
1 Dermatology and Oncology

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Epidemiology and Burden of Disease

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Introduction

Due to recent advances in cancer therapies, patients are now living longer than ever before. For all diagnosed cancers, the 5-year relative survival has increased from 50% in 1975–1977 to 66% in 1996–2004 [1]. From 1990 to 2003, all-site cancer deaths in the United States decreased by 1% per year and these declines were especially pronounced for some of the most common malignancies including breast, prostate, colorectal, and lung cancers [2]. In the United States in 2009, there were 1 479 350 new cancers expected to be diagnosed [1], of which 52–87% were treated with surgery, 24–35% with chemotherapy, and 47–51% with radiation therapy (based on 2002 data for breast, lung, and colorectal cancers) [3]. Fifty to sixty thousand hematopoietic stem cell transplants are performed worldwide per year [4].

The large number of people being diagnosed with cancer in combination with increased survival rates have led to an increased number of patients living with a history of cancer, estimated to be 11.1 million in 2005 in the United States [1], of which 270 000 are survivors of pediatric cancers [5]. The increased number of patients living with and after cancer has revealed a number of dermatologic issues specific to this population: affecting cutaneous health, causing a financial burden, decreasing health-related quality of life, and impairing consistent drug dosing.

Dermatologic health in cancer patients and survivors

The relationship between the skin, hair, and nails and internal malignancies is manifested in various ways and in all phases of a patient's experience with cancer (Figure 1.1). Even before a diagnosis of cancer is made, the skin may be affected by genetic

syndromes with an increased cancer risk, environmental carcinogens leading to both skin conditions and internal malignancies, or paraneoplastic syndromes. Before treatment begins, patients can be affected by a number of dermatologic problems, most commonly tinea pedis/onychomycosis, pruritus, and xerosis [6]. After the diagnosis of cancer is made, cancer treatments (systemic agents, radiation, therapeutic transplants, and surgeries) can result in a number of skin, hair, and nail adverse events (AEs) that develop either as a result of idiosyncratic reactions or as an effect on rapidly proliferating cells (of which the skin, hair, and nails are prototypical structures).

The number of dermatologic AEs of chemotherapeutic agents is large and continues to expand as new agents come into use (see Appendix 1.1). In 2008, of approximately 384 000 routine AEs for phase I and II studies were reported to the Cancer Therapy Evaluation Program (CTEP) via the Clinical Data Update System (CDUS), 30 834 (8.04%) were dermatologic in nature (personal communication, Clinical Data Update System). Actual numbers of dermatologic AE to therapy may be higher than these estimates because of underreporting and inaccurate grading of AEs [14]. These inaccuracies have at least partly been brought about by difficulty applying existing grading systems to distinct dermatologic AEs, as has been demonstrated with other toxicities [15]. Another difficulty is grading AEs that are of low grade but prolonged duration [16]. Improved reporting of dermatologic AE is expected as focused grading scales are created [17].

In addition to the primary dermatologic toxicity of therapy, secondary skin infections are a frequent complication. In one study of patients receiving epidermal growth factor receptor inhibitors (EGFRIs), 38% of patients showed evidence of infection at sites of dermatologic toxicities [18]. Treatment modalities other than chemotherapy including radiation therapy, cancer-related surgery, and hematologic transplants are associated with distinct dermatologic toxicities and secondary infections (Figure 1.2).

Financial burden

In addition to the psychosocial effects (discussed in Chapter 6), dermatologic AEs also result in a financial cost to patients. Overall costs of treating cancer have increased by 75% from 1995 to

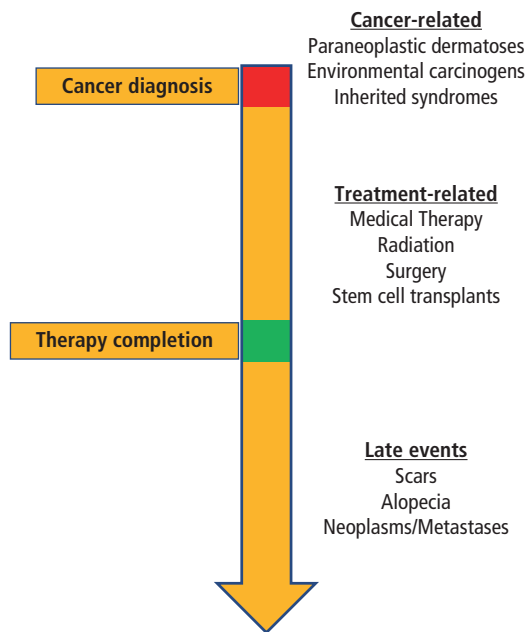


Figure 1.1 Dermatologic events in the life of the cancer patient and/or survivor [7]. GVHD, graft versus host disease. Adapted from Agha, 2007 [7].

2004 [3]. A portion of this cost can be attributed to supportive dermatologic care. Median medical costs per patient treated for head and neck or nonsmall cell lung cancer with radiochemotherapy are \$39,313 per patient with mucositis/pharyngitis and \$20,798 per patient without mucositis/pharyngitis [19]. Much of the increased cost was attributed to increased length of hospital stay [19]. For dermatologic AEs in patients treated with EGFRIs or platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) inhibitors, mean cost of treatment for dermatologic toxicities was \$2,496 per patient [20]. Costs associated with stem cell transplantation can be increased by as much as \$28,100 by development of acute graft versus host disease (GVHD) [21]. It is plausible that a prophylactic approach to managing treatment-induced AEs could decrease these associated costs.

Health-related quality of life

All of the described dermatologic toxicities due to cancer treatment can have a significant impact on a patient's health-related quality of life (HRQL). Patients most frequently report dermatologic AE as carrying a negative impact and of being unanticipated prior to therapy, with 67% of patients reporting that dermatologic AEs are worse than their initial belief [22]. Fifty-eight percent of patients rate chemotherapy-induced alopecia as the most traumatic side effect from their therapy and 8% of patients would decline chemotherapy because of fear of hair loss [23]. In a study of breast cancer patients receiving radiation therapy, the skin

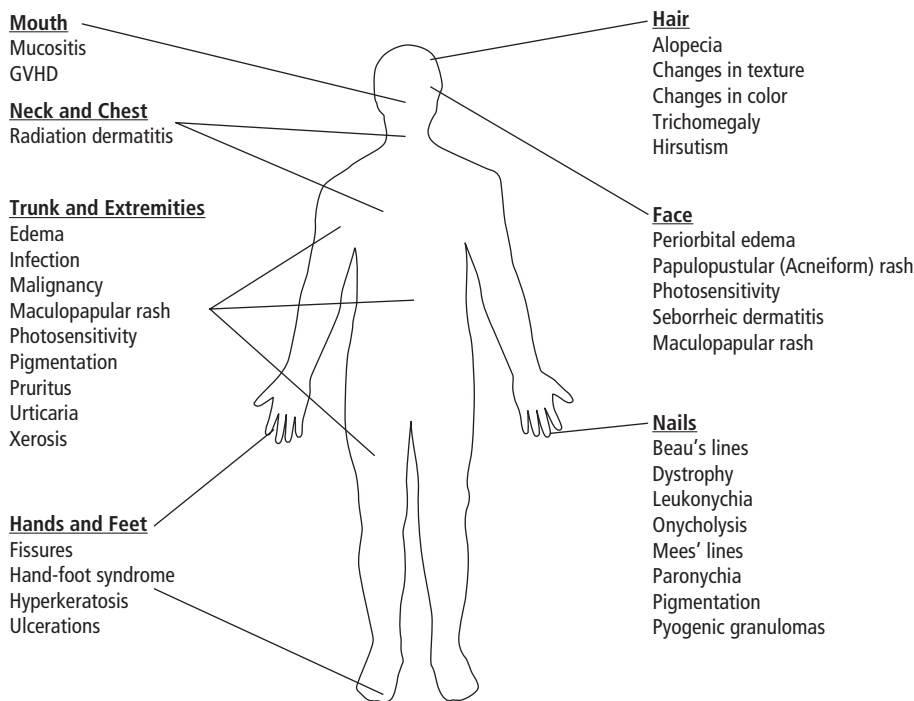


Figure 1.2 Locations of therapy-induced dermatologic toxicities.

changes induced by radiotherapy were found to negatively impact physical well-being, body image, emotional well-being, functional well-being, and treatment satisfaction [24]. Scars resulting from oncologic surgical procedures can lead to psychologic problems in 15% of survivors of childhood cancers [25]. In a prospective study measuring the frequency and impact on quality of life of dermatologic toxicities in women receiving chemotherapy, 34% of women reported dermatologic AEs as most important during treatment and they were the most common significant contributor to overall HRQL [26]. Of those who develop dermatologic AEs, 69% feel significantly limited in their daily activities [26].

Dosing of chemotherapy

Perhaps the most imposing challenge offered by dermatologic AE is their ability to result in dose modifications of anticancer therapies. Although the effects of anticancer therapy dose modification on progression-free survival or overall survival have not been evaluated, one can surmise that by reducing dose intensity, clinical outcome will be negatively affected. Studies linking the frequency and severity of dermatologic AEs to a longer median survival underscore the importance of managing dermatologic events, as patients who develop these untoward events are those most likely to benefit from their antineoplastic therapy [27]. Most notably, the papulopustular (acneiform) eruption to the EGFRIs (e.g., erlotinib, cetuximab, and panitumumab) has been shown to correlate with increased progression-free and overall survival in a variety of solid tumors [28,29].

In patients receiving cetuximab for example, up to 11.3% will develop a grade 3 or higher skin rash, necessitating dose reductions [30]. The development of mucositis is shown to lead to a twofold increased risk of chemotherapy dose reduction and limits the ability to give methotrexate for prevention of GVHD following autologous stem cell transplants [31]. Effectively recognizing and treating dermatologic toxicities to chemotherapy can minimize dose reductions and treatment interruptions as shown in the STEPP trial in which 12 doses were delayed in the prophylactic skin treatment arm, compared to 21 doses in the reactive arm [32].

Conclusions

The increasing number of cancer patients and survivors has led to an increased awareness of the HRQL components and treatment-related dermatologic manifestations seen in this patient population. These dermatologic toxicities are diverse and can have an enormous impact on the cutaneous health of patients, overall costs of treatment, healthcare-related quality of life, and consistent anticancer therapy. The recognition of all of these factors has led to a new field within dermatology: supportive oncodermatology, which is focused on the addressing the aforementioned dermatologic issues facing cancer patients and survivors.

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Appendix 1.1 Anticancer agents and associated adverse events affecting the skin, mucosa, hair, and nails. Based on data from Litt JZ, 2009 [8].

Drug	Skin	Mucosal/ENT	Hair	Nails
Alkylating agents				
Busulfan	Churg–Strauss syndrome, bullous dermatitis, eccrine squamous syringometaplasia, macular erythema (>10%), erythema multiforme (<1%), exanthems, Kaposi sarcoma, pigmentation (1–10%), purpura, urticaria (>10%), vasculitis, xerosis	Cheilitis, dysgeusia, mucositis, pigmentation	Alopecia (>10%)	Pigmentation
Thiotepa	Allergic reactions (1–10%), angioedema, eccrine squamous syringometaplasia, leukoderma, pigmentation (1–10%), pruritus (1–10%), rash (1–10%), urticaria (3%)	Stomatitis (<1%)	Alopecia (1–10%)	
Mechlorethamine	Acanthosis nigricans, angioedema, bullous dermatitis, cellulitis, cyst, dermatitis, erythema multiforme (<1%), exanthems (<1%), fungal dermatitis, herpes zoster (>10%), pigmentation, pruritus, purpura, squamous cell carcinoma, SJS, urticaria, xerosis	Dysgeusia (1–10%), tinnitus	Alopecia (1–10%)	
Melphalan	Angioedema, eccrine squamous syringometaplasia, edema, exanthem (4%), petechiae, pruritus (1–10%), purpura, rash (1–10%), scleroderma, urticaria, vasculitis (1–10%), vesiculation (1–10%)	Mucositis	Alopecia (1–10%)	Beau lines
Chlorambucil	Angioedema, edema, exanthem, facial erythema, herpes simplex, herpes zoster, Kaposi sarcoma, lupus erythematosus, necrosis, perianal irritation, photosensitivity, pruritus, psoriasis, purpura, rash (1–10%), Sézary syndrome, SJS, TEN, urticaria	Oral lesions	Alopecia	
Cyclophosphamide	Allergic reaction, angioedema, carcinoma, dermatitis, dermatitis herpetiformis, dermatofibromas, eccrine squamous syringometaplasia, edema, eosinophilic pustular folliculitis, erythema multiforme (<1%), exanthem, facial burning, graft versus host reaction, hand-foot syndrome, herpes zoster, lupus erythematosus, lymphoma, myxedema, neutrophilic eccrine hidradenitis, pemphigus, photo-recall, pigmentation (<1%), pruritus, purpura, scleroderma, SJS, TEN (<1%), urticaria, vasculitis	Gingival pigmentation, mucositis (10%)	Alopecia (universal and severe in one-third)	Beau lines, dystrophy, leukonychia, onychodermal band, pigmentation (<1%)
Ifosfamide	Allergic reaction (1–10%), dermatitis (1–10%), pigmentation (1–10%)	Oral lesions, sialorrhea (<1%), stomatitis (<1%)	Alopecia (50–100%)	Ridging (1–10%)
Carmustine	Dermatitis (<1%), eccrine squamous syringometaplasia, erythema, exanthems, telangiectasia, tenderness	Stomatitis (1–10%)	Alopecia (1–10%)	
Streptozocin	Edema, exanthems, pruritus, purpura, TEN			
Dacarbazine	Actinic keratoses, angioedema, erythema, exanthems, fixed eruption, photo-recall, photosensitivity (<1%), rash (1–10%), urticaria, vasculitis	Dysgeusia (1–10%), stomatitis (48%)	Alopecia (1–10%)	Pigmentation
Temozolomide	Allergic reactions, edema, hand-foot syndrome, Kaposi sarcoma, peripheral edema (11%), pruritus (8%), rash (8%)		Alopecia	
Etoposide	Allergic reactions (1–2%), diaphoresis, eccrine squamous syringometaplasia, erythema, erythema multiforme, exanthems, facial edema, hand-foot syndrome, neutrophilic eccrine hidradenitis, photo-recall, pigmentation, pruritus, purpura, rash, SJS, urticaria	Dysgeusia, mucositis (>10%), tinnitus, tongue edema	Alopecia (8–66%)	Beau lines, onychopathy
BCNU	Dermatitis (<1%), eccrine squamous syringometaplasia, erythema, exanthems, pigmentation, telangiectasia, tenderness	Stomatitis (1–10%)	Alopecia (1–10%)	

(Continued)

Section 1 Dermatology and Oncology

Drug	Skin	Mucosal/ENT	Hair	Nails
Antimetabolites				
Methotrexate	Acne, acral erythema, allergic reactions, angiomas, bullous dermatitis, capillaritis, carcinoma, dermatitis, dermatofibromas, eccrine squamous syringometaplasia, edema, eosinophilic pustular folliculitis, erosion of psoriatic plaques, erythema (>10%), erythema multiforme, exanthems (15%), furunculosis, herpes simplex, herpes zoster, lymphadenopathy, lymphoma, melanoma, molluscum contagiosum, necrosis, nodular eruption, non-Hodgkin lymphoma, photo-recall, photosensitivity (5%), pigmentation (1–10%), pruritus (1–5%), purpura, Raynaud phenomenon, SJS, telangiectasia, TEN (<1%), urticaria, vasculitis (>10%)	Aphthous stomatitis, dysgeusia, gingivitis (>10%), glossitis (>10%), mucositis	Alopecia (1–6%), pigmented bands	Discoloration, paronychia, pigmentation
Pemetrexed	Allergic reactions, desquamation (22%), edema, photo-recall, pressure necrosis, pruritus, purpura, rash (42%), vasculitis	Aphthous stomatitis, gingivitis, mucositis (5–17%)		
Capecitabine	Dermatitis (37%), diaphoresis (0.2%), edema (9%), erythema, exfoliative dermatitis (31–37%), hand-foot syndrome (7–58%), lupus erythematosus, photo-recall (<1%), photosensitivity, pigmentation, pruritus, purpura (0.2%), pyogenic granuloma, ulcerations, vesiculation, vitiligo, xerosis	Mucositis, oral candidiasis (0.2%), stomatitis (24%)	Alopecia (<1%)	Hyponychial dermatitis, nail loss, onychomadesis, paronychia, subungual hyperkeratosis
Cytarabine	Allergic reactions (<1%), angioedema (<1%), dermatitis, diaphoresis, edema (<1%), erythema, exanthems, lichenoid eruption, lupus erythematosus, peripheral edema, photosensitivity, purpura, urticaria, vasculitis	Dysgeusia, tinnitus, xerostomia (1–10%)		
Gemicitabine	Acral necrosis, allergic reactions (4%), cellulitis, dermatitis, diaphoresis, edema (13%), erysipelas, exanthems, hand-foot syndrome, linear IgA dermatosis, lipodermatosclerosis, livedo reticularis, necrotizing vasculitis, petechiae (16%), photo-recall (<74%), pruritus (13%), pseudolymphoma, rash (30%), Raynaud phenomenon, scleroderma, SJS, TEN	Dysgeusia, mucositis, stomatitis (11%)	Alopecia (15%)	
6-Mercaptopurine	Dermatitis (2%), edema, exanthems (<1%), herpes zoster, lichenoid eruption, lupus erythematosus, melanoma, neoplasms, palmar-plantar erythema, petechiae, photo-recall, photosensitivity, pigmentation (1–10%), pruritus, purpura, TEN, urticaria, vasculitis	Glossitis (<1%), mucositis (1–10%), oral lesions (1–5%), stomatitis (1–10%)	Alopecia	Nail loss
6-TG	Exanthems, malignancies, palmar erythema, petechiae, photosensitivity (<1%), pruritus, psoriasis, purpura, rash (1–10%)	Stomatitis (1–10%), xerostomia	Alopecia	
Fludarabine	Edema (>10%), exanthems, herpes simplex, paraneoplastic pemphigus, petechiae, rash (>10%), squamous cell carcinoma	Dysgeusia (<1%), stomatitis (>10%)	Alopecia (1–10%)	
Cladribine	Allergic reactions, diaphoresis (1–10%), edema (6%), eosinophilic cellulitis, erythema (6%), erythroderma, exanthems (27–50%), halogenoderma, herpes, petechiae (8%), pruritus (6%), purpura (10%), rash (27%), SJS, TEN, transient acantholytic dermatosis, urticaria, vasculitis			

Drug	Skin	Mucosal/ENT	Hair	Nails
Topoisomerase-interacting agents				
Irinotecan	Allergic reactions (9%), diaphoresis (16%), edema (10.2%), exanthems, hand-foot syndrome, photosensitivity, pigmentation, pruritus, pyogenic granuloma, rash (<21%)	Dysgeusia, mucositis (2%), sialorrhea	Alopecia (13–60.5%)	
Topotecan	Allergic reactions, erythema (<1%), fixed eruption, neutrophilic eccrine hidradenitis, purpura (<1%), scleroderma	Mucositis, stomatitis (24%)	Alopecia (59%)	Pigmentation
Doxorubicin	Actinic keratoses, allergic reactions (<1%), angioedema, cellulitis, dermatitis, dermatitis herpetiformis, diaphoresis, exanthems, exfoliative dermatitis, fixed eruption, hand-foot syndrome, inflammation, intertrigo, keratoderma, necrosis, photo-recall, pigmentation, pruritus, psoriasis, purpura, rash, Raynaud phenomenon, scleroderma, toxic erythema, urticaria (<1%)	Ageusia, mucositis, oral lesions, pigmentation, stomatitis (>10%), tongue pigmentation	Alopecia (>10%)	Beau lines, melanonychia, Muehrcke lines
Daunorubicin	Angioedema, dermatitis, erythema, exanthems, exfoliative dermatitis, folliculitis, hand-foot syndrome, hypomelanosis, neutrophilic eccrine hidradenitis, pigmentation, pruritus, rash (<1%), urticaria (<1%)	Mucositis	Alopecia (>10%)	Pigmentation (<1%)
Idarubicin	Acral erythema, bullous dermatitis, exanthems (<1%), neutrophilic dermatosis, photo-recall, rash (>10%), urticaria (>10%)	Mucositis (50%)	Alopecia (77%)	Pigmentation
Mitoxantrone	Allergic reactions (<1%), diaphoresis (1–10%), edema (>10%), erythema, fungal dermatitis (>15%), necrosis, petechiae (>10%), bluish pigmentation, purpura (>10%), rash (<1%), ulcerations, urticaria, vitiligo		Alopecia (20–60%)	
Dactinomycin	Acne (>10%), actinic keratoses, bullous pemphigoid, cellulitis, dermatitis, erythema, erythema multiforme, exanthems, folliculitis, reactivation of keratoses, lichenoid eruption, photo-recall (>10%), pigmentation, pruritus, pustules, TEN, urticaria	Cheilitis, oral lesions, ulcerative stomatitis (>5%)	Alopecia (>10%)	
Teniposide	Facial edema, rash, urticaria	Mucositis, stomatitis (3%)	Alopecia (31%)	
Epidermal growth factor receptor/Anaplastic lymphoma kinase/Vasular endothelial growth factor inhibitors				
Erlotinib	Acne, acute generalized exanthematous pustulosis, erythema (18%), fissures, folliculitis, papulopustular eruption, photosensitivity, pruritus (13%), rash (75%), telangiectasia, xerosis (12%)	Aphthous stomatitis (17%)	Alopecia, eyelash hypertrichosis, trichomegaly	Paronychia, pyogenic granulomas
Gefitinib	Acne (39–52%), acute generalized exanthematous pustulosis, desquamation (39%), erosive pustular dermatosis, exanthems, folliculitis, glucagonoma syndrome, hand-foot syndrome, pigmentation, pruritus, pyoderma gangrenosum, rash (52%), rosacea, scaling, seborrhea, ulcerations, urticaria, xerosis	Epistaxis, oral ulceration, stomatitis	Abnormal texture, alopecia, hypertrichosis	Paronychia (6%), pyogenic granulomas, nail changes (17%)
Cetuximab	Acne (88%), allergic reactions, burning, erythema, exanthems, fissures, folliculitis, papulopustular eruption, peripheral edema (10%), pruritus (10%), rash, transient acantholytic dermatosis, xerosis	Stomatitis (11%)	Alopecia (5%)	Nail changes (16%), paronychia
Panitumumab	Acne (57%), eczema, erythema (65%), exfoliative dermatitis (25%), fissures (20%), peripheral edema (12%), photosensitivity, pigmentation, pruritus (57%), rash (22%), telangiectasia, xerosis (10%)	Oral mucositis (6%)	Hair changes	Nail changes, paronychia (25%), pyogenic granulomas
Crizotinib [33]	Edema (16%)			
Ziv-aflibercept [34]		Stomatitis (20%)		

(Continued)

Drug	Skin	Mucosal/ENT	Hair	Nails
Multikinase small molecule tyrosine kinase inhibitors				
Imatinib	Acne, acute febrile neutrophilic dermatosis, acute generalized exanthematous pustulosis, carcinoma, dermatomyositis, eccrine squamous syringometaplasia, edema (1–5%), erythema, exanthems, exfoliative dermatitis, hypomelanosis, lichen planus, mycosis fungoides, necrolysis, neutrophilic eccrine hidradenitis, palmar-plantar hyperkeratosis, petechiae (1–10%), photosensitivity, pigmentation, pityriasis rosea, pruritus (6–10%), psoriasis, rash (32–39%), SJS, TEN, urticaria, vasculitis	Oral lichenoid eruption	Follicular mucinosis	Dystrophy, pigmentation
Dasatinib	Acne, dermatitis, hyperhidrosis, photosensitivity, pigmentation, pruritus (11%), rash (39%), urticaria, xerosis	Dysgeusia, mucositis (16%)	Alopecia	
Nilotinib [9]	Pruritus (17%), rash (22%), xerosis (12%)		Alopecia (6%)	
Sunitinib	Bullous dermatitis, edema, hand-foot syndrome, peripheral edema (17%), pigmentation, pyoderma gangrenosum, rash (14–38%, xerosis (17%)	Dysgeusia (21–43%), glossodynia (15%), mucositis (29–53%), stomatitis	Alopecia (5–12%), pigmentation	
Sorafenib	Acne (1–10%), inflammation of actinic keratoses, desquamation (40%), eczema (<1%), eruptive facial cysts, erythema (>10%), erythema multiforme (<1%), folliculitis (<1%), hand-foot syndrome (30%), hyperkeratosis, pruritus (19%), rash (40%), seborrheic dermatitis, squamous cell carcinoma, urticaria (<1%), vasculitis, xerosis (11%)	Angular stomatitis, cheilitis, dysphagia (1–10%), glossodynia (1–10%), mucositis (1–10%), rhinorrhea (<1%), xerostomia (1–10%)	Alopecia (27%)	Splinter hemorrhages
Pazopanib [10]	Decubitus ulcer (3%), edema (3%), flushing (3%), hand-foot syndrome (3%), hyperhidrosis (3%), hypopigmentation (3%), pruritus (3%), xerosis (3%)	Epistaxis (11%)		
Vandetanib [35]	Rash (26%), photosensitivity (16%)			
Ponatinib [36]	Rash (32%), acneiform dermatitis (14%), dry skin (14%), erythema nodosum (2%), melanoma (1%)			
Axitinib [37]	Palmar-plantar erythrodysesthesia (27%), rash (13%)	Mucosal inflammation (15%), stomatitis (15%)	Alopecia (4%)	
Cabozantinib [38]	Rash (13%), palmar-plantar erythrodysesthesia (30%)	stomatitis (11%), mucosal inflammation (21%)		
Bosutinib [39]	Rash (20%)			
Regorafenib [40]	Hand-foot skin reaction (56%), rash (18%)	Oral mucositis (38%)	Alopecia (24%)	

Drug	Skin	Mucosal/ENT	Hair	Nails
Antimicrotubule agents				
Paclitaxel	Allergic reactions (15%), angioedema, desquamation (7%), edema (21%), erythema, exanthems (<1%), fixed eruption, folliculitis, hand-foot syndrome, lupus erythematosus, photo-recall (<1%), photosensitivity, pigmentation, pruritus (<1%), purpura, pustules, rash (12%), scleroderma, SJS, urticaria	Mucositis (>10%), oral lesions (3–8%), stomatitis (2–39%)	Alopecia (87–100%), alopecia areata	Nail changes, leukonychia, Mees lines, paronychia, pigmentation (2%), subungual hyperkeratosis, thickening
Docetaxel	Allergic reactions, angioedema, edema (1–20%), erythema (0.9%), exanthems, fixed eruption, hand-foot syndrome, lupus erythematosus, photo-recall, photosensitivity, pigmentation, pruritus, radiodermatitis, rash (0.9%), scleroderma, seborrheic keratoses, squamous syringometaplasia, SJS, TEN, urticaria, xerosis	Dysgeusia, dysphagia, mucositis, nasal septal perforation, stomatitis (5–42%)	Alopecia (80%)	Beau lines, discoloration, dystrophy, hyponychial dermatitis, nail loss, paronychia, pigmentation, subungual abscess, subungual hemorrhage, subungual hyperkeratosis, transverse superficial loss of nail plate
Albumin-bound paclitaxel [11]			Alopecia (86.9%)	
Vincristine	Actinic keratoses, allergic reactions angioedema, dermatitis herpetiformis, edema, erythroderma, exanthems, hand-foot syndrome, pigmentation, pruritus, rash (1–10%), Raynaud phenomenon, urticaria	Dysgeusia (1–10%), oral lesions (1–10%), oral ulceration (1–10%), stomatitis (<1%)	Alopecia (20–70%)	Beau lines, leukonychia, Mees lines, Muehrcke lines, onychodermal band, pigmentation
Vinblastine	Acne, acral necrosis, angioedema, bullous dermatitis (<1%), cellulitis, dermatitis (1–10%), erythema, erythema multiforme, exanthems, photo-recall, photosensitivity (1–10%), pigmentation, purpura, Raynaud phenomenon (1–10%), ulcerations, urticaria	Dysgeusia (>10%), oral lesions (1–5%), oral vesiculation, ototoxicity, stomatitis (>10%)	Alopecia (>10%), hair changes	
Vinorelbine	Angioedema, erythema, hand-foot syndrome, pigmentation, pruritus, rash (<5%), TEN, vasculitis	Dysgeusia (>10%), mucositis, stomatitis (>10%)	Alopecia (12%)	
Estramustine	Acne, allergic reactions, angioedema, edema (>10%), exanthems, facial flushing, pigmentation (<1%), pruritus (2%), purpura (3%), rash (1%), urticaria, xerosis (2%)		Alopecia (<1%)	

(Continued)

Drug	Skin	Mucosal/ENT	Hair	Nails
Histone deacetylase, proteasome inhibitors, retinoids, and demethylating agents				
Vorinostat	Angioedema (9%), exfoliative dermatitis (9%), peripheral edema (13%), pruritus (12%)	Dysgeusia (28%), xerostomia (16%)	Alopecia (19%)	
Romidepsin [12]	Skin and subcutaneous disorder (4%)	Dry mouth (4%)		
Arsenic trioxide	Acral desquamation, carcinoma, bullous dermatitis, dermatitis, dermatofibrosarcoma protuberans, edema, ephelides, erythema, erythema multiforme, erythema nodosum, exanthems, exfoliative dermatitis, fixed eruption, follicular keratosis, herpes simplex, herpes zoster, hyperhidrosis, hyperkeratosis of the palms and soles (40%), hypomelanosis, keratoses, leukomelanosis, lichen planus, livedo reticularis, melanoma, melanosis, merkel cell carcinoma, morphea, palmar-plantar erythema, palmar-plantar hyperhidrosis, parapsoriasis, photo-recall, photosensitivity, pityriasis rosea, pruritus, psoriasis, purpura, rash, Raynaud phenomenon, SJS, ulcerations, urticaria, vitiligo, xerosis	Dysgeusia, oral mucosal eruption (8%), oral pigmentation, stomatitis	Alopecia	Leukonychia, Mees lines, pigmentation
All-trans retinoic acid	Acne (1%), acute febrile neutrophilic dermatosis, bullous dermatitis, burning (10–40%), carcinoma, cellulitis (1–10%), crusting, dermatitis, desquamation (14%), diaphoresis (20%), edema (29%), erythema (1–49%), erythema nodosum, facial edema (1–10%), flaking (23%), hyperkeratosis (78%), hypomelanosis (5%), irritation (5%), pallor (1–10%), palmar-plantar desquamation (1–10%), photosensitivity (10%), pigmentation (5%), pruritus (10–40%), pyogenic granuloma, rash (54%), retinoic acid–APL syndrome (25%), scaling (10–40%), shivering (63%), stinging (1–26%), ulcerations (penile), vasculitis, vesiculobullous eruption, xerosis (49–100%)	Cheilitis (10%), gingivitis (<1%), xerostomia (10%)	Alopecia areata (14%)	
Bexarotene	Acne (<10%), allergic granulomatous angiitis, bacterial infections (1.2–13.2%), burning, cold extremities, dermatitis, erythema, exanthems (<10%), exfoliative dermatitis (10–28%), facial edema, irritation, necrosis, nodular eruption (<10%), peripheral edema (13.1%), photosensitivity, pruritus (20–30%), pustules, rash (16.7%), stinging, ulcerations (<10%), vasculitis, vesiculobullous eruption (<10%), xerosis	Cheilitis (<10%), gingivitis (<10%), xerostomia (<10%)	Alopecia (4–11%)	
Miscellaneous agents				
L-Asparaginase	Allergic reactions, angioedema, diaphoresis, edema, exanthems, pruritus (<1%), TEN, urticaria (1–15%)	Aphthous stomatitis (1–10%), oral lesions (26%)	Alopecia	
Bleomycin	Acral necrosis, acral sclerosis, allergic reactions, angioedema, bullous dermatitis (1–5%), calcification, dermatitis, digital gangrene, eccrine squamous syringometaplasia, erythema, erythema gyratum, exanthems, fixed eruption, flagellate erythema/pigmentation, hand-foot syndrome, hyperkeratosis of the palms and soles, intertrigo, neutrophilic eccrine hidradenitis, nodular eruption, palmar nodules, photo-recall, pigmentation (50%), pruritus (>5%), rash, Raynaud phenomenon (>10%), scleroderma, SJS, striae, urticaria, vesiculation, xerosis.	Glossitis, oral papillomatosis, oral ulceration, stomatitis (>10%), tongue erosions	Alopecia (50%), graying of the hair	Beau lines, dystrophy, reduced growth, nail loss, onychodystrophy
Procarbazine	Allergic reactions (<1%), angioedema, dermatitis (<1%), diaphoresis, edema, exanthems (4–9%), exfoliative dermatitis, fixed eruption, herpes zoster, petechiae, photosensitivity, pigmentation (1–10%), pruritus (<1%), purpura, rash, TEN, urticaria (9%)	Oral lesions (1–5%), stomatitis (>10%), xerostomia	Alopecia (1–10%)	

Drug	Skin	Mucosal/ENT	Hair	Nails
Miscellaneous agents				
Thalidomide	Bullous dermatitis (5%), burning, dermatitis, desquamation, diaphoresis, edema, erythema, erythema multiforme, erythema nodosum, erythroderma, exanthems, exfoliative dermatitis, facial erythema, nodular eruption, palmar erythema, pruritus, psoriasis, purpura, pustuloderma, rash (11–50%), SJS, TEN, ulcerations, urticaria (3%), vasculitis, xerosis	Xerostomia	Alopecia	Brittle nails
Lenalidomide	Acute febrile neutrophilic dermatosis, diaphoresis (8%), erythema (5.4%), peripheral edema (20%), pruritus (42%), rash (36%), xerosis (14%)	Dysgeusia (6%), rhinitis (7%), stomatitis, xerostomia (7%)		
Vemurafenib [41]	Keratoacanthomas (6%), cutaneous squamous cell carcinoma (12%), rash (10%), pruritus (6%)		Alopecia (8%)	
Ingenol mebutate [42]	Erythema (34%), flaking/scaling (29%), crusting (9.2%), erosion/ulceration (1.9%), hypopigmentation/hyperpigmentation (19.8%), scarring (0.6%)			
Vismodegib [43,44]	Xerosis	Keratitis (3%), corneal abrasion (3%)	Alopecia (63.8%)	
Everolimus [45]	Acne-like skin lesions (22%), eczema (10%)	Stomatitis (48%), mouth ulceration (19%), aphthous stomatitis (19%)		
Biotherapy				
Interferon-a2a Interferon-a2b	Acne (1%), acral sclerosis, allergic reactions, angioedema, atrophie blanche, Behçet disease, bullous dermatitis, dermatitis, dermatitis herpetiformis, dermatomyositis, diaphoresis (22%), eczema, edema (11%), erythema, erythema nodosum, exanthems, fungal dermatitis (<1%), halo dermatitis, herpes simplex (1%), Kaposi sarcoma, keratoses, lichen myxedematosus, lichen planus, lichenoid eruption, linear IgA dermatosis, livedo reticularis, lupus erythematosus, melanoma, necrosis, nodular eruption, pemphigus, photo-recall, photosensitivity (<1%), pigmentation (<1%), capillaritis, pityriasis versicolor, pruritus (13%), psoriasis, purpura, rash (44%), Raynaud phenomenon, sarcoidosis, scleroderma, seborrheic dermatitis, telangiectasia, ulcerations, urticaria (<3%), vasculitis, vitiligo, xerosis (17%)	Ageusia, anosmia, aphthous stomatitis, dysgeusia (25%), oral lichen planus, oral pemphigus, sialopenia, stomatitis (1–10%), xerostomia (>10%)	Alopecia (1–10%), alopecia areata, curly hair, hypertrichosis, pigmentation, straight hair	
Interleukin 2	Allergic granulomatous angiitis, allergic reactions (<1%), angioedema, bullous dermatitis, bullous pemphigoid, dermatitis, desquamation, edema (47%), erythema (41%), erythema multiforme, erythema nodosum, erythroderma, exanthems, exfoliative dermatitis (14%), intertrigo, Kaposi sarcoma, linear IgA dermatosis, necrosis, pemphigus, petechiae (4%), photosensitivity, pruritus (48%), psoriasis, purpura (4%), rash (26%), sarcoidosis, scleroderma, SJS, TEN, urticaria (2%), vasculitis, vitiligo, xerosis (15%)	Aphthous stomatitis, dysgeusia (7%), glossitis, oral mucosal eruption, oral ulceration, stomatitis 932%), xerostomia	Alopecia (<1%)	

(Continued)

Drug	Skin	Mucosal/ENT	Hair	Nails
Monoclonal antibodies				
Trastuzumab	Acne (2%), allergic reactions (3%), angioedema (<1%), cellulitis (<1%), diaphoresis, edema (8%), hand-foot syndrome, herpes simplex (2%), herpes zoster (1%), peripheral edema (10%), photosensitivity, rash (18%), ulcerations (1%)	Stomatitis (<1%)	Alopecia	Dystrophy
Bevacizumab	Exfoliative dermatitis, pigmentation, ulcerations, xerosis, hand-foot syndrome	Dysgeusia, oral ulceration, stomatitis, xerostomia	Alopecia	Changes
Rituximab	Angioedema (>10%), dermatitis, diaphoresis, exanthems, herpes zoster, Kaposi sarcoma, necrosis, paraneoplastic pemphigus, peripheral edema, pruritus (10%), rash (10%), SJS, TEN, urticaria (10%)	Orogenital ulceration, otitis, perianal ulcerations, rhinitis		
Alemtuzumab	Abscess, allergic reactions (<1%), angioedema (<1%), angioedema (<1%), bullous dermatitis (<1%), cellulitis (<1%), facial edema (<1%), hematomas (<1%), herpes simplex, herpes zoster, peripheral edema (13%), pruritus, purpura (8%), rash, squamous cell carcinoma (<1%), urticaria	Dysgeusia (<1%), gingivitis (<1%), sinusitis, stomatitis (14%), stomatodynia		
Gemtuzumab	Herpes simplex (22%), peripheral edema (21%), petechiae (21%), rash (23%)	Mucositis (<4–25%), stomatitis (32%)		
Ibritumomab	Allergic reactions (2%), angioedema (5%), bullous dermatitis, diaphoresis (4%), erythema multiforme, exfoliative dermatitis, peripheral edema (8%), petechiae (3%), pruritus (9%), purpura (7%), rash (8%), SJS, TEN, urticaria (4%)	Mucositis	Alopecia	
Tositumomab	Allergic reactions, angioedema, carcinoma, diaphoresis (8%), peripheral edema (9%), pruritus, rash (17%)	Rhinitis (10%)		
Ipilimumab [46]	Vitiligo (2.3%), rash (19.1%), pruritus (24%)		Alopecia	
Pertuzumab [47]	Pruritus (6%), dry skin (6%), acneiform rash (13%)	Mucosal inflammation (7%)		
Endocrine agents				
Tamoxifen	Dermatomyositis, diaphoresis, edema (2–6%), exanthems (3%), lupus erythematosus, photo-recall, pruritus, purpura, radiodermatitis, rash (1–10%), sarcoma, urticaria, vasculitis, xerosis (7%)	Dysgeusia, vaginal pruritus, xerostomia (7%)	Alopecia, hirsutism, hypertrichosis, pigmentation	
Toremifene	Dermatitis, diaphoresis (20%), edema (5%), pigmentation, pruritus			
Raloxifene	Capillaritis, diaphoresis (3.1%), edema, peripheral edema (3–5%), rash (5.5%), vitiligo	Vaginitis (4.3%)		
Anastrozole	Angioedema, diaphoresis, erythema multiforme, lupus erythematosus, peripheral edema (10.1%), pruritus (2–5%), rash (7.5%), shivering, SJS, urticaria	Vaginal dryness (1.7%), xerostomia	Alopecia (2–5%)	
Letrozole	Diaphoresis (<5%), exanthems (5%), pruritus (2%), psoriasis (5%), rash (1–10%), TEN, vesiculation (5%)		Alopecia (<5%)	
Exemestane	Diaphoresis (6–12%), edema (7%), hyperhidrosis, peripheral edema (9%), pruritus (2–5%), rash (2–5%)		Alopecia (2–5%)	
Fulvestrant	Diaphoresis (5%), edema (9%), rash (7%)	Vaginitis		

Drug	Skin	Mucosal/ENT	Hair	Nails
Endocrine agents				
Leuprolide	Acne, allergic granulomatous angiitis, dermatitis (5%), dermatitis herpetiformis, diaphoresis, edema (1–10%), exanthems, lupus erythematosus, nodular eruption, photosensitivity, pigmentation (<5%), pruritus (<5%), purpura (<1%), rash (1–10%), stickiness, urticaria, xerosis (<5%)	Dysgeusia (<5%), vaginitis,	Alopecia (<5%), hypertrichosis (<1%)	
Flutamide	Bullous dermatitis, diaphoresis, edema (4%), erythema, exanthems, lupus erythematosus, photosensitivity, rash (3%), TEN, urticaria			
Bicalutamide	Angioedema, carcinoma, diaphoresis (6%), edema (2–5%), exanthems (<1%), herpes zoster, pruritus (2–5%), rash (6%), urticaria, xerosis (2–5%)	Xerostomia	Alopecia	
Nilutamide	Diaphoresis (6%), edema (2%), pruritus (2%), rash (5%), urticaria, xerosis (5%)	Xerostomia (2%0	Alopecia	
Fluoxymesterone	Acne (>10%), dermatitis, edema (>10%), exanthems, furunculosis, lichenoid eruption, lupus erythematosus, pruritus, psoriasis, purpura, seborrhea, striae, urticaria	Stomatitis	Alopecia, hirsutism (1–10%)	
Estradiol	Acanthosis nigricans, acne (5%), allergic granulomatous angiitis, angioedema, bullous dermatitis, chloasma (<1%), dermatitis, eczema, edema (<1%), erythema multiforme, erythema nodosum, exanthems, exfoliative dermatitis, fixed eruption (<1%), hyperkeratosis, livedo reticularis, lupus erythematosus, Mucha–Habermann disease, osteoma cutis, papulovesicular eruption, photosensitivity, pigmentation, porphyria cutanea tarda, pruritus, pseudolymphoma, purpura, rash (<1%), Raynaud phenomenon, scleroderma, spider nevi, striae, telangiectasia, urticaria, vasculitis, vesiculation	Gingival hyperplasia/hypertrophy, mucosal eruption, pigmentation, vulvovaginal candidiasis	Alopecia (9%), hirsutism (<5%), straight hair	
Octreotide	Allergic granulomatous angiitis, allergic reactions, cellulitis (1–4%), diaphoresis, edema (1–10%), exanthems, petechiae (1–4%), pruritus (1–4%), purpura (1–4%), rash (<1%), Raynaud phenomenon (1–4%), urticaria (1–4%)	Vaginitis (1–4%), xerostomia	Alopecia (<1%)	
Megestrol	Acne, acute generalized exanthematous pustulosis, angioedema, dermatitis, diaphoresis (31%), edema, erythema multiforme, erythema nodosum, exanthems, hemorrhage, melasma, pruritus, rash, telangiectasia, urticaria		Alopecia, hirsutism	
Medroxyprogesterone acetate	Acne (1–5%), allergic reactions (<1%), angioedema, chloasma (1–10%), diaphoresis (<31%), edema (>10%), erythema nodosum, exanthems, hemorrhage, Mucha–Habermann disease, photosensitivity, pigmented purpuric eruption, pruritus (1–10%), rash (1–5%), scleroderma (<1%), striae, urticaria, xerosis (<1%)	Bromhidrosis (<1%), vaginitis (1–5%)	Alopecia (1–5%), hirsutism (<1%)	

(Continued)

Section 1 Dermatology and Oncology

Drug	Skin	Mucosal/ENT	Hair	Nails
Agents for management of hematologic reactions				
Epoetin Alfa	Acne, angioedema (1–5%), dermatitis, edema (17%), erythroderma, exanthems, lichenoid eruption, photosensitivity, pruritus, rash (1–10%), urticaria		Alopecia, alopecia totalis, hypertrichosis	
Darbepoetin	Edema (21%), pruritus (8%), rash (7%), urticaria			
Filgrastim Sargramostin	Abscess, acne, acral erythema, acute febrile neutrophilic dermatosis, allergic granulomatous angiitis, allergic reactions (19%), diaphoresis, edema, erythema, erythema nodosum, exanthems (5–63%), exfoliative dermatitis (10%), folliculitis, graft versus host reaction, lichenoid eruption, linear IgA dermatosis, lupus erythematosus, neutrophilic eccrine hidradenitis, palmar-plantar pustulosis, pruritus (1–5%), psoriasis, pyoderma gangrenosum, rash (<40%), urticaria, vasculitis	Dysgeusia, mucositis (40%), stomatitis (>10%)	Alopecia (>10%)	
Pegfilgrastim	Acute febrile neutrophilic dermatosis, allergic reactions (<1%), peripheral edema, pyoderma gangrenosum, rash (<1%), urticaria (<1%)	Dysgeusia, mucositis, stomatitis	Alopecia	
Oprelvekin [13]	Peripheral edema (4%), rash (1%)	Tearing (1%)		
Low molecular weight heparin	Allergic reactions (1–10%), angioedema (<1%), baboon syndrome, burning, dermatitis, erythema, erythema nodosum exanthems, fixed eruption, hemorrhage, livedo reticularis, necrosis, peripheral edema, petechiae, pruritus (<1%), purpura (>10%), rash, scleroderma, toxic dermatitis, TEN, ulcerations, urticaria (<1%), vasculitis	Gingivitis (>10%)	Alopecia	Discoloration
Warfarin	Abscess, acral purpura, angioedema (<1%), bullous dermatitis, dermatitis, exanthems, exfoliative dermatitis, hematomas, hemorrhage, livedo reticularis, necrosis (>10%), pruritus (<1%), purple toe syndrome, purplish erythema of the feet and toes (<1%), purpura, rash (<1%), ulcerations, urticaria, vasculitis, vesiculation	Oral ulceration (<1%), tongue hemorrhage	Alopecia (>10%)	
APL, acute promyelocytic leukemia; Ig, immunoglobulin; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.				