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Introduction to Anticancer Therapies

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Overview: Cancer Incidence and Types of Systemic Anticancer Therapies

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

anticancer therapies and their associated dermatologic AEs (Figure 1.1; also see Tables 1.1 and 1.2). The main subjects of each dermatologic manifestation will be discussed in the following chapters.

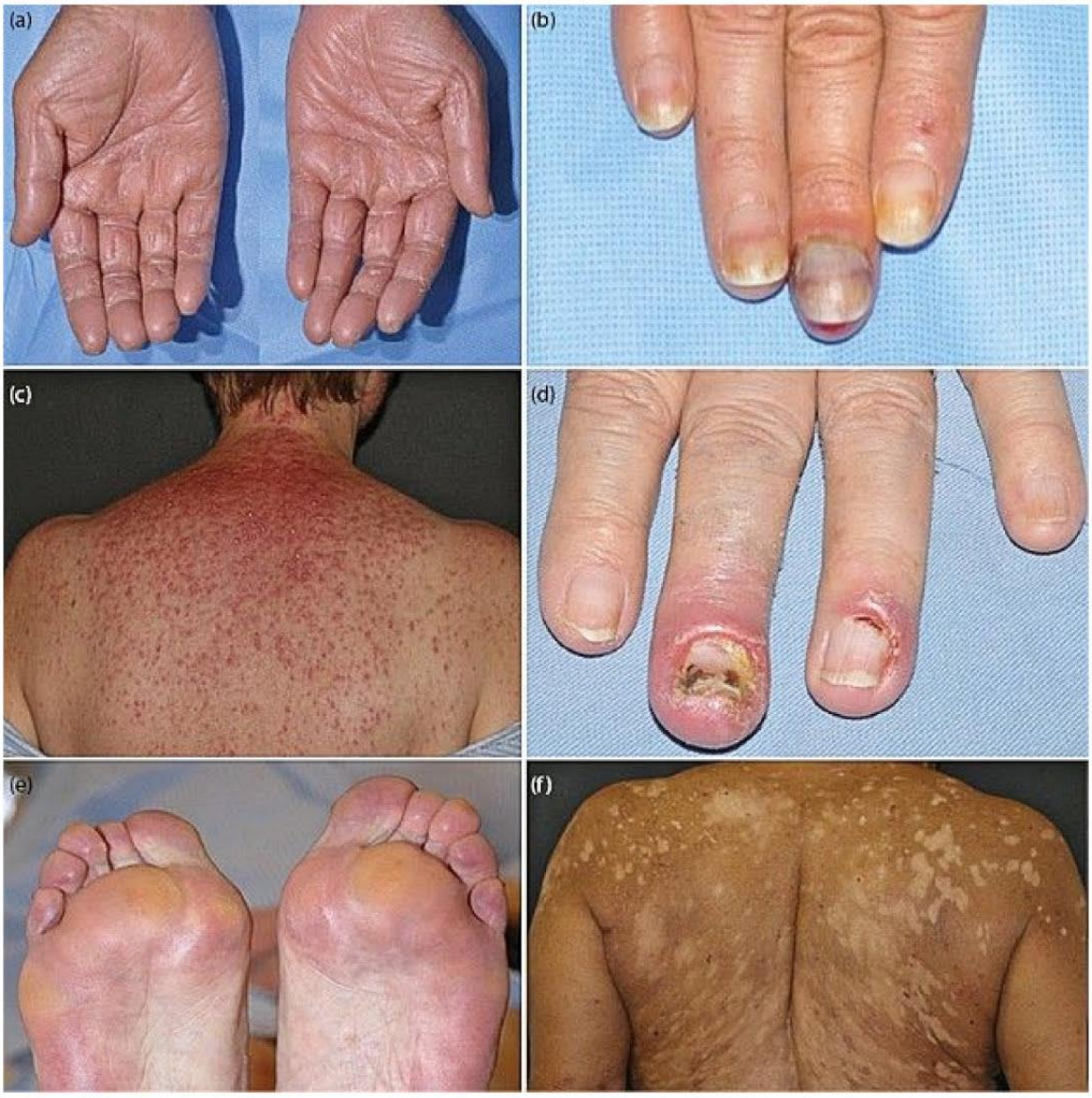

FIGURE 1.1 Dermatologic adverse events to anticancer therapies. (a) Hand-foot syndrome induced by capecitabine (b) swelling of fingertips, subungual hemorrhage, and onycholysis related to docetaxel. (c) Papulopustular eruption related to EGFRI. (d) Paronychia related to EGFRI. (e) Hand-foot skin reaction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

TABLE 1.1

Summary of Anticancer Therapies and Their Associated Dermatologic Adverse Events

Types of Systemic Anticancer	Dermatologic Adverse Events	Common Culprits (Incidence %)

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

	face (5–9%) (79), and HFSR (80)	
MEK inhibitors		Trametinib, cobimetinib
BRAF inhibitors plus MEK inhibitors		
Hedgehog inhibitors	Alopecia, follicular dermatitis, hypersensitivity reaction, KAs and cutaneous SCCs	Vismodegib, sonidegib
Immune checkpoint inhibitors	Rash, pruritus, vitiligo	Immune checkpoints inhibitors: Anti-CTLA4, anti-PD1, anti-PD-L1
	Autoimmune bullous dermatosis	Anti-PD1 and anti-PD-L1
	Severe cutaneous adverse reactions (SCARs)	Anti-CTLA4, anti-PD1 and anti-PD-L1
Chimeric antigen receptor modified T lymphocytes (CAR-T cell) therapy	Rash (cytokine releasing syndrome [CRS])	CAR-T cell therapy
Radiation therapy	Radiation dermatitis (RD)	Ionized radiation
Hematopoietic stem cell transplantation (HSCT)	Cutaneous graft-versus-host disease (GVHD)	HSCT
Other cutaneous adverse reactions from cancer treatment	Skin infections associated with anticancer treatment (63)	
	Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	SJS: Bendamustine TEN: Bendamustine, busulfan, chlorambucil, fludarabine, lomustine, and procarbazine (Food and Drug Administration Adverse Event Reporting System [FAERS])

TABLE 1.2

CTCAE Grading of Dermatologic Adverse Events Associated with Anticancer Therapies

Papulopustular Eruption or Acneiform Eruption

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

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

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

Pigmentary Changes

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

Hair and Nail Changes

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

Mammalian Target of Rapamycin Inhibitors

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

EGFRI-induced PPE (64), which are thought to be related to the inhibition of the PI3K-Akt-mTOR signaling, one of the downstream effector pathways of the EGFR (50).

Multitargeted Kinase Inhibitors

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

Hand-Foot Skin Reaction

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

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

BRAF Inhibitors

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

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

Skin Rashes