of daily living (ADLs; Table 3) (National Cancer Institute, 2017). For a low-grade rash (i.e., minimal changes without pain), topical emollients, keratolytics (e.g., urea cream, ammonium lactate), and avoidance of irritants (e.g., wearing gloves while doing dishes, gentle soap-free cleansers) are recommended. For higher-grade presentations, topical corticosteroids (e.g., clobetasol ointment) for the hands and feet may be helpful and can be applied under occlusion of cotton gloves to enhance the therapeutic effect. Nonsteroidal anti-inflammatory

drugs or ice packs/cold compresses may be helpful for pain relief (von Moos et al., 2008).

Treatment interruption or a dose reduction may be required for severe cases of HFS (Gressett et al., 2006). Dose reductions of PLD have been studied in several RCTs of women with gynecologic cancers, and the majority of trials concluded that lower doses (<40 mg/m<sup>2</sup> every 4 weeks) reduced the incidence of HFS compared with the higher dose arm (Al-Batran et al., 2006; Coleman et al., 2006; Markman et al., 2000; Rose, 2005; Tanyi et al., 2009). Extending the intervals between dosages has also been shown to be effective (Lyass et al., 2000; Ranson et al., 1997). However, HFS has been associated with a clinical response to 5-fluorouracil (5-FU) and capecitabine (Degen et al., 2010; Hofheinz et al., 2015); thus, alternative treatment strategies instead of dose reductions or interruptions are desirable.

The prevention guidelines for HFS currently consist of avoidance of extreme temperature, irritants, or friction and application of emollients (Qiao and Fang, 2012). Small prospective and retrospective studies investigating regional cooling (ice packs applied to the wrists and ankles or frozen gloves/socks) during PLD infusion in patients with ovarian and other gynecologic cancers showed a significantly reduced incidence or delayed onset of HFS (Bun et al., 2018; Mangili et al., 2008; Molpus et al., 2004; Sayer et al., 2006). Some cancer centers offer regional cryotherapy as a preventive measure. In addition to regional cooling, antiperspirants applied to the palms and soles may also be effective in preventing HFS from PLD (Templeton et al., 2014).

Other medical therapies have been investigated for the prevention and treatment of HFS, including pyridoxine, which has been studied in the setting of capecitabine and PLD with mixed results (Braik et al., 2014; Kang et al., 2010; Toyama et al., 2018; Von Gruenigen et al., 2010; Yap et al., 2017). A systematic review by Chen et al. (2013) showed that a higher dose of pyridoxine (400 mg) demonstrated efficacy in treating HFS; however, these results have not been reproduced in an RCT (Chalermchai et al., 2010; Corrie et al., 2012; Jo et al., 2015; Yoshimoto et al., 2010). Other agents that have been reported to successfully treat HFS in small series or prospective studies include cod-liver oil (Kanis et al., 2009), topical dimethylsulfoxide (Lopez et al., 1999), corticosteroids (Drake et al., 2004), nicotine patches (Kingsley, 1994), and celecoxib (Fabi et al., 2008; Huang et al., 2018; Kohne et al., 2008; Macedo et al., 2014; Zhang et al., 2011). Urea-containing creams have also been investigated, with mixed results (Hofheinz et al., 2015; Wolf et al., 2010). Bag balm (hydroxyquinoline sulfate-containing ointment) and amifostine (cryoprotectant) have also shown efficacy in treating HFS (Gressett et al., 2006).

## Mucositis

Mucosal surfaces are common sites of toxic events from traditional chemotherapy due to the susceptibility of the rapidly dividing epithelium, with turnover every 7–14 days, to cytotoxic agents (Sonis and Fey, 2002). Chemotherapies also have growth-slowing effects on basal epithelial cells that may lead to atrophy of the oral, gastrointestinal, and anogenital mucosae (Sonis and Fey, 2002). Some of the most common causative agents include PLD, bleomycin, dactinomycin, docetaxel, doxorubicin, 5-FU, methotrexate (MTX), and topotecan (Susser et al., 1999). Oral mucositis has an incidence of 40% to 60% in drugs targeting DNA synthesis, such as antimetabolites and purine analogues, and 40% to 70% in combination regimens (Chaveli-López and Bagán-Sebastián, 2016).

Several studies have reported that women experience chemotherapy-related oral mucositis more often than men (Chansky et al., 2005; Sloan et al., 2000; Valeh et al., 2018), with one study of 148 patients showing that female sex was an independent risk factor for chemotherapy-induced oral mucositis (Vokurka et al., 2006). Although the mechanism for this difference has not been fully elucidated, some studies show that chemotherapeutic drugs responsible for oral mucositis may be cleared at a lower rate in women, especially 5-FU (Milano et al., 1992; Port et al., 1991). Dihydropyrimidine dehydrogenase, the enzyme responsible for 5-FU clearance, may exhibit decreased activity in women, leading to increased toxicity (Milano et al., 1999).

Advanced oral mucositis may be a dose-limiting toxicity of traditional chemotherapy. The clinical and economic burden may be substantial, given its effect on nutritional status and dietary needs, increased need for pain medications, interruption of cancer therapy, increased infectious risk, longer hospital stays, and the need for gastrostomy tubes or total parenteral nutrition. These factors associated with oral mucositis were estimated by one study to cost up to \$6000 per patient (Elting et al., 2007).

Studies have found that affected patients demonstrate decreased physical and emotional wellbeing compared with patients with cancer without mucositis (Cheng, 2007; Kim et al., 2012), including higher rates of depression (Gutiérrez-Vargas et al., 2016). Affected individuals also have a significantly higher risk of associated severe pain and weight loss >5% (Lalla et al., 2008).

### Clinical presentation

Clinically, oral mucositis first manifests as oral erythema, mucosal atrophy, pain, burning, and/or xerostomia 3–5 days after chemotherapy induction. It subsides within approximately 3 weeks (Chaveli-López and Bagán-Sebastián, 2016; Susser et al., 1999). Mucositis may progress to ulceration, which may be focal or diffuse and may be accompanied by a pseudomembrane that can become necrotic (Lalla et al., 2008). Oral pain, burning, and ulcerations may progress and impede swallowing, eating, drinking, or talking. Table 3 shows the grading criteria.

The location of mucositis can differ depending on the causative agent. The soft palate and tongue are the most commonly involved with traditional chemotherapy. With the addition of radiation therapy, the hard palate may be involved as well, with higher doses of radiation leading to more severe mucositis (Lalla et al., 2008). Mucositis can also affect the anogenital mucosa. Infections with fungal (candidal thrush), bacterial, or viral organisms (herpes simplex virus) are serious sequelae of oral mucositis and are of particular concern in immunosuppressed patients (Chaveli-López and Bagán-Sebastián, 2016). Superficial cultures help rule out these diagnoses. Superinfection should be treated with appropriate antifungal (e.g., fluconazole and nystatin suspension) or antiviral (e.g., valacyclovir) agents until the infection has cleared.

Erosive mucositis from MTX has been reported and may herald impending cytopenias, which may progress to fatal bone marrow failure (Demirkan et al., 2017; Knoll et al., 2016). Risk factors include dose escalations or treatment reinitiation, hypoalbuminemia, renal insufficiency, and use of certain drugs that displace MTX from plasma proteins or decrease its excretion, such as nonsteroidal anti-inflammatory drugs, sulfonamides, aspirin, or other antibiotics (Dervisoglou and Matiakis, 2015; Knoll et al., 2016). Folate or folinic acid substitution, as well as alkalization of the urine, may hasten reversal of MTX-induced erosive mucositis (Dervisoglou and Matiakis, 2015; Knoll et al., 2016).

### Prevention and treatment

According to clinical practice guidelines, the management of oral mucositis should be broadly approached in six categories: pain control, nutritional support, oral decontamination, xerostomia treatment, bleeding control, and therapeutic interventions for the mucositis itself (Lalla et al., 2008). Pain is the primary manifestation of oral mucositis and can be controlled via saline rinses, ice chips, and other rinses that contain topical anesthetics, diphenhydramine, doxepin, sucralfate, and/or aluminum hydroxide/magnesium hydroxide/simethicone (Lalla et al., 2008; Sio et al., 2019). Topical dexamethasone suspension may be used for symptomatic and painful ulcers, whereas systemic opioids may be required for higher-grade mucositis (Lalla et al., 2008).

Nutritional intake should be closely monitored and appropriate dietary modifications or interventions, such as liquid diets or gastrostomy tubes, should be initiated when required (Lalla et al., 2008). Proper oral hygiene to prevent superinfection is extremely important in patients with mucositis. Antifungal or chlorhexidine-containing mouthwashes may be helpful as adjunctive treatments (Lalla et al., 2008). Concurrent xerostomia can be treated with frequent water intake, sodium bicarbonate (baking soda) rinses, sugarless gum, or cholinergic drugs for severe cases. Some patients may be at a higher risk for bleeding from oral lesions (e.g., thrombocytopenic patients from intense chemotherapy); if this occurs, bleeding may be managed with topical hemostatics, such as fibrin glue (Lalla et al., 2008).

Many therapies have been investigated to prevent or treat the mucositis itself, and maintaining oral hygiene using soft toothbrushes and baking soda rinses or antimicrobial mouthwashes, such as chlorhexidine, may be helpful. A Cochrane review showed that aloe vera, amifostine (cytoprotective), granulocyte-colony stimulating factor, intravenous glutamine, honey, laser therapy, polymyxin/tobramycin/amphotericin tablet, cryotherapy, keratinocyte growth factor (palifermin), and sucralfate were beneficial to some degree in preventing or treating mucositis, but only the latter three were significantly beneficial (Chaveli-López and Bagán-Sebastián, 2016). Oral cooling with ice chips, ice-cold water, ice cream, or popsicles has been shown to be particularly effective for agents with a short half-life, such as 5-FU, and is generally tolerable and safe (Chaveli-López and Bagán-Sebastián, 2016; Riley et al., 2016).

### Chemotherapy-induced nail toxicities

Chemotherapy-induced nail toxicities can occur from many agents but are most common in taxane- and anthracycline-based therapies, which are often used as first-line therapies for women with breast and other gynecologic cancers (Balagula et al., 2011). The incidence may be as high as 80% with docetaxel and 20% with paclitaxel (Capriotti et al., 2015; Gilbar et al., 2009; Minisini et al., 2003; Winther et al., 2007). Nail toxicity appears to be cumulative and related to the number of chemotherapy cycles, with more frequent and numerous cycles linked to increased incidence (Hong

et al., 2007; Zawar et al., 2019). This is especially relevant for women with breast cancer, who often receive weekly docetaxel to prevent myelosuppression.

These nail conditions are not only cosmetically undesirable and emotionally disturbing to women with cancer but may also be painful, limit manual activities and disrupt quality of life in 32% to 43% of patients, and occasionally lead to treatment interruption (Gilbar et al., 2009). Winther et al. (2007) found that 40% of patients with docetaxel-induced nail changes had functional problems, 37% had trouble finding comfortable shoes, and 33% had difficulty ambulating. Furthermore, nail changes such as periungual erythema, edema, and suppurative onycholysis are prone to secondary infections, which can occur in up to 33% of patients (Balagula et al., 2011) and are especially dangerous in neutropenic patients (Capriotti et al., 2017).

### Clinical presentation

Toxic insult to the nail matrix secondary to chemotherapy use may lead to brittle nails in addition to dyschromia, slowed nail growth, and other conditions. Among cytotoxic agents, taxanes are the most commonly implicated drugs with nail changes, which typically manifest as painful subungual hemorrhage (Fig. 2B), subungual abscesses, and onycholysis. Other observed toxicities include Beau's lines, Mees' lines, onychoschizia, onychomadesis, melanonychia, hyperpigmentation, Muehrcke's lines, splinter hemorrhages, pyogenic granuloma formation, and paronychia (Gilbar et al., 2009). The fingernails are more commonly affected than the toenails (Zawar et al., 2019). In severe instances, paronychia infection, onycholysis, and subungual abscess may result in loss of the nail plate. Grading for nail changes, including nail infections and onycholysis, is shown in Table 3.

### Prevention and treatment

Preventive measures include maintenance of nail integrity by avoidance of activities that induce irritation, friction, or damage to the nails (e.g., cuticle trimming); avoidance of ultraviolet light; nail moisturization; and proper nail cutting (Gilbar et al., 2009; Hussain et al., 2000). Topical or oral antimicrobials may help reduce secondary infections (Gilbar et al., 2009), and nail polish application can be used as a means of hiding nail changes until the nails grow, in the absence of infection.

Localized cryotherapy with the use of frozen gloves and socks (FGS) during treatment infusion has demonstrated efficacy in phase 2 trials, where the treated limb had significantly less nail toxicity than the other control limb (Sakurai et al., 2009; Scotté et al., 2005; 2008). A review of existing trials noted that four of six established studies supported FGS as an effective preventive strategy for chemotherapy-induced nail toxicities (Can et al., 2012; Marks et al., 2018; Sakurai et al., 2009; Scotté et al., 2005; 2008). The potential adverse effects of FGS include pain, discomfort, and frostbite (Marks et al., 2018). Other therapies that have been investigated with promising results include the use of hydrating nail solution, which significantly reduced the incidence of onycholysis in a RCT of patients with breast cancer (Kim et al., 2017), and polyphenol-rich nail bed balm, which reduced the incidence of onycholysis in a double-blind RCT in the United Kingdom (Thomas et al., 2018).

In the event of paronychia infection, superficial wound cultures should be obtained and appropriate topical/oral antibiotics should be initiated. Topical antibiotic agents (e.g., mupirocin, clindamycin, and gentamicin) may be applied around and under the nail fold to treat superficial infections (Ouwerkerk and Boers-Doets, 2010), and antiseptic washes (e.g., dilute white vinegar soaks or dilute peroxide) can be helpful in treating secondary

infection or bacterial colonization (Guggina et al., 2017). Recently, an RCT showed a 2% povidone-iodine solution to be an effective treatment for chemotherapy-associated paronychia (Capriotti et al., 2019).

### Targeted therapies

Over the last decade, targeted therapies have emerged as effective anticancer drugs directed at crucial pathways needed for cell growth and proliferation. Many common malignancies, including lung, colon, and breast, are treated with targeted agents. There are numerous classes of targeted agents, including epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, fibroblast growth factor receptor inhibitors, B-Raf proto-oncogene, serine/threonine kinase (BRAF) inhibitors, tyrosine kinase inhibitors, mitogen-activated protein kinase (MEK) inhibitors, human epidermal growth factor receptor-2 inhibitors (HER2), mammalian target of rapamycin (mTOR) inhibitors, sonic hedgehog (sHH) inhibitors, and multikinase inhibitors (MKIs) that target a combination of these pathways (Table 1; Macdonald et al., 2015).

Compared with traditional chemotherapy, patients receiving targeted therapies may have a significantly higher incidence of dermatologic adverse events. One study estimated that 75% of patients experienced  $\geq 2$  dermatologic toxicities (Rosen et al., 2013). This may be explained by the high expression of several of the corresponding targets (e.g., EGFR, fibroblast growth factor receptor) in the skin, hair, and nails (Rosen et al., 2013).

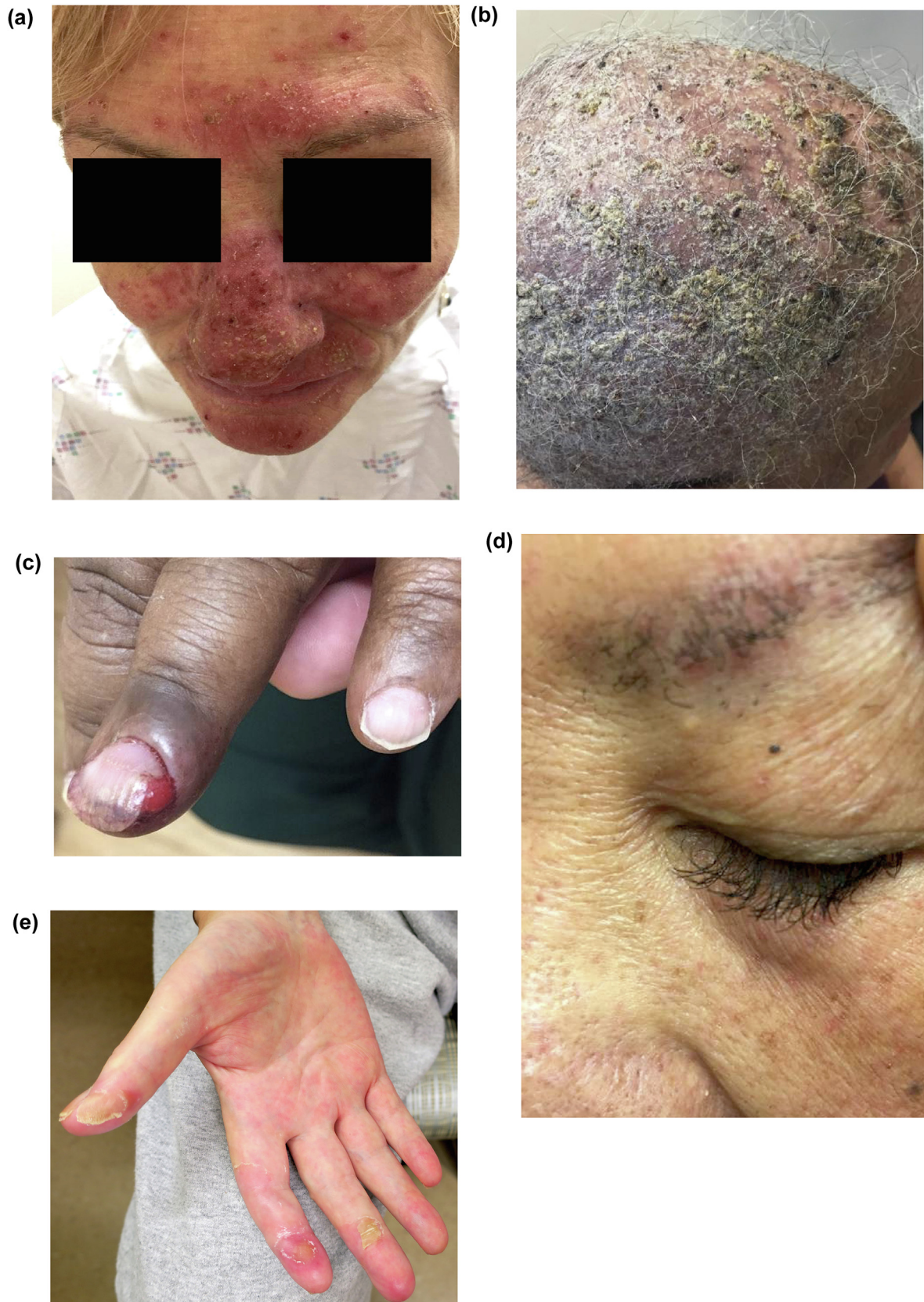
In addition, studies have demonstrated that cutaneous toxicities from targeted agents result in significantly poorer quality of life (as measured by the Dermatology Life Quality Index) and are more likely to disrupt personal relationships and cause negative emotions (as measured by the Skindex-16) compared with dermatologic toxicities from traditional chemotherapy or radiation (Gandhi et al., 2010; Lee et al., 2018; Ra et al., 2013; Rosen et al., 2013). Furthermore, one study found that women on targeted therapies experienced greater dermatologic quality-of-life disruptions than men with the same toxicities (Lee et al., 2018).

This section will discuss the most common reactions, including papulopustular eruption, paronychia, HFSR, and hair changes.

### Papulopustular (acneiform) eruption

The papulopustular (acneiform) rash is the most common side effect of targeted therapies, with an incidence of 50–85% reported for patients on EGFR inhibitors, human epidermal growth factor receptor-2 HER2 inhibitors, MEK inhibitors, and MKIs (Lacouture and Sibaud, 2018). EGFR inhibitors are correlated with a higher frequency and severity of the papulopustular eruption, with rates as high as 85%, particularly among patients treated with monoclonal antibodies (cetuximab, panitumumab) compared with those treated with tyrosine kinase inhibitors (erlotinib, gefitinib, lapatinib, afatinib; Clabbers et al., 2016). Patients receiving MKIs typically present with a milder rash than those receiving EGFR inhibitors (Hu et al., 2007; Rosenbaum et al., 2008).

The papulopustular rash has been linked to significant perturbations in patients' quality of life, including increased reports of depression and withdrawal from social activities secondary to pain, burning, pruritus, xerosis, and skin sensitivity (Clabbers et al., 2016; Joshi et al., 2010; Wagner and Lacouture, 2007). One study suggested that frustration associated with targeted therapy-associated acneiform rash is greater than that experienced with eczematous dermatitis and acne vulgaris (Joshi et al., 2010).



**Fig. 3.** (A) Inflammatory papules and pustules with impetiginization (positive culture for methicillin-resistant *Staphylococcus aureus*) on the face consistent with the papulopustular eruption during epidermal growth factor receptor (EGFR) inhibitor therapy for lung cancer; (B) scarring alopecia as a result of severe EGFR inhibitor-induced papulopustular eruption involving the scalp or a woman with lung cancer; (C) periungual erythema and swelling with painful pyogenic granuloma-like lesion along the lateral nailfold due to EGFR inhibitor therapy; (D) eyelash trichomegaly in a patient on EGFR inhibitor therapy; (E) hand-foot skin reaction manifesting as focal hyperkeratotic plaques with an erythematous base on the fingertips during treatment with sorafenib.

### Clinical presentation

The papulopustular eruption typically manifests as erythematous follicular papules and pustules without comedones on seboreic surfaces such as the face, scalp, neck, chest, and back (Fig. 3A; Pinto et al., 2011). The eruption typically develops within weeks after targeted therapy initiation, peaks within 4 weeks, and often fades gradually thereafter, but it may have a delayed presentation (Hu et al., 2007; Scope et al., 2007). The rash may be exacerbated by sunlight exposure and heat (Burtness et al., 2009). Increases in plasma creatine kinase have been associated with acneiform rash and may positively correlate with rash severity (Moreno Garcia et al., 2012).

Although initial pustules are sterile, secondary bacterial infections can occur, particularly with *Staphylococcal aureus* (both methicillin-sensitive and -resistant *Staphylococcal aureus*) and rarely with herpetic or dermatophytic organisms (Qi et al., 2014). A recent analysis found that 38% of patients on EGFR inhibitors experienced superinfection (Eilers et al., 2010) and that these drugs significantly increased the risk of developing severe sepsis (Qi et al., 2014).

Furthermore, unlike acneiform eruptions secondary to other drugs, an EGFR inhibitor-induced acneiform rash may be pruritic in up to 58% of cases (Clabbers et al., 2016; Hu et al., 2007). Coexisting skin xerosis may occur in up to 35% of patients (Guggina et al., 2017; Pinto et al., 2011), which may give way to painful cracks and fissures on the tips of the fingers and toes (Ouwkerk and Boers-Doets, 2010). Although the papulopustular rash usually fades within several weeks of discontinuing the offending agent, postinflammatory changes, such as telangiectasias, diffuse erythema, and hyperpigmentation, may occur (Burtness et al., 2009; Hu et al., 2007).

Up to 38% of patients on EGFR inhibitors will experience grade 3 or 4 dermatologic toxicity (Hu et al., 2007; Lacouture and Sibaud, 2018; Pinto et al., 2011), with 32% and 76% of clinicians reporting holding or discontinuing EGFR inhibitor therapy due to rash, respectively (Boone et al., 2007). The presence of acneiform eruption may be positively associated with anti-tumor response to EGFR inhibitors in certain tumors (Hu et al., 2007); therefore, aggressive management is indicated to avoid treatment interruption in patients who may benefit the most from the drug.

### Prevention and treatment

Preventive measures for acneiform rash include the use of sunscreen and sun protective behavior, (Burtness et al., 2009) and keeping the skin hydrated by using emollients and avoiding long hot showers and irritating soaps (Ouwkerk and Boers-Doets, 2010). Several phase 2 studies have evaluated the utility of prophylactic oral tetracyclines in combination with topical steroids, sunscreen, and moisturizers for the prevention of the acneiform rash, with overall promising results that demonstrated a reduced incidence of severe rash (Belum et al., 2017; Grande et al., 2013; Kobayashi et al., 2015; Lacouture et al., 2010, 2016; Lacouture and Sibaud, 2018; Scope et al., 2007).

Topical menadione (vitamin K3) has been investigated for the prevention of acneiform rash but did not show efficacy in a Phase 1 trial (Eriksen et al., 2017). In a single-center study, topical phytonadione (vitamin K1) applied prophylactically did reduce the incidence of rash (Pinta et al., 2014; Tomková et al., 2013), but larger, controlled studies are needed to validate this finding.

Treatment of the papulopustular rash depends on the grade (Table 3). For mild or low-grade rash, observation or topical antibiotics (e.g., clindamycin, dapson, or erythromycin) and/or low potency topical corticosteroids (e.g., hydrocortisone 2.5%) may be

used. The addition of an oral tetracycline (doxycycline or minocycline 100 mg twice daily) and higher-potency topical corticosteroids may be required for rashes that fail to respond or progress to grade 2 or 3 (Pinto et al., 2011).

Superficial wound cultures should be obtained from the pustules, and appropriate antibiotics should be initiated. For more severe presentations, oral tetracyclines and mid- to high-potency topical corticosteroids should be initiated; oral corticosteroids may be added for grade 3 or intolerable grade 2 rashes (prednisone equivalent of 0.5–1 mg/kg/day) along with temporary treatment interruption until the rash improves (Pinto et al., 2011). Oral isotretinoin has also been used for severe acneiform rash that is refractory to antibiotics and corticosteroids with good effect (Chiang and Anadkat, 2013; Requena et al., 2012), but its use may exacerbate xerosis and lead to retinoid dermatitis. Dose modifications may be required if the rash recurs and remains intolerable (Pinto et al., 2011).

Life-threatening grade 4 rashes associated with severe superinfection warrant permanent discontinuation of targeted therapy, along with hospitalization, supportive care, and initiation of appropriate antibiotics and oral or intravenous corticosteroids (prednisone equivalent of 1–2 mg/kg/day). Of note, topical retinoids and benzoyl peroxide are generally avoided because they may be irritating (Burtness et al., 2009; Scope et al., 2007); however, with increasing reports of bacterial resistance in this setting, benzoyl peroxide or antiseptic washes should be considered (Hirostu et al., 2019). Steroid-sparing drugs, such as calcineurin inhibitors, may be used but are less effective (Burtness et al., 2009; Scope et al., 2009). Anecdotal reports demonstrated that topical and oral ivermectin (15 mg weekly for 4 weeks) may be helpful in refractory cases, and topical astringents such as aluminum acetate and antiseptic washes (e.g., dilute Dakin's solution) may help. In general, ointments and creams are preferred over gels and solutions. For scalp involvement, topical corticosteroid shampoos or high-potency topical corticosteroids may be helpful. Severe cases of scalp involvement may result in irreversible, scarring alopecia (Fig. 3B; Burtness et al., 2009; Donovan et al., 2008).

Associated pruritus may improve with treatment of the underlying rash. Adjunctive treatments for symptomatic relief include cold compresses, antihistamines, gabapentin or pregabalin, or aprepitant for more severe pruritus (Guggina et al., 2017; Mir et al., 2011; Porzio et al., 2006; Vincenzi et al., 2010). For cracks and fissures, cyanoacrylate, propylene glycol 50% with occlusion, protective coverings (e.g., hydrocolloid dressings), emollients, Monsel's solution, or zinc oxide cream may be used (Burtness et al., 2009; Hu et al., 2007). Long-term prophylactic nasal mupirocin ointment and antiseptic washes may help patients with recurrent infection due to *S. aureus* colonization (Burtness et al., 2009).

### Paronychia and other nail abnormalities

Up to 60% of patients on targeted therapies report nail abnormalities, which may involve the nailfold, nail bed, and/or nail plate. Paronychia occurs more commonly with EGFR inhibitors than with other targeted agents and is frequently associated with pain, inflammation, and a negative impact on manual ADLs (Chang et al., 2004; Hu et al., 2007). One study found that paronychia from targeted therapy lowered women's quality of life more than any other dermatologic toxicity resulting from anticancer drugs (Lee et al., 2018). Furthermore, women with these nail disorders have been reported to have a lesser quality of life than men with the same disorders (Belyayeva et al., 2013; Gupta and Gupta, 2013; Lee et al., 2018; Reich and Szepietowski, 2011).

### Clinical presentation

Patients may present with paronychia (erythema of the nailfold with purulence), ingrown nails, brittle nails, hyperpigmentation, onycholysis, and painful hypergranulation pyogenic granuloma-like lesions along the lateral nailfold (Fig. 3C). The great toe and thumb are the most frequently affected, although any digit may be involved. These nail toxicities are the most common with EGFR, MEK, and mTOR inhibitors, whereas splinter hemorrhages are prevalent with MKIs, especially with sorafenib (Capriotti et al., 2017; Gilbar et al., 2009; Lacouture and Sibaud, 2018). Nail changes usually develop within 1–2 months after starting the drug but may take up to 6 months to manifest (Hu et al., 2007).

In addition, compared with the associated rash, nail changes may be slow to regress even after discontinuation of the offending agent (Pinto et al., 2011). Secondary infections are common, especially with *S. aureus* (Burtneess et al., 2009; Busam et al., 2001; Fox, 2007).

### Prevention and treatment

Gentle nail care is essential in the prevention of targeted therapy-induced paronychia and includes regular nail trimming, avoidance of trauma to the nails (e.g., biting and manicuring), and avoidance of undue pressure to the nailfolds by wearing properly fitting shoes (Gilbar et al., 2009; Marks et al., 2018). Nail lacquers (e.g., hydroxypropyl chitosan and polyurethane 16%) have been shown to prevent nail dehydration and improve nail strength (Guggina et al., 2017).

Several approaches exist for management and prevention. Most strategies involve treating secondary infection, eliminating excess painful granulation tissue or ingrown nails, and decreasing periungual inflammation. Topical antibiotics (mupirocin, clindamycin) and topical corticosteroids may be used to treat acute bacterial infection and chronic paronychia, respectively (Hu et al., 2007; Pinto et al., 2011). Daily soaks in solutions such as white vinegar, dilute peroxide, iodine, or bleach are helpful in treating secondary infections (Burtneess et al., 2009; Guggina et al., 2017). If infection is suspected, the nail should be cultured and appropriate antibiotic therapy initiated (Ouwerkerk and Boers-Doets, 2010).

Oral tetracyclines or cephalosporins are frequently used; intravenous antibiotics may be necessary for higher-grade infections. In the event of pyogenic granuloma-like development, topical silver nitrate or electrodesiccation may be warranted (Hu et al., 2007). Propranolol 1% cream and 0.5% topical timolol gel have been used more recently (Cubiró et al., 2018; Piraccini et al., 2016). One study demonstrated efficacy with platelet-rich plasma in treatment of recalcitrant paronychia from EGFR inhibitor therapy (Kwon et al., 2012). In refractory cases, nail plate avulsion or surgical debridement may be required for painful ingrown nails (Gilbar et al., 2009).

### Hair changes

Up to 50% of patients on EGFR inhibitors may experience hair abnormalities, including changes in hair texture, color, or volume that may progress to alopecia, most often after several months on treatment (Dai et al., 2017; Hu et al., 2007; Pinto et al., 2011). Hair often becomes brittle (Hu et al., 2007) or dyspigmented in up to 50% of patients (Freites-Martinez et al., 2019a,b), but a case report also described repigmentation of gray hair after erlotinib therapy (Cheng et al., 2014). Cheng and Lai (2013) described the utilization of microscopic hair sheath examination to predict EGFR inhibitor-induced hair toxicity, where the arrow sign or degeneration of the distal root sheaths with a distal split of the proximal

remnant was useful in identifying patients experiencing such hair changes.

In addition to EGFR inhibitors, hair changes are also common with MKIs. In one study, 25% of patients on sunitinib experienced alopecia and 64% experienced hair discoloration, specifically hypopigmentation with pazopanib and sunitinib (Favre et al., 2006; Freites-Martinez et al., 2019a,b; Rosenbaum et al., 2008). The sHH inhibitor vismodegib is strongly correlated with the development of alopecia in up to 57% of cases (Belum et al., 2015). In general, alopecia associated with targeted agents is usually mild and diffuse, although uncommonly scarring may develop, as in the case of a severe papulopustular eruption (Fig. 3B; Burtneess et al., 2009; Donovan et al., 2008; Freites-Martinez et al., 2019a,b; Yang et al., 2011).

Other hair changes may occur, including trichomegaly, or excessive growth of the eyelashes and/or eyebrows (Fig. 3D; Bétrian et al., 2017; Hu et al., 2007), likely as a result of the increased terminal differentiation of the hairs secondary to EGFR inhibition (Hu et al., 2007). Trichomegaly is not only cosmetically disturbing when resulting in long and unruly eyelashes, but it can result in serious ocular complications in the event of trichiasis, or ingrown eyelashes; Hu et al., 2007). Ophthalmology referral is indicated if there are signs of blepharitis, keratitis, or refractory trichiasis (Burtneess et al., 2009; Guggina et al., 2017; Hu et al., 2007). Interestingly, a review of published cases revealed that trichomegaly, like an EGFR inhibitor-induced rash, developed mainly in patients who responded to therapy (Alexandrescu et al., 2009). In addition to trichomegaly, hirsutism of the upper lip is another common sequela of targeted therapies that may be particularly bothersome to women (Macdonald et al., 2015).

Treatment of hair changes from targeted drugs depends on the adverse effect. For nonscarring alopecia, topical minoxidil may be useful to improve hair regrowth (Macdonald et al., 2015), and aggressive management of scalp rashes as described previously is important to prevent scarring (Guggina et al., 2017). For trichomegaly, routine eyelash trimming is necessary. For hirsutism, women may opt to shave or pluck their upper lip hairs, but in severe cases, topical eflornithine or laser hair removal can be trialed to slow the growth of terminal hairs or (Macdonald et al., 2015). Women should be counseled on the increased sensitivity of their skin to irritation, xerosis, and superinfection should these treatments be recommended. Fortunately, most hair changes are reversible after discontinuation of therapy (Guggina et al., 2017; Pinto et al., 2011).

### Hand-foot skin reaction

HFSR is a common adverse effect of MKIs such as sorafenib, sunitinib, regorafenib, cabozantinib, and axitinib and is the dermatologic toxicity that results in the most frequent dose reduction and interruption for targeted drugs (Belum et al., 2016; Huggins et al., 2008). HFSR has an incidence of up to 62% in patients receiving sunitinib or sorafenib and may be augmented when MKIs are used in conjunction with VEGF inhibitors such as bevacizumab (Chu et al., 2008; Lipworth et al., 2009; Rosenbaum et al., 2008).

Similar to HFS from traditional chemotherapy, studies have shown an increased incidence of MKI-induced HFSR in women (Dranitsaris et al., 2012; Maki et al., 2009; Tsuchiya et al., 2013), although the reason is unknown. Furthermore, HFSR significantly affects patients' quality of life, as demonstrated in multiple studies. Nardone et al. (2012) used the Skindex-16 scale to assess the impact of MKI-induced HFSR on health-related quality of life and found that although HFSR affects the physical domain the most, a significant impact on the emotional and functional domain was noted, correlating with the severity of HFSR (Huggins et al., 2008). In addition, Komatsu et al. (2019) interviewed 20 patients with chemotherapy-induced HFS or targeted therapy-induced

HFSR and reported that patients with these toxicities expressed helplessness, social withdrawal, and decreased willingness to continue anticancer therapy.

### Clinical presentation

MKI-induced HFSR has distinct differences from HFS secondary to traditional chemotherapy. Although HFSR may also result in dysesthesia and erythema on the palms and soles, it typically presents with hyperkeratosis and painful callosities with underlying erythema (Fig. 3E; Degen et al., 2010; McLellan and Kerr, 2011). Because of these characteristic hyperkeratotic lesions, HFSR has also been referred to as palmar-plantar epidermal hyperplasia (Degen et al., 2010). Blister development may occur in more severe cases.

HFSR may occur over the digit tips, interphalangeal joints, and thenar and hypothenar eminences (Gomez and Lacouture, 2011). Unlike HFS, HFSR has not been reported to occur in intertriginous areas (Degen et al., 2010). HFSR is usually reported during the second to fourth week of sorafenib therapy and the first to third month of sunitinib therapy (Degen et al., 2010). Friction likely plays a role in pathogenesis because these lesions often affect pressure-bearing or trauma-prone areas on the palms and soles (Chu et al., 2008; McLellan and Kerr, 2011). A vascular mechanism has also been suggested, in contrast to the eccrine-associated mechanism of HFS (Degen et al., 2010).

### Prevention and treatment

Preventive measures focus on minimizing friction to vulnerable areas by wearing supportive socks (e.g., running socks), gel inserts, and soft shoes; avoiding mechanical irritation of the hands; and avoiding temperature extremes (Chu et al., 2008). The removal of existing calluses prior to treatment is also recommended (McLellan et al., 2015), and referral to podiatry can be particularly helpful. Urea cream was recently investigated as a preventive measure for HFSR in a RCT with promising results (Ren et al., 2015).

HFSR is graded similarly to HFS, as described previously in Table 3. Grades 1 and 2 HFSR are commonly managed with non-pharmacologic strategies such as emollients and topical keratolytics (e.g., 10–40% urea-based cream or 5–10% topical salicylic acid; Chu et al., 2008; McLellan et al., 2015; Rosenbaum et al., 2008). Tazarotene 0.1% cream, fluorouracil 5% cream, and clobetasol propionate 0.05% ointment may also be used for higher-grade rashes on hyperkeratotic and erythematous areas (McLellan and Kerr, 2011). Application under occlusion of cotton gloves/socks may help. A recent RCT demonstrated superior performance of ceramide-containing hydrocolloid dressing compared with urea creams in patients with grade 1 HFSR on the feet (Shinohara et al., 2014). Due to the substantial impact on quality of life, grade 3 HFSR typically warrants a 50% dose reduction, and the targeted agent can often be restarted after symptom resolution without recurrence (McLellan and Kerr, 2011; Rosenbaum et al., 2008).

Case reports and small studies have described the successful use of topical calcipotriol (Demirkan et al., 2017), taohongsiwu (a traditional Chinese medication; Zhao et al., 2014), heparin ointment (Li et al., 2013), vitamin E (Bozkurt Duman et al., 2011), and phototherapy with psoralen and ultraviolet A (Bos et al., 2012) or B (Hung et al., 2012). For associated dysesthesia, gabapentin or pregabalin may be tried (Lilly et al., 2015).

### Miscellaneous skin reactions

Although we have discussed the most common dermatologic adverse effects of several classes of targeted therapy, a variety of other cutaneous reactions may occur. For instance, maculopapular

exanthems may develop during treatment with BRAF inhibitors, MKIs, and imatinib, among other agents (Balagula et al., 2011). BRAF inhibitors may also result in phototoxicity and panniculitis mimicking erythema nodosum, and other MKIs (e.g., imatinib) may result in periorbital edema and pigmentary changes (McClelland et al., 2010; Sollfrank et al., 2019; Vance et al., 2017; Zimmer et al., 2012). VEGF inhibitors including bevacizumab and MKIs that also target VEGF, such as sunitinib or sorafenib, may lead to mucocutaneous hemorrhage. This may present as epistaxis, hemoptysis, or sometimes life-threatening pulmonary or gastrointestinal bleeding; therefore, these drugs should not be started in the presence of preexisting skin or mucosal bleeding (Libert et al., 2010).

BRAF inhibitors have been associated with squamous proliferations, including verrucae, squamous cell carcinomas, and keratoacanthomas, although combination BRAF-MEK inhibitor therapy has reduced the incidence of these occurrences (Balagula et al., 2011). Stomatitis and acneiform rash may occur from mTOR inhibitors, and sHH inhibitors may result in dysgeusia (Macdonald et al., 2015).

### Immune checkpoint inhibitors

ICPIs have emerged as robust antitumoral agents that harness the immune system to combat cancer. These antibodies block immune checkpoints, which are used by tumor cells to evade immune surveillance. The main classes include anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4), anti-programmed cell death protein 1 (anti-PD1), and anti-programmed death-ligand 1 (anti-PD-L1) antibodies. ICPIs are approved for use in numerous cancers (Table 1). Although these drugs promote an impressive antitumoral response, they may also result in autoimmune and inflammatory reactions, referred to as immune-related adverse events (irAEs), as a consequence of immune disinhibition.

Dermatologic toxicities are among the most common irAEs, with an overall risk of 24% and an incidence of up to 68% according to some studies (Curry et al., 2017; Lacouture and Sibaud, 2018; Lacouture et al., 2014; Minkis et al., 2013). Furthermore, a combination of anti-CTLA-4/anti-PD-1 therapy is correlated with more frequent and severe irAEs (Sibaud, 2018). Although irAEs can affect almost any organ system, the skin is often the first affected, with an average latency of onset of 4 weeks after treatment initiation (Coleman et al., 2019).

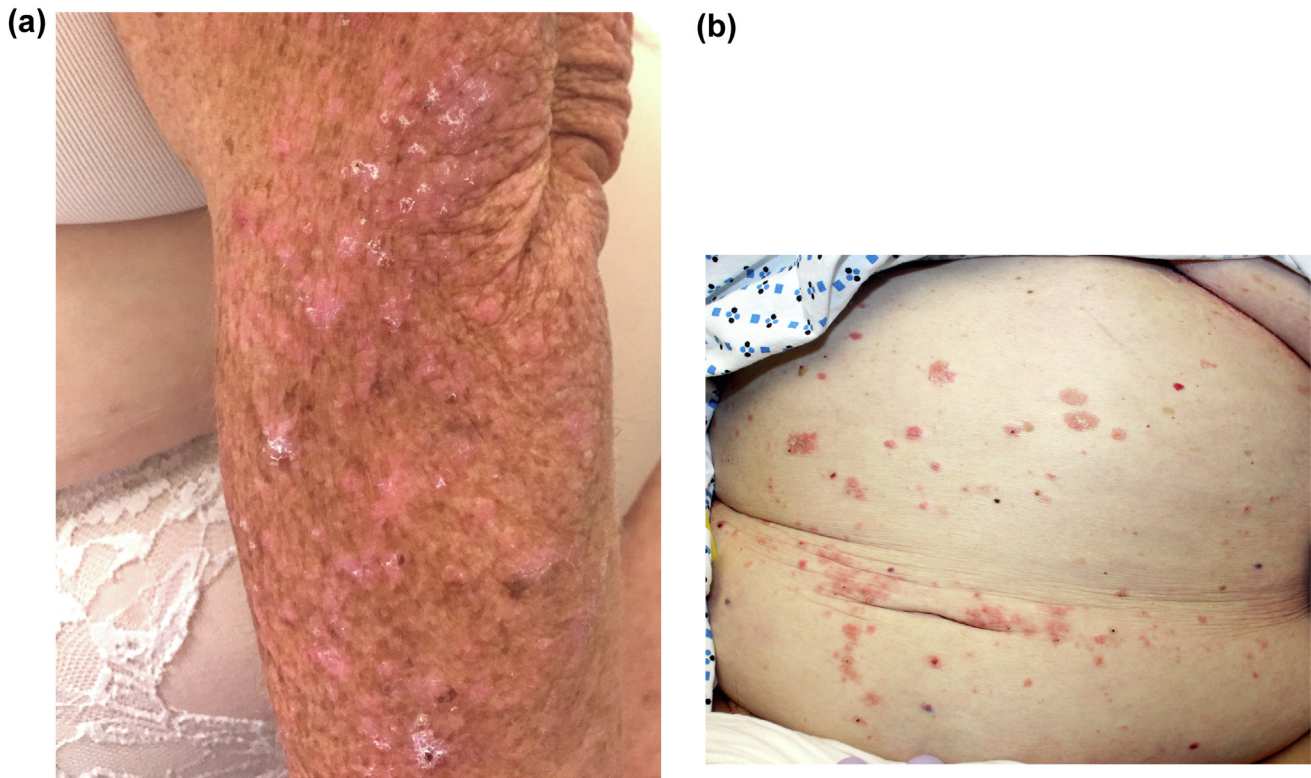
Interestingly, dermatologic irAEs may be a surrogate marker for response rates. One multivariate survival analysis showed that ICPI-induced rash was the only class of irAE associated with a statistically significant increase in overall survival (Freeman-Keller et al., 2016). Other studies have also shown that dermatologic irAEs are positively correlated with tumor response (Rogado et al., 2019).

Not surprisingly, dermatologic irAEs to ICPIs frequently affect patients' quality of life. For example, ICPI-induced pruritus was reported in one study to not only compromise quality of life but also cause functional and emotional impairment (Phillips et al., 2019b). Furthermore, the same study found that ICPI-induced pruritus caused a greater decrease in quality of life in women than in men (Phillips et al., 2019b).

Given the wide spectrum of dermatologic reactions that generally affect men and women equally, we will briefly highlight the most common toxicities.

### Clinical presentation

Pruritus, maculopapular eruptions or exanthems, lichenoid dermatitis, and vitiligo are the most common dermatologic irAEs



**Fig. 4.** (A) Lichenoid dermatitis presenting as discrete pink-violaceous papules and plaques with overlying white scale on the arm during treatment with the anti-PD-1 agent nivolumab; (B) tense bullae and urticarial plaques on the abdomen characteristic of bullous pemphigoid in a patient on anti-PD-1 therapy for metastatic melanoma.

encountered with ICPIs. In addition, eczematous, psoriasiform, immunobullous, granulomatous, and severe cutaneous adverse reactions may occur (Coleman et al., 2019; Curry et al., 2017; Lacouture and Sibaud, 2018; Sibaud, 2018; Siegel et al., 2018a,b).

Pruritus may develop in up to one-third of patients and can vary from mild to severe or even be debilitating. Maculopapular reactions may present as exanthematous reactions similar to those seen from antibiotics (Coleman et al., 2019).

Lichenoid dermatitis can manifest similarly to lichen planus with discrete pruritic, pink-violaceous papules or plaques with overlying white scale; it favors the trunk and extremities (Fig. 4A), but erosive mucosal presentations can occur (Coleman et al., 2019; Collins et al., 2017; Lacouture and Sibaud, 2018). Vitiligo-like leukoderma typically develops in patients with melanoma but has been occasionally reported in patients with other malignancies. Clinically, the depigmentation can vary from that seen in classical vitiligo (periorificial/acral) and present in a more widespread and photodistributed manner, favoring the head, neck, trunk, and extremities (Coleman et al., 2019).

Life-threatening severe cutaneous adverse reactions are fortunately rare and include cases of Stevens-Johnson syndrome/toxic epidermal necrolysis-like presentations (may present classically or with an insidious onset in a progressing exanthem), drug reaction with eosinophils and systemic symptoms, and acute generalized exanthematous pustulosis (Lacouture and Sibaud, 2018). Immunobullous reactions may occur in approximately 1% of patients on PD-1 axis blockers and generally present more severely than other irAEs (Siegel et al., 2018a,b). Most cases manifest as bullous pemphigoid (urticarial plaques, tense vesicles/bullae; Fig. 4B), although bullous lichenoid reactions, erythema multiforme, linear immunoglobulin A bullous dermatosis, and lichen planus pemphigoides presentations may also occur (Siegel et al., 2018a,b).

#### Grading and management

ICPI-associated rashes are generally graded according to body surface area (BSA) involvement and affect ADLs as discussed in previous sections (Table 3). Grades 1 and 2 dermatologic irAEs are typically managed with topical corticosteroids and antipruritic agents. For higher-grade or persistent rashes, oral or intravenous corticosteroids or treatment interruption may be indicated (Phillips et al., 2019a,b). Life-threatening reactions, such as Stevens-Johnson syndrome/toxic epidermal necrolysis, require the discontinuation of immunotherapy, hospitalization, and intravenous corticosteroids and adjunctive agents if necessary (e.g., cyclosporine, intravenous immune globulin, and anti-tumor necrosis factor blockers). In addition, treatment should be directed against the specific type of reaction (e.g., phototherapy or acitretin for psoriasiform or lichenoid rashes; doxycycline/niacinamide, omalizumab, rituximab for bullous pemphigoid; Coleman et al., 2019; Phillips et al., 2019a,b). Pruritus can be treated with antihistamines, but gabapentin, pregabalin, aprepitant, phototherapy, doxepin, and/or systemic corticosteroids may be required in more severe cases (Coleman et al., 2019; Collins et al., 2017).

#### Endocrine therapy

Breast cancer is the most frequently diagnosed cancer in women, and an estimated 60% to 75% of breast cancers are estrogen receptor positive (Bray et al., 2018; Poggio et al., 2017; Siegel et al., 2018a,b). The mainstay of therapy for estrogen receptor-positive tumors involves surgical resection with possible radiation therapy, followed by adjuvant endocrine therapy for 5–10 years with or without additional adjuvant chemotherapy (Burstein et al., 2016; Goss et al., 2016; Poggio et al., 2017; van Maaren



et al., 2016). Although most women who receive endocrine therapy are being treated for breast cancer, it is also used for other malignancies, such as endometrial and adrenocortical carcinoma (Else et al., 2014; Qin et al., 2016; Ushijima et al., 2007).

In this section, we review the most common dermatologic adverse events associated with adjuvant breast cancer treatment, including aromatase inhibitors (anastrozole, letrozole, exemestane) and selective estrogen receptor modulators (e.g., tamoxifen, toremifene, and raloxifene).

### Flushing

Selective estrogen receptor modulators and aromatase inhibitors, as well as gonadotropin-releasing hormone agonists such as leuprolide (used for ovarian suppression in breast cancer treatment), can cause a pharmacologic menopause reaction characterized by flushing and night sweats (Burstein et al., 2016; Moon et al., 2017; Sadeghian et al., 2017). In general, tamoxifen results in more frequent and severe hot flashes than aromatase inhibitors such as exemestane (Jones et al., 2007). In addition, chemotherapy can compound this risk by inducing early menopause through premature cessation of ovarian function (Fenlon et al., 2018; Runowicz et al., 2016).

Hot flashes as a result of breast cancer treatment are often more severe than menopausal hot flashes in healthy women (Harris et al., 2002). The severity of hot flashes in patients with breast cancer negatively correlates with perceived quality of life and is associated with increased sleep disturbances, greater pain levels, and psychological dysfunction including depression (Chang et al., 2016; Gupta et al., 2006; Moon et al., 2017).

### Clinical presentation

Hot flashes begin with a sudden sensation of warmth, followed by flushing, sweating, and sometimes anxiety and palpitations (Moon et al., 2017; Sadeghian et al., 2017). The flush, which is a vasomotor phenomenon characterized by cutaneous vasodilation, is usually distributed over the face, neck, and chest because the cutaneous vasculature in these regions is superficial (Sadeghian et al., 2017).

Although the precise mechanism of hot flashes is not fully understood, they are thought to be related to dysfunctional hypothalamic temperature regulation as a result of declining estrogen levels (Archer et al., 2011).

### Treatment

First-line treatment involves avoiding triggers such as heat, alcohol, hot beverages and food, and stress (Sadeghian et al., 2017; Wilkin, 1993). If behavioral modifications fail, pharmacologic management may be necessary. Hormone replacement therapy is contraindicated in patients with a history of breast cancer (Moon et al., 2017), but nonhormonal treatment options include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and gabapentin. The selective serotonin reuptake inhibitors that are safe to use with tamoxifen include citalopram, sertraline, and escitalopram (Barton et al., 2010; Freeman et al., 2011; Loprinzi et al., 2009); paroxetine and fluoxetine should be avoided because they inhibit the cytochrome P450 2D6 pathway (Carris et al., 2014; Hemeryck and Belpaire, 2002; Kelly et al., 2010).

In addition, both venlafaxine (75 mg/day) and higher doses of gabapentin (at least 900 mg/day) have been reported to decrease the hot flash score over the first 4 weeks of treatment by 61% and 49%, respectively (Loprinzi et al., 2000; 2009; Pandya et al., 2005). For severe and refractory cases, stellate ganglion blockade

may be considered, although further controlled studies are needed (Lipov et al., 2008; Van Gastel et al., 2012). Cognitive behavioral therapy has also been shown to reduce the perceived burden of breast cancer treatment-induced menopausal symptoms and hot flash frequency (Duijts et al., 2012; Fenlon et al., 2018).

### Alopecia

A meta-analysis of endocrine therapy-induced alopecia found that 2.2% to 2.5% of patients receiving anastrozole, exemestane, or letrozole in clinical trials experienced hair loss, and the incidence of alopecia in clinical trial participants on tamoxifen therapy was 9.3% (Saggar et al., 2013). Furthermore, the incidence of alopecia increases when endocrine therapies are combined or sequentially administered. For example, in clinical trial participants receiving tamoxifen followed by anastrozole, the incidence of all-grade alopecia was 14.7% (Saggar et al., 2013).

Endocrine therapy-induced alopecia is thought to have a physiology similar to that of androgenetic alopecia. In androgenetic alopecia, increased dihydrotestosterone concentration in the hair follicle has been implicated in the shortening of the anagen phase of hair growth, eventually leading to follicular miniaturization (Olsen et al., 2005). Similarly, aromatase inhibitors block the conversion of peripheral androgens into estrogen, thereby increasing the amount of androgen available for conversion into dihydrotestosterone (Rossi et al., 2013).

In addition, there is increased expression of follicular androgen receptors in areas of tamoxifen-induced alopecia, suggesting that like the aromatase inhibitors, tamoxifen may also increase androgen receptor signaling in the hair follicle (Nonomura et al., 2012). Furthermore, estradiol is thought to prolong the anagen phase in the human scalp skin, and tamoxifen's antagonistic effects on the estrogen receptor could also play a role in shortening the anagen phase of hair growth, ultimately resulting in follicular miniaturization (Nonomura et al., 2012).

As discussed previously, alopecia in women with cancer frequently affects quality of life. One study of 112 patients with endocrine therapy-associated alopecia found that most patients presented with a mild form of alopecia (grade 1 or <50% hair loss); however, an alopecia-related quality of life survey indicated that it had a negative emotional impact (Freites-Martinez et al., 2018).

### Clinical presentation

Endocrine therapy-associated alopecia typically manifests as female pattern hair loss, which is characterized by two predominant patterns (Freites-Martinez et al., 2018; Olsen et al., 2005; Rossi et al., 2013): most commonly a diffuse thinning over the top of the scalp without recession of the frontal hairline (Fig. 5; Olsen, 2001), and hair loss accentuated at the front of the scalp creating a Christmas tree pattern at the center part (Olsen et al., 2005).

In addition, the frontotemporal recession that is more characteristic of male pattern androgenetic alopecia has been reported in women undergoing endocrine therapy for breast cancer (Freites-Martinez et al., 2018; Nonomura et al., 2012; Rossi et al., 2013). In a recent single-institution study of 112 female patients with a diagnosis of alopecia attributed to endocrine therapy for breast cancer, 83% of patients exhibited mild-to-moderate alopecia over the crown of the scalp, and 76% had more prominent bitemporal than mid-anterior hairline recession, suggesting a combination of both male and female patterns hair loss (Freites-Martinez et al., 2018). The mean onset of alopecia was 16.8 months from the start of endocrine therapy, and in 92% of study participants the alopecia was classified as grade 1 per the Common Terminology Criteria for Adverse Events (Freites-Martinez et al., 2018).



**Fig. 5.** Hair thinning over the crown of scalp during tamoxifen therapy for breast cancer, consistent with endocrine therapy-associated female pattern hair loss.

#### Treatment

It is important to first rule out other causes of hair thinning or hair loss, such as thyroid gland dysfunction or low levels of iron, vitamin D, or zinc (Saggar et al., 2013). In addition, a thorough scalp examination should be performed to exclude alopecia areata and other forms of alopecia.

Treatment with 5% topical minoxidil resulted in a moderate to significant improvement of alopecia in 80% of female patients with breast cancer (Freites-Martinez et al., 2018), but the use of oral minoxidil has not been well studied in this population. For severe alopecia that is refractory to topical minoxidil, spironolactone may be considered for its antiandrogenic effects after discussion with oncology, given the theoretical risk of increasing estrogen levels in patients with hormone-positive breast cancer (Olsen et al., 2005; Saggar et al., 2013).

One recent review of 95 women treated with spironolactone from four retrospective cohort studies, one case study, and one double-blind crossover study found that estrogen levels were increased in only 26% of patients, decreased in 6.3% of patients, and unchanged in 67% of patients (Rozner et al., 2019). With regard to 5- $\alpha$  reductase inhibitors, there is a lack of sufficient evidence to support its use in breast cancer. In addition to medical approaches, wigs, tattooing, and tinted powders may be considered as camouflaging techniques, and hair transplantation can be considered in patients with regions of high-density donor hair for transplantation to localized areas of hair loss, as opposed to patients with diffuse thinning over the entire scalp (Olsen et al., 2005).

#### Vulvovaginal atrophy

Due to the high estrogen receptor expression in the vulva, anti-estrogen therapies may cause vulvovaginal dryness and atrophy (Moeggele et al., 2012). In a cross-sectional study of postmenopausal patients with breast cancer, 40% of patients on adjuvant tamoxifen therapy and 74% of patients on an adjuvant

aromatase inhibitor reported insufficient vaginal lubrication. In the same study, dyspareunia was reported in 31% of patients with breast cancer taking tamoxifen and 57% of patients taking aromatase inhibitors. These results suggest that, although the symptoms of vulvovaginal atrophy are common in patients who take either form of adjuvant endocrine therapy, they are more prevalent in patients taking aromatase inhibitors (Baumgart et al., 2011).

Other adverse effects of anti-estrogen therapy on sexual health include low sexual interest, orgasmic dysfunction, and overall dissatisfaction with sex life (Baumgart et al., 2011). Importantly, these adverse effects on sexual health significantly affect patients' quality of life. Low sexual interest and dyspareunia are associated with depressed mood in patients with breast cancer who receive aromatase inhibitors, and the sequelae of vulvovaginal atrophy has also been shown to be related to poor body image and lower relationship satisfaction (Baumgart et al., 2011; Boquiren et al., 2016; Falk and Bober, 2016).

#### Clinical presentation

Hypoenestrogenism causes thinning of the vulvovaginal epithelium, decreased dermal collagen and elastin content, loss of vaginal rugae, and decreased blood flow to the vulvovaginal region. As a result, the vulvovaginal skin appears pale, dry, and smooth and has decreased elasticity. In addition, there is thinning of the pubic hair, resorption of the labia minora, and loss of subcutaneous fat pads (Falk and Bober, 2016; Lev-Sagie, 2015).

Typically, the first symptom of vulvovaginal atrophy is loss of vaginal lubrication during intercourse (Lev-Sagie, 2015). Later, vaginal dryness, soreness, burning, irritation, and pruritus may occur both with daily activities and with sexual activity (Lev-Sagie, 2015). Dyspareunia, lacerations around the introitus from intercourse due to skin fragility, and secondary vaginismus from painful sexual experiences are also common adverse effects of selective estrogen receptor modulators and aromatase inhibitors (Falk and Bober, 2016).

#### Treatment

Treatment involves improving vaginal elasticity and increasing vaginal lubrication (Falk and Bober, 2016). The use of vaginal dilators and pelvic floor physical therapy has been reported to improve vaginal elasticity within 4 to 8 months of therapy (Falk and Bober, 2016). For vaginal lubrication, the first-line therapies are nonhormonal agents, including short-acting lubricants for sexual activity and longer-acting moisturizers for replacement of normal vaginal secretions (Falk and Bober, 2016; Sinha and Ewies, 2013).

Although vaginal estrogen therapy has excellent outcomes in healthy menopausal women who experience vulvovaginal atrophy, the use of local estrogen therapy is controversial in patients with breast cancer. A small study of six patients with breast cancer on aromatase inhibitors who also received vaginally administered estrogen reported significantly elevated serum estrogen levels in the first 2 weeks after starting therapy (Kendall et al., 2006). The early elevation in systemic estrogen is attributed to increased estrogen resorption due to the thin vaginal epithelium that is present at the start of therapy, as serum estrogen levels return to normal postmenopausal levels after the initial 2-week elevation (Falk and Bober, 2016).

However, a more recent case-control study examined rates of breast cancer recurrence in patients treated with tamoxifen or aromatase inhibitors with local estrogen therapy and did not find an increased risk of breast cancer recurrence (Le Ray et al., 2012). Therefore, careful assessment and discussion with patients and their oncologist is recommended before initiating vaginal estrogen

therapy in patients with breast cancer who are concurrently taking antiestrogen therapies.

## Conclusion

Dermatologic adverse effects commonly affect women with cancer and range in presentation from mild to severe or even life-threatening toxicities. These cutaneous adverse effects may affect the skin, hair, nail, and mucosal surfaces and develop from multiple classes of anticancer systemic therapies, including traditional chemotherapy, targeted and immune checkpoint inhibitor therapy, and endocrine therapy.

Dermatologic toxicities of oncologic therapy are particularly burdensome to women with cancer and can lead to physical and emotional distress (Gandhi et al., 2010; Hackbarth et al., 2008; Lee et al., 2018; Ra et al., 2013). Involvement of the mucosal surfaces can impair nutritional status, but hand/foot toxicities may lead to functional impairment. Close attention should be paid to alopecia, papulopustular rash, and nail infections/onycholysis, which may negatively affect women's quality of life.

The dermatologic stigmata of cancer therapy may be so potent that women may develop depression, anxiety, and social withdrawal and may even decline further cancer therapy, highlighting the importance of early dermatologic intervention (Boone et al., 2007; Wagner and Lacouture, 2007). When severe toxicities lead to disruption of cancer therapy, patients' overall survival and response to treatment may also be affected. Therefore, timely diagnosis and management of these conditions by dermatologists and oncologists in a multidisciplinary team is crucial for the comprehensive care of women with cancer.

This article is accompanied by a Patient Page, a short summary to guide patients who may wish to access credible information with regard to dermatologic conditions in women with cancer and strategies for prevention and management.

## Conflict of Interest

None.

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## Study Approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

## Appendix A. Supplementary data

For patient information on skin cancer in women, please click on Supplemental Material to bring you to the Patient Page. Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijwd.2019.10.003>.

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