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Chemotherapeutic agents and the skin: An update

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Chemotherapeutic agents give rise to numerous well described adverse effects that may affect the skin, hair, mucous membranes, or nails. The mucocutaneous effects of longstanding agents have been extensively studied and reviewed. Over the last 2 decades, a number of new molecular entities for the treatment of cancer have been approved by the United States Food and Drug Administration (FDA). This article reviews the cutaneous toxicity patterns of these agents. It also reviews one drug that has not received FDA approval but is in use outside the United States and is important dermatologically. Particular emphasis is placed on the novel signal transduction inhibitors as well as on newer literature pertaining to previously described reactions. (J Am Acad Dermatol 2008;58:545-70.)

Learning objectives: At the completion of this learning activity, participants should able to list the newer chemotherapeutic agents that possess significant mucocutaneous side effects and describe the range of reactions that are seen with each drug. In addition, they should be able to formulate appropriate management strategies for these reactions.

C hemotherapeutic agents give rise to numerous well described mucocutaneous side effects. The effects of longstanding agents have been extensively studied and reviewed.[1] Over the last 2 decades, many newer drugs have emerged as inciting agents. Chemotherapeutic agents may be classified according to their mechanism of action. Table I lists newly-approved drugs with significant mucocutaneous side effects that will be discussed in this article.

SIGNAL TRANSDUCTION INHIBITORS

Major advances in current cancer therapy have been realized recently with the development of drugs that act through inhibition of signal transduction. Two categories of agents will be discussed: small molecules and monoclonal antibodies that inhibit the epidermal growth factor receptor (EGFR)

Abbreviations used:

5-FU:	5-fluorouracil
AGEP:	acute generalized exanthematous pustulosis
ATP:	adenosine triphosphate
CLL:	chronic lymphocytic leukemia
CML:	chronic myeloid leukemia
EGFR:	epidermal growth factor receptor
FDA:	United States Food and Drug Administration
FIP1L1-PDGFRα:	Fip1-like-1 platelet-derived growth factor receptor alpha
GIST:	gastrointestinal stromal tumor
NSCLC:	non—small cell lung cancer
PDGFRα:	platelet-derived growth factor receptor alpha
PLD:	pegylated liposomal doxorubicin
PNP:	paraneoplastic pemphigus
SCC:	squamous cell carcinoma
VEGFR:	vascular endothelial growth factor receptor

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and the multi-kinase inhibitors, including imatinib mesylate, sorafenib, and sunitinib.

Epidermal growth factor receptor inhibitors

The EGFR is a transmembrane protein encoded by the c-erbB protooncogene. It consists of an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and an intracellular domain that possesses tyrosine kinase activity. Upon ligand binding, the EGFR dimerizes and subsequently activates tyrosine kinase activity, which in turn phosphorylates a number of molecules that activate intracellular

Table I. Classification of newer chemotherapeutic agents

Class	Chemotherapeutic agent
Signal transduction inhibitors	Epidermal growth factor receptor antagonists: gefitinib, cetuximab, erlotinib, and panitumumab
	Multikinase inhibitors: imatinib, dasatinib, nilotinib, sorafenib, and sunitinib
Proteasome inhibitors	Bortezomib
Spindle inhibitors	Taxanes: docetaxel and paclitaxel
	Vinca alkaloids: vinorelbine
Antimetabolites	Purine analogs: fludarabine and cladribine
	Pyrimidine analogs: capecitabine, tegafur, gemcitabine, and pemetrexed
Genotoxic agents	Alkylating agents: carboplatin and oxaliplatin
	Anthracyclines: liposomal doxorubicin, liposomal daunorubicin, and idarubicin
	Topoisomerase I inhibitors: topotecan and irinotecan

Table II. Cutaneous effects of epidermal growth factor receptor inhibitors

Abnormal scalp, face hair, and/or eyelash growth
Anaphylactic infusion reaction (cetuximab)
Papulopustular eruption
Paronychia with/without pyogenic granulomas
Telangiectasias
Xerosis

Table III. Cutaneous effects of the epidermal growth factor receptor inhibitors: Case reports

Cutaneous effect	Gefitinib	Erlotinib	Cetuximab
Grover's disease	—	—	1
Necrolytic migratory erythema	1	—	—
Psoriatic exacerbation	1	—	—
Radiation field—sparing	1	1	—
Vasculitis	1	—	—

pathways.[2] The net effect of these pathways is the induction of cell proliferation and migration, as well as angiogenesis. Agents that inhibit the EGFR have been effectively employed in the advanced stages of a number of malignancies that overexpress the receptor, including colorectal, breast, and pancreatic cancers, non—small cell lung cancer (NSCLC), and squamous cell carcinoma (SCC) of the head and neck.[3] Gefitinib (ZD1839) and erlotinib (OSI-774) are orally-administered small molecules that inhibit EGFR tyrosine kinase activity by occupying its intra-cellular adenosine triphosphate (ATP)-ligand site and preventing tyrosine phosphorylation. Gefitinib was approved in the United States as monotherapy for locally advanced or metastatic NSCLC under the US Food and Drug Administration's (FDA's) acce-lerated approval program after failure of both plati-num-based therapy and docetaxel in 2003. Tumor response has subsequently been observed in only a small subgroup of patients, so approval is now limited to patients who have shown previous benefit. The recommended dose of gefitinib is 250 mg daily. Tumor-specific characteristics, including mutations in the ATP-binding pocket of the EGFR tyrosine kinase domain,[4] seem to influence responsiveness to gefitinib. Erlotinib is approved by the FDA for the treatment of locally advanced or metastatic NSCLC after failure of at least one previous chemotherapeu-tic regimen. It is also approved in combination with

gemcitabine for locally advanced, unresectable, or metastatic pancreatic cancer. The recommended dose is 150 mg daily. Cetuximab (IMC-225) is an intravenously administered human—mouse chimeric monoclonal antibody that inhibits tyrosine kinase activity by binding to the extracellular domain of the EGFR, thereby preventing ligand binding. Cetuximab is approved by the FDA for the treatment of advanced colon cancer in combination with irinotecan, a topoisomerase I inhibitor. The recommended initial loading dose is 400 mg/m^2, followed by a weekly dose of 250 mg/m^2. Panitumumab is ap-proved by the FDA for the treatment of patients with EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following standard regimens. The recommended dose is 6 mg/kg daily for 14 days.

Because the EGFR is also expressed by basal keratinocytes, sebocytes, the outer root sheath, and some endothelial cells,[5] agents that inhibit EGFR are associated with dermatologic side effects (Tables II and III). These were initially observed in clinical trials. In general, cutaneous side effects were the most common, and most patients experienced a mild to moderate eruption that did not necessitate with-drawal of treatment.

Papulopustular eruption. A papulopustular eruption was the most frequent side effect seen in clinical trials varying from 24% to 62% in patients on

Fig 1. Severe pyoderma faciale—like eruption from erlotinib. (Photo courtesy of Olympia Kovich, MD.)

Fig 2. Mild follicular eruption and xerosis from gefitinib.

Fig 3. Erlotinib eruption on the arms. (Photo courtesy of Kenneth Katz, MD.)

Fig 4. Moderate rosacea-like eruption from cetuximab.

gefitinib,[6,7] 48% to 67% in patients on erlotinib,[8,9] and 75% to 91% in patients receiving cetuximab.[10-12] A dose-dependent relationship between both incidence and severity of the eruption was further observed in these early trials.[13] Numerous studies have since documented the characteristics of the eruption more fully.[5,14-20] The median time after initiation of treatment to onset of the eruption is 7 to 10 days,[18] and maximum severity is reached in the second week.[21] Most cases resolve without scarring after completion of therapy, but partial or complete resolution may be seen despite continued therapy.[3,15,21]

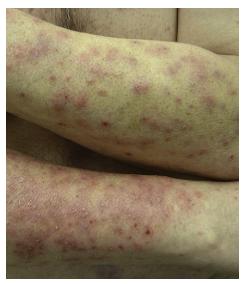The eruption is usually distributed in the seborrheic areas, including the scalp, face (predominantly the centrofacial area; Fig 1), neck, chest, shoulders (Fig 2), upper back, and behind the ears.[19] Less commonly, the extremities (Fig 3) and the lower back and abdomen are involved.[16] The primary lesions are follicular papules and pustules. Comedones are rarely seen,[5] which has prompted a move away from the terms "acneiform" and "acne-like" to describe this eruption. Palms and soles are spared.[22] In more severe cases, confluent erythematous plaques, confluent pustules, hemorrhagic crusts, or eschars with ulceration may be seen.[5,17,19] Scattered telangiectasias have also been reported to develop on the face, on and behind the ears, and on the chest, back, and limbs, usually near follicular pustules. This may give rise to a rosacea- or pyoderma faciale—like appearance of the face, depending on severity (Fig 4). The telangiectasias tend to fade over months and usually leave some hyperpigmentation.[19] The eruption may be asymptomatic or accompanied by pruritus, and it tends to improve over time despite continued therapy.

Histopathologically, the earliest findings are a T-cell infiltrate around the follicular infundibulum.[5]

Then a suppurative folliculitis is seen, with destruction of the hair follicle and subsequent granuloma formation in more severe cases.[15] A sparse periecrine neutrophilic infiltrate and focal acantholysis have each been noted in 2 patients.[15] Cultures are usually sterile, although growth of *Propionibacterium acnes* and superinfection with *Staphylococcus aureus* have been reported.[5,16]

The pathomechanisms of these findings are thought to be related to EGFR blockade. While the exact mechanisms in humans require elucidation, the EGFR is known to play a crucial role in hair cycle regulation. Disruption of the EGFR allele in mice results in short, wavy hair that eventually becomes atrophic, ultimately resulting in alopecia. Other observed phenomena include a lack of progression from anagen to telogen and destruction of the hair follicle by an inflammatory infiltrate.[5] Upregulation of negative growth regulator p27^{kip1}, which normally binds to and inactivates cyclin-dependent kinase 2 leading to cell cycle arrest in G1, increases apoptosis and maturation and may thereby be the mechanism by which cetuximab affects follicular and epidermal homeostasis.[15,23] Two cases of a follicular eruption sparing radiation sites have been reported.[24,25] Local radiation-induced sebaceous gland or follicular atrophy may explain this phenomenon.

Therapeutically, there is no gold standard for the papulopustular eruption. In clinical trials, a variety of topical and oral treatments were employed, including clindamycin gel, tretinoin, and minocycline. Hydroxyzine was given for pruritus and, interestingly, topical and oral steroids were given for severe disease.[13] Whether this was therapy was intended for the follicular eruption or the dry skin is unclear. Gefitinib-induced folliculitis has been treated with either minocycline 100 mg daily or tretinoin 0.025% cream topically twice daily, with improvement. Recently, 3 cases of papulopustular folliculitis were successfully treated with a combination of topical metronidazole with or without systemic tetracyclines.[26] Therapeutic options for cetuximab-induced folliculitis were studied in a small group of 13 patients and results supported treatment with classical acne therapeutics.[27] In particular, good results were seen in the 4 patients treated with doxycycline. The combined use of topical metronidazole and isotretinoin has also been shown to efficaciously treat cetuximab-induced acneiform rash in 2 cases.[28]

Prophylactic therapy with tetracyclines, including minocycline and lymecycline, has been shown to be effective in blocking the emergence of the eruption associated with cetuximab treatment.[29]

A number of studies have found that the presence and severity of rash are indicators of tumor response as well as overall survival.[30-34] Other studies failed to show the association of rash and tumor response, rash and tumor survival, or rash and both tumor response or survival.[7,8,13,35-39] Discrepancies between studies may stem from a number of factors, including: the agent studied; what the term "rash" was meant to connote (the majority of studies do not designate the morphology of the eruption studied); the scoring of toxicities (a separate category for grading the papulopustular eruption in the Common Toxicity Criteria of the National Cancer Institute was only introduced in 2003); and that the majority of studies were posthoc analyses. Prospective randomized trials examining this question specifically, rather than in a retrospective fashion, will be required to truly understand the associations that may exist between rash and tumor response.

Xerosis. Dry skin is commonly observed in patients receiving the EGFR inhibitors, with reported rates of 12% to 35% in clinical trials.[9] Some investigators have reported concomitant greasy scales or flaking and dryness of the nasolabial folds, resembling seborrheic dermatitis.[19] Histologically, the epidermis is thin and compact with variable parakeratosis. In vitro inhibition of the EGFR causes keratinocyte growth arrest and initiates terminal differentiation, events that would give rise to the clinical effects seen.[5] Vaginal dryness and itching, perineal dryness, and "eye irritation," including blepharitis, have also been reported.[21] A case of ocular toxicity is detailed with cetuximab therapy.[40] Three weeks after beginning cetuximab therapy, ocular symptoms characterized by bilateral ocular discomfort, pruritus around bilateral eyelids, photophobia, foreign body sensation, tearing, oil secretions, and crusty scaling consistent with squamous blepharitis were reported by the patient. Cessation of cetuximab therapy for 1 week led to the resolution of symptoms, and reintroduction of therapy led to the recurrence of squamous blepharitis after 2 weeks. It has been suggested that cetuximab may target the EGFR-expressing cells of Meibomian glands, thereby altering their secretory function.[40]

Nail changes. Nail changes have been observed in 10% to 15% of patients and are typically a later event during treatment, starting between 4 and 8 weeks. Paronychia affecting the great toe is often the first sign and can be very painful in cases where pyogenic granuloma of the nail fold develops.[41-44] Painful fissures can develop in the nail fold, and secondary bacterial infection is not uncommon. Four patients who were treated with gefitinib presented with pain, erythema, and proliferation of granulation tissue around several finger- and toenails and ingrown nails at a median time of 2 months from

beginning of therapy. One patient was treated with partial nail-plate excisions and the other 3 were treated with muciprocin ointment.[43] Paronychia with progressive painful periungual abscesses over fingers and toes has also been described.[41] The periungual abscesses responded to minocycline therapy; however, paronychia persisted and waned only with discontinuation of gefitinib. Paronychia is also reported from cetuximab. *Staphylococcus aureus* was cultured from some lesions; however, paronychiae persisted despite antibiotic therapy.[15,45,46] A recent case report has shown rapid and successful treatment of debilitating cetuximab-induced paronychia with 100 mg doxycycline over 6 weeks.[47] The pathogenesis of EGFR inhibitor—associated paronychia is unknown. It may arise secondary to skin fragility associated with treatment, because stratum corneum thinning and reduced keratinocyte proliferation rates are observed with therapy.[15]

Hair abnormalities. A number of hair abnormalities have been reported. Scalp hair may become brittle, finer, and curly.[5] This finding has been seen on the extremities as well.[22] Slower growth of the beard, with a decreased need for shaving, has also been reported.[18] A case of extensive inflammatory nonscarring alopecia associated with gefitinib therapy has been reported. Patchy alopecia progressed between 24 and 30 months after initiation of gefitinib therapy. It was most pronounced on the crown of the scalp and was associated with erythema and scale. These symptoms resolved without therapy upon discontinuation of gefitinib treatment.[48] In another report of abnormal hair growth with cetuximab therapy, a patient developed abnormally long and thick diffusely distributed chest hair that resulted in persistent grade 3 folliculitis after 1 year of continuous cetuximab and carboplatin therapy. Punch biopsy showed "disoriented and short inserted hair follicles associated to an irregular architecture in keratinocytes of the inner and outer root sheaths, associated to a faint lymphocytic inflammatory infiltrate." Abnormal hair growth resolved 3 months after cessation of therapy.[49]

Trichomegaly and a marked increase in the length of eyebrows have also been observed after approximately 7 weeks to 5 months of therapy.[50-52] These observations suggest that mechanisms regulating hair growth may differ at different locations of the body.

The constellation of the papulopustular eruption, xerosis, and nail and hair changes along with pruritus are specific for this class of agents, which has prompted proposal of the term PRIDE syndrome (*P*apulopustules and/or paronychia, *R*egulatory abnormalities of hair growth, *I*tching, *D*ryness

caused by *E*pidermal growth factor inhibitors) for EGFR inhibitor—associated cutaneous findings.[53]

Miscellaneous. Severe anaphylactic infusion reactions have been reported in 1.2% to 3.5% of patients receiving cetuximab and up to 1% of patients receiving panitumumab, necessitating premedication with intravenous diphenhydramine in all patients.[54,55] The first administration of cetuximab is the most common time when a severe allergic or infusion reaction is observed.[56]

A single case of a small-vessel vasculitis secondary to gefitinib therapy has been reported.[57] The EGFR is expressed in the dermal vasculature, so it is postulated that the disturbance of normal small vessel vasculature function resulted in this phenotype. One case of exacerbation of psoriasis has been reported.[58] A 69-year-old male patient with a history of stable plaque-type psoriasis involving the palms, elbows, knees, and nails previously controlled with topical emollients and medium potency topical corticosteroids received gefitinib therapy. After 1 month of therapy, the patient experienced worsening of his existing psoriatic lesions, developed new lesions on the soles of his feet, and noted arthritis of his distal interphalangeal joints. Rapid improvement of the psoriatic lesions was noted with discontinuation of gefitinib therapy. A case of necrolytic migratory erythema was reported in a patient on gefitinib and sodium valproate.[59] This 55-year-old patient with NSCLC developed painful, migratory plaques with erosions on the trunk and legs. No medical causes of the eruption were identified in this patient, although it is probable that this eruption was induced by gefitinib. Withdrawal of gefitinib along with oral corticosteroid therapy resulted in resolution of this eruption. A single case of transient acantholytic dermatosis during cetuximab therapy is reported in the literature.[60]

Multikinase inhibitors

The cutaneous effects of the multikinase inhibitors are summarized in Tables IV and V.

Imatinib. Imatinib (imatinib mesylate, STI571) is an oral drug that is approved in the United States as first-line therapy for chronic myeloid leukemia (CML) and for the rarer gastrointestinal stromal tumor (GIST). It has also shown efficacy in the treatment of metastatic dermatofibrosarcoma protuberans,[61] hypereosinophilic syndrome,[62] other chronic myeloproliferative diseases,[63] and AIDS-related Kaposi's sarcoma[64] Imatinib exerts its effects by specifically binding to and inhibiting a number of tyrosine kinases (Table VI). A subset of patients with systemic mastocytosis and associated eosinophilia who have the FIP1L1-PDGFRα oncogene also

Table IV. Cutaneous effects of multikinase inhibitors

Cutaneous effect	Imatinib	Dasatinib	Nilotinib	Sorafenib	Sunitinib
Acne		X			
Acral erythema		X		X	X
Alopecia		X	X	X	
Bullous dermatosis					X
Edema	X			X	X
Facial erythematous rash				X	
Flushing				X	
Hair depigmentation					X
Hair repigmentation	X				
Hyperhidrosis		X			
Hypopigmentation	X				
Lichenoid eruption	X				
Morbilliform eruption (exanthem)	X	X	X		
Ocular toxicity	X				
Photosensitization	X	X			
Pruritus	X	X	X		
Skin discoloration					X
Stevens—Johnson syndrome	X				
Stomatitis		X		X	X
Subungual splinter hemorrhages				X	X
Urticaria		X			
Xerosis	X	X	X		

achieve complete remission with imatinib.[65] In melanoma, the level of PDGFRα is correlated with metastatic potential of tumor cells. Imatinib has been shown in vivo to block PDGFRα in melanoma in mice, but does not influence the growth of melanoma cells or size of tumor in treated versus untreated mice,[66] and has been shown to have little to no efficacy in the treatment of metastatic melanoma in humans.[67]

In CML, the recommended imatinib dose is 400 to 600 mg/day for chronic phase and 600 to 800 mg/day for accelerated phase. In GIST, the recommended dose is 400 to 600 mg/day. Most adverse reactions to imatinib are mild to moderate and include nausea, edema, myalgia, and diarrhea.[68] In a phase II trial, edema was experienced by 64% of patients and "dermatitis" by 22% of patients.[69] A mild or moderate "dermatitis" was more frequently observed among patients treated with 600 mg rather than 400 mg per day. In the largest series published thus far, 171 (32%) of 532 late chronic-phase CML patients receiving 400 mg of imatinib daily developed a rash; 16 of these were severe.[70]

Two prospective studies sought to characterize the adverse cutaneous reactions to imatinib more definitively.[71,72] Fifty-four patients with CML received doses of imatinib ranging from 300 to 1000 mg/day. Forty-eight patients (88.9%) experienced at least 1 cutaneous reaction: rash in 36, edema in 35, and pruritus in 22. The rash observed was an exanthem in most cases, manifesting as erythematous macules and/or papules involving the face, arms, and/or trunk and, less frequently, the lower extremities, scalp, and intertriginous areas. The rash was classified as severe or life-threatening in 5 patients, necessitating withdrawal of the drug in 3 patients. The dosage that these patients received was not stated. Edema primarily localized to the face, especially the eyelids, the ankles, and the forearms was seen in 35 of these patients. The prevalence of edema also increased in a dose-dependent fashion. It is postulated that inhibition of the PDGFR is responsible for the edema, because signaling through this receptor is known to mediate interstitial fluid balance, and therefore associated pressure.[73] Ocular complaints related to edema are also reported. Twelve patients receiving imatinib developed epiphora (overflow of tears) as their major ocular complaint.[74] This was thought to be secondary to periorbital edema and conjunctival chalasis or chemosis in these cases. One case of retinal edema has been reported.[75]

Drummond et al[71] examined a large cohort of imatinib-treated patients prospectively over 1 year to further characterize the cutaneous side effects. Nine of 72 patients (12%) had eruptions that were attributed directly to imatinib (6 of these at a dose of 600 mg or greater). One of these patients developed dermatitis on the limbs and face, prompting discontinuation of the drug. On rechallenge, the patient

Table V. Cutaneous effects of multikinase inhibitors: Case reports

Cutaneous effect	Imatinib	Dasatinib	Sorafenib
Acute generalized exanthematous pustulosis	4	—	—
B-cell lymphoproliferative disorder	1	—	—
Eccrine squamous syringometaplasia	1	—	—
Erythema nodosum	1	—	—
Follicular mucinosis	1	—	—
Hyperpigmentation	1	—	—
Inflammatory actinic keratoses	—	—	2
Mycosis fungoides—like eruption	2	—	—
Nail dystrophy	3	—	—
Nail hyperpigmentation	1	—	—
Panniculitis	—	2	—
Papuloerythroderma of Ofuji	1	—	—
Pityriasis rosea—like eruption	4	—	—
Porphyria cutanea tarda exacerbation	1	—	—
Psoriasiform acral hyperkeratosis	3	—	—
Psoriatic exacerbation	1	—	—
Stomatitis	1	—	—
Sweet syndrome	1	—	—
Vasculitis	1	—	1

developed an exfoliative dermatitis that necessitated permanent treatment cessation. This study also reported the first case of biopsy-proven graft-versus-host—like drug reaction, erythema nodosum, and small vessel vasculitis from imatinib.[71]

Other serious adverse reactions linked to imatinib are Stevens—Johnson syndrome (SJS) and acute generalized exanthematous pustulosis (AGEP). Hsiao et al[76] observed a 42-year-old patient with blast crisis of CML who developed SJS 1 week after beginning imatinib therapy. Imatinib was thought to be the probable cause, because multiple pruritic vesicles and bullae appeared within 24 hours after rechallenge with a single dose of 600 mg. Five additional cases of SJS have since been reported.[77-81] In 2 of these cases, rechallenge at a lower dose after clearing of the initial eruption did not provoke the same reaction again.[80,81] To date, 4 cases of imatinib-induced AGEP have been described, in 1 patient described as a "scarlatiniform erythema with non-follicular pustules confined to flexural areas."[82,83] A single patient developed an acute generalized exanthematous pustulosis-like reaction reported as

Table VI. Tyrosine kinases targeted by imatinib mesylate

Chronic myelomonocytic leukemia	BCR-ABL
Gastrointestinal stromal tumor	c-kit
Hypereosinophilic syndrome	FIP1L1-PDGFRα
Systemic mastocytosis	FIP1L1-PDGFRα
Chronic myelomonocytic leukemia	TEL-PDGFRβ
Dermatofibrosarcoma protuberans	COL1A1-PDGFβ
Melanoma	PDGFRα
Kaposi's sarcoma	PDGF, c-kit

"fever, exfoliative dermatitis and non-follicular pustules."[72] All patients developed the eruption within 1 to 3 months following the start of imatinib therapy. A similar case of severe pustular eruption associated with imatinib and voriconazole therapy was reported in a 42-year-old CML patient. This eruption was not classified as AGEP because the lesions presented more than 3 months after the beginning of imatinib therapy, were confined to the face and trunk and spared body folds, and contained neutrophilic infiltrates in the superficial dermis without epidermal involvement.[84] It has been postulated that imatinib induces AGEP via inhibition of tyrosine kinases by a mechanism of action similar to that seen in mercury-induced AGEP.[82]

Reports are accumulating of pigmentary abnormalities secondary to imatinib therapy. Raanani et al[85] described the first case of imatinib-induced hypopigmentation in a patient who received 400 to 600 mg/day. Depigmentation of the penis and distal hands was seen 6 months into treatment. Both hypo- and depigmentation have since been reported, predominantly in patients of darker skin types. Thirteen patients developed localized, patchy, or diffuse (even generalized) hypopigmentation that was noted immediately or up to 3 months after initiation of therapy.[72,86] In a large Indian study, localized or generalized depigmentation was reported in 41% of 118 patients at 6 months of treatment. The median time of onset of pigmentary changes was 4 weeks (range, 2-14 weeks) after the start of therapy and progression of the extent of depigmentation was noted over time.[87] In general, the pigmentary dilution was found to be reversible, with repigmentation occurring on dose reduction or drug withdrawal. An additional 13 patients of Asian descent developed gradual skin depigmentation.[88] One patient in this series reported an inability to tan despite hours of sun exposure, and another reported increased pigmentation upon discontinuing imatinib therapy and decreased pigmentation upon reintroduction. Five lighter-skinned individuals noticed photosensitivity and inability to tan on imatinib, and patchy

depigmentation was seen in 1 of these patients.[72,89] One case series of 8 cases of photosensitization in CML patients treated with imatinib has been reported.[90] The only patient with a darker skin type in this series was noted to develop diffuse hypopigmentation in association. It is hypothesized that this phenomenon is not rarer in lighter skin but is instead less noticeable and therefore underreported. A case of a white patient with CML and near generalization of already preexisting widespread vitiligo has also been reported, whereby a welcome cosmetic outcome was achieved for the patient.[91] Pathomechanistically, it is presumed that inhibition of C-kit by imatinib is responsible for this effect. C-kit and its ligand stem cell factor are implicated in melanogenesis, melanocyte homeostasis, and ultraviolet B−induced pigmentation.[92] While the exact mechanisms have not yet been fully elucidated, it is known that mutations in the encoded tyrosine kinase region of KIT cause piebaldism.[86]

Paradoxical hyperpigmentation of the skin[87] and abnormal pigmentation of the hair and nails have also been reported. Darkening of hair color[72] and progressive repigmentation of gray scalp and body hair over a median time of 5 months in 5 men and 4 women while on imatinib has been seen.[93] A case of nail hyperpigmentation involving approximately two-thirds of the nail after approximately 4 months of imatinib therapy has also been reported. The hyperpigmentation was noted to be increased in the middle of the nails, and all nails; toenails were involved, though to a lesser degree.[94]

Both cutaneous and oral lichenoid eruptions have also been reported from imatinib.[95-99] Development of a mycosis fungoides−like eruption has been reported in 2 patients. In one case, the eruption was treated with triamcinolone cream and hydroxyzine and subsided after 1 year on continued imatinib therapy.[100] In a second case, the eruption gradually disappeared over 2 months after cessation of treatment.[101] A case of follicular mucinosis developed on the face during imatinib therapy and was attributed to the drug.[102] Other rare eruptions include a pityriasis rosea−like eruption (4 cases),[103,104] biopsy-confirmed Sweet syndrome (2 cases),[105,106] a case of neutrophilic eccrine hidradenitis,[107] a case of eccrine squamous syringometaplasia,[108] and a case resembling papuloerythroderma of Ofuji.[109] The latter eruption resolved on continued therapy after 4 months of oral and topical glucocorticoids.

A single case of exacerbation of psoriasis on imatinib therapy that recurred on rechallenge[110] and 3 cases of psoriasiform palmoplantar hyperkeratosis and nail dystrophy in patients without a history of psoriasis have been reported.[111] All cutaneous findings in these latter patients subsided with discontinuation of reduction of imatinib therapy. A case of porphyria cutanea tarda, which was histopathologically and serologically confirmed, developed on imatinib therapy. Photoexposed bullae resolved off therapy and serum porphyrin levels returned to normal off therapy. Rechallenge with the drug led to reactivation of the disease.[112] A case of primary cutaneous Epstein−Barr virus (EBV)−related B-cell lymphoproliferation from imatinib that presented as a rapidly growing, ulcerated scalp tumor is reported. The tumor resolved on lowering the dose of imatinib.[113]

Dasatinib and nilotinib. Resistance to imatinib has developed with point mutations within the BCR-ABL kinase domain or increased levels of BCR-ABL tyrosine kinase being the primary mechanisms.[114,115] Dasatinib and nilotinib are second-generation BCR-ABL tyrosine kinase inhibitors. Dasatinib binds both active and inactive BCR-ABL, as well as the majority of ABL mutants, thereby overcoming resistance. Nilotinib has greater binding affinity than imatinib.[116] Both drugs gained accelerated approval by the FDA for chronic and accelerated phase of CML with resistance or intolerance to previous therapy with imatinib. Dasatinib is also approved for myeloid or lymphoid blast phase CML and the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to previous therapy. Besides BCR-ABL, dasatinib is a potent inhibitor of the SRC family kinases, c-kit, PDGFR and ephrin A receptor kinase.[116] Nilotinib can also inhibit TEL-PDGFRβ (which causes chronic myelomonocytic leukemia), FIP1L1-PDGFRα (which causes hypereosinophilic syndrome), and c-kit.[117]

Thirty-five percent of 911 patients in one phase I trial and five phase II trials with dasatinib experienced eruptions. These included localized and generalized erythema, macular and papular eruptions, and "exfoliative rash." Sixteen percent of study patients experienced mucositis and/or stomatitis, and 11% experienced pruritus. The package insert notes that frequent adverse dermatologic events included hyperhidrosis, alopecia, xerosis, acne, urticaria, dermatitis, a photosensitivity reaction, "nail disorder," and "pigmentation disorder." Infrequent dermatologic adverse events included skin ulcers, acute febrile neutrophilic dermatosis, bullous conditions, and palmar−plantar erythrodysesthesia syndrome.[118-120]

Two cases of dasatinib-induced panniculitis have also been described.[121] A 55-year-old female developed a fever to 38.1°C and painful subcutaneous nodules with overlying erythema on her thighs

during her fourth week of therapy. Her symptoms resolved with discontinuation of therapy but recurred with reinitiation of therapy with subsequent involvement of her arms, legs, and vulva. Lobular panniculitis with massive infiltration by neutrophils was seen histologically. Dasatinib therapy was discontinued again and subsequently successfully restarted in conjunction with prednisone 70 mg daily. A minimum of prednisone 5 mg daily was required to prevent recurrence. In a second case, a 67-year-old female developed a lobular panniculitis after 4 months of dasatinib. This resolved with discontinuation of therapy. A case of possible small vessel vasculitis in the setting of dasatinib-induced alveolitis has also been described. A biopsy was not performed, and the eruption as well as the alveolitis responded to intravenous methylprednisone therapy.[122]

The most frequent nonhematologic side effects to nilotinib in a phase I study were mild to moderate rashes "of all types" (specific morphologies not stated, 20% of total study patients), pruritus (15%), and dry skin (12%). These events were seen at all doses, although a dose-related increase in incidence was noted. Alopecia was also noted in 6% of study patients.[123] In a subsequent phase II study, "rash" was reported in 28% of patients (with 3% noted to be severe) and pruritus in 24%.[124]

Sorafenib and sunitinib. Sorafenib (BAY 439006) is an oral small-molecule multi-kinase inhibitor that is approved in the United States for the treatment of renal cell carcinoma. The European Commission also recently approved this agent for the treatment of hepatocellular carcinoma. Sorafenib was initially developed as a specific inhibitor of Raf kinase, which functions in the Ras signaling pathway. Mutations in this pathway are found in approximately 20% of all malignancies.[54,125-127] Subsequent studies found that sorafenib also blocks VEGFR-2, VEGFR-3, FLT3, and PDGFRβ signaling.[128,129] Early trials have demonstrated the antitumor potential of sorafenib in patients with hepatocellular carcinoma,[130] melanoma,[131] NSCLC, cancers of the pancreas[132] and colon,[133] and other solid tumors.[134-136] The recommended dose is 400 mg twice daily. In a phase II study, the most common treatment-emergent adverse events were fatigue (73% of patients), rash/desquamation (66%), hand−foot skin reaction (62%), pain (58%), and diarrhea (58%). The majority of these events were grade 1 or 2 in severity, and mild-to-moderate skin toxicity was common and easily reversed with treatment interruption and/or dose reduction. Alopecia (53%), stomatitis/pharyngitis (35%), dry skin (23%), flushing (16%), and edema (15%) were other noted side effects.[137] A facial

eruption resembles seborrheic dermatitis and is commonly seen with sorafenib. It arises 1 to 2 weeks after the onset of treatment, can be preceded by or associated with scalp dysesthesia, and may disappear after several weeks of treatment. The rash can be aggravated by hot temperatures. The onset of inflammatory actinic keratoses is described in a single patient on sorafenib. These lesions responded well to imiquimod. New onset of four (SCCs) is described in another patient. The authors postulate that sorafenib may cause this by acting through dysregulation of the Ras pathway or inhibition of VEGFR and PDGFRβ, all of which are important in the development of SCCs.[53]

Sunitinib (SU11248) is a novel oral small-molecule multitargeted receptor tyrosine kinase inhibitor that has demonstrated direct antiproliferative and antiangiogenic action by targeting VEGFR-2, PDGFRβ, FLT3, and c-KIT. In January 2006, the FDA approved sunitinib for the treatment of metastatic renal cell cancer and imatinib-resistant GIST. Ongoing studies continue to evaluate the efficacy of this therapeutic agent in anthracycline- and taxane-resistant metastatic breast cancer,[138] acute myeloid leukemia,[139,140] thyroid cancer,[141] and neuroendocrine tumors. The recommended dose is 50 mg/day administered in repeated 6-week cycles of daily therapy for 4 weeks, followed by a 2-week cessation period.[142] In phase I and II trials, dose-limiting toxicities included reversible fatigue, hypertension, bullous skin toxicity, and symmetric acral erythemas. Skin toxicity typically occurred after 3 to 4 weeks of treatment. Periorbital edema, dry skin, stomatitis, asymptomatic subungual splinter hemorrhages, and sore mouth were also reported. Interestingly, transient yellow skin discoloration with associated yellow discoloration of urine secondary to the excretion of the drug and metabolites was noted after 1 week of therapy (Fig 5). Hair depigmentation is also reported; it is noted 5 to 6 weeks after the onset of therapy and is reversible within 2 to 3 weeks after therapy discontinuation. Studies in mice have shown that follicular melanocytes persist; therefore, depigmentation is caused by functional inhibition rather than structural destruction. The inhibition of stem cell factor or cKIT signaling by sunitinib, which is linked to hair pigmentation via the modulation of tyrosinase genes, is the hypothesized etiology for this side effect. Mild to moderate facial edema is reported in 50% of patients given sunitinib. Edema is seen mainly on the eyelids and is not associated with weight gain. Hypothesized mechanisms contributing to periorbital edema in these cases are similar to those seen with imatinib-related periorbital edema—namely fluid retention or elevated vascular

Fig 5. Yellowish discoloration of the skin in a patient with Fitzpatrick skin type II from sunitinib. The patient also suffered from interleukin-2—induced bullous pemphigoid. (Photo courtesy of Heather Brandling-Bennett, MD.)

permeability secondary to PDGFR inhibition.[18] Alopecia has not been observed.[143,144]

Robert et al[18] also reported cases of acral erythema and subungual splinter hemorrhages secondary to sorafenib and sunitinib therapy. Acral erythema arises 2 to 4 weeks after the onset of therapy. It presents as "painful symmetrical erythematous and edematous areas on the palms and soles, commonly preceded or accompanied by paresthesias."[18] These lesions can also appear on the lateral sides of fingers or in periungual areas. Acral erythema may be associated with hyperkeratosis and desquamation, and may be aggravated by hot temperatures. Clinically, this syndrome is distinct from the acral erythema seen with docetaxel and other classic chemotherapy agents in that plaques seem to be more discrete and hyperkeratotic. Histopathologically, there is a thin granular layer with areas of parakeratosis, enlarged epidermal cells in the superficial stratum spinosum, and many mitoses in the basal and suprabasal layers. Dyskeratotic keratinocytes may also be seen. While the pathogenesis of acral erythema is unknown, its dose dependence may point to a direct toxic effect of sorafenib. This side effect seems to resolve rapidly after discontinuation of treatment. "Multiple, painless distal subungual splinter hemorrhages" have also been reported with both of these agents.[145] These hemorrhages developed 2 to 4 weeks after the onset of therapy in 60% of patients receiving sorafenib and in 30% of patients receiving sunitinib, and were not associated with thrombotic or embolic events. Inhibition of VEGFR, which may play a role in the renewal of capillaries that sustain frequent microinjuries at distal fingers, is a proposed cause of this side effect.[145]

PROTEASOME INHIBITORS
Bortezomib

Bortezomib is the first proteasome inhibitor to enter clinical trials in cancer patients; in 2003, it was approved by the FDA for the treatment of advanced multiple myeloma. The proteasome is a protein complex that resides in the cytoplasm and nucleus of all cells and is responsible for the degradation of cellular proteins, including proteins involved in the cell cycle. Bortezomib selectively and reversibly inhibits the proteasome, resulting in increased apoptosis in malignant cells.[146] The adverse effects of bortezomib are usually mild, comprising gastrointestinal symptoms (diarrhea, nausea, constipation, and vomiting), cytopenia, fatigue, and peripheral neuropathy.

Reports of adverse skin reactions related to the use of bortezomib have been documented in the literature.[146] In one observational analysis of 47 patients, 5 patients developed erythematous nodules or plaques and 1 patient developed fever, a generalized morbilliform exanthema, and ulcerations on the trunk. The range of time to onset of cutaneous lesions from the first administration of bortezomib was 30 to 65 days. Two histopathologic patterns were seen: a predominantly lymphocytic perivascular dermatitis and a mixed pattern with both an interface dermatitis and interstitial dermatitis. The eruptions generally resolved in 4 to 7 days after treatment with low-dose prednisone and/or antihistamines. A retrospective analysis of 140 patients with non-Hodgkins lymphoma who received bortezomib as monotherapy identified 26 patients who developed an erythematous maculopapular rash on the trunk, neck, and upper extremities.[147] Six patients underwent biopsy of the eruption, which revealed a small vessel necrotizing vasculitis. In the majority of cases, the rash appeared during the third or fourth cycle of bortezomib and resolved following 5 to 7 days after the last dose in the cycle. No patient had evidence of a systemic vasculitis. This study suggested that the development of this eruption is a highly specific (but not a sensitive predictor) of response. Further prospective, randomized studies are warranted to confirm a relationship between rash and clinical response to therapy.

Other reported cutaneous associations described in single case reports include Sweet syndrome,[148,149] the development of a single black eschar,[150] and clinical response of cutaneous SCC to bortezomib given for myeloma.[151]

SPINDLE INHIBITORS

Taxanes act as microtubule stabilizing agents, thereby promoting tubulin assembly and preventing depolymerization of the formed polymers. As microtubule bundles accumulate, cell division is interrupted and cell death ensues.[152] Vinca alkaloids act by binding to specific sites on tubulin, thereby

Table VII. Cutaneous effects of taxanes

Docetaxel	Alopecia
	Mucositis
	Erythema
	Pruritus
	Urticaria
	Exanthem
	Acral erythema
	Fixed erythrodysesthesia plaque
	Radiation recall
	Psoriasiform/photodistributed dermatitis
	Pseudoscleroderma
	Subacute cutaneous lupus erythematosus
	Nail abnormalities: onycholysis, Beau's lines, onychomadesis, subungual erythema, subungual hemorrhage, and hyperpigmentation
Paclitaxel	Alopecia
	Mucositis
	Hypersensitivity reactions
	Nail abnormalities: onycholysis
	Single case reports: acral erythema, acute generalized exanthematous pustulosis, fixed drug eruption, pseudoscleroderma, and subacute cutaneous lupus erythematosus

preventing polymerization of tubulin dimers and disrupting formation of microtubules.[153]

Taxanes

Docetaxel is a semisynthetic molecule consisting of a modified extract of the needles of the European yew, *Taxus baccata*.[152,154] Paclitaxel is derived from the bark of the Pacific yew tree, *Taxus brevifolia*. The cutaneous effects of the taxanes are summarized in Table VII.

Docetaxel. Docetaxel is approved by the FDA for locally advanced or metastatic breast cancer and NSCLC. Its major dose-limiting toxicity in all phase I and II studies was neutropenia. Mucositis, alopecia, and other cutaneous adverse events, including erythema, pruritus, macular eruption, and desquamation were also recognized in these early trials.[154]

Acral erythema, or hand–foot syndrome, is a common and well documented side effect of docetaxel therapy.[155-159] In fact, docetaxel, along with cytarabine, doxorubicin, liposomal doxorubicin, and 5-fluorouracil, is most frequently associated with the condition.[160] Clinically, there are discrete erythematous or violaceous patches or edematous plaques that arise on the palms and soles and may progress to involve the dorsal surfaces of the hands (Fig 6) and feet. The eruption may be more extensive with truncal involvement. Plaques may be asymptomatic,

Fig 6. Acral erythema from docetaxel. (Photo courtesy of Benjamin N. Rosenberg, MD.)

painful, or itchy.[155] Other sensory abnormalities, including numbness, tingling, and burning have been reported, especially with the recurrence of erythema, prompting some authors to refer to this side effect as acral erythrodysesthesia[159] or palmar–plantar erythrodysesthesia syndrome.[1] Most cases of acral erythema resolve within 3 weeks of desquamation.[155] However, sensory abnormalities may be more persistent.[1]

Histopathologically, mild epidermal spongiosis with lichenoid features, including scattered dyskeratotic keratinocytes and vacuolar interface changes, is observed. The dermis has a sparse superficial perivascular lymphohistiocytic infiltrate.[1] Syringosquamous metaplasia and eccrine neutrophilic hidradenitis may also be seen.[161,162] Although the causes of acral erythema and erythrodysesthesia are unknown, it has been postulated that docetaxel is concentrated in and secreted by eccrine glands, causing direct toxic damage to the glandular structure.[161] The propensity of this eruption for palms and soles is likely related to the high density of eccrine glands in these areas.

Therapies for acral erythema have not been rigorously examined through controlled trials. Dose reduction, interval prolongation, and symptomatic treatment are standard maneuvers. Cooling of acral areas during chemotherapy infusion may decrease the severity of the reaction.[163] Topical and oral steroids have been deemed useful in small studies. Pyridoxine at a dose of 100 to 300 mg/day has been successful in treating and preventing the reaction and the associated dysesthesia.[160]

A presumed variant of acral erythema, termed fixed erythrodysesthesia plaque (FEP), is a cutaneous reaction that is characteristic of intravenous injection of docetaxel.[164] FEP develops as a fixed, solitary erythematous plaque proximal to the infusion site that does not involve the palms and soles (Fig 7). It usually resolves with desquamation, leaving hyperpigmentation 5 to 6 weeks later.[164]

Fig 7. Fixed erythrodysesthesia plaque from docetaxel. (Photo courtesy of Benjamin N. Rosenberg, MD.)

Histopathologic findings are similar to those seen in acral erythema.

Other well characterized cutaneous toxicities reported with docetaxel include radiation recall, urticaria, exanthems, and nail changes, including onycholysis, Beau's lines, onychomelanosis, onychomadesis, subungual erythema, and subungual hemorrhage.[1,164-166] Rarely, docetaxel has been associated with scleroderma-like changes of the lower extremities occurring in 3 phases: first, there is edema that is unresponsive to diuretic therapy; second, tightening and induration of the skin occurs; and finally, a softening phase begins after docetaxel discontinuation. Scleroderma-like changes were first reported from docetaxel in 2 patients in a phase I study.[167] Since then, 3 further cases have been reported. These patients developed induration of their lower extremities after 7 to 13 cycles. Serologic evaluation for collagen vascular disease was negative in all patients. Histopathologic findings resembled scleroderma with dermal sclerosis and thickening of subcutaneous septae.[152] Complete resolution of the pseudosclerodermatous changes occurred in 2 of the 3 patients; bound-down skin with limited range of motion was present in the third patient at the 1-year follow-up. A more diffuse sclerotic reaction occurred in 2 patients with metastatic breast cancer.[168,169] The first received 18 cycles of docetaxel followed by the development of sclerosis involving 50% of the skin, including the lower trunk and distal arms as well as the lower extremities.[168] Again, a serologic work-up for scleroderma was negative. Complete resolution was evident 6 weeks after the discontinuation of docetaxel. The second patient developed progressive sclerosis with facial telangiectasias and a reduction in size of the mouth aperture.[169] There was marked resolution 6 months after cessation of therapy and with the use of prednisone and penicillamine. Anti-Scl and anti-centromere antibodies were not performed in this case.

Most recently, docetaxel-induced subacute cutaneous lupus erythematosus has been recognized. Three women with metastatic breast cancer developed a photodistributed eruption 1 to 6 months after receiving their first cycle of docetaxel. The morphology varied from erythematous papules to annular patches and plaques. Biopsies revealed epidermal atrophy, an interface dermatitis, and dermal mucin in all cases. Direct immunofluorescence displayed granular nuclear or cytoplasmic deposition of IgG and C5-9 within keratinocytes, and serologic studies were positive for the anti-Ro antibody in all cases. Lesions resolved on discontinuation of treatment.[170]

Many chemotherapeutic agents cause local toxicity if extravasation occurs. Docetaxel acts as a tissue irritant on extravasation. Acutely, there is local pain, erythema, bullae formation, or phlebitis[1,153] which resolves over weeks, leaving residual hyperpigmentation.[1,171] Necrosis is not seen with irritant reactions. A single vesicant reaction with subsequent necrosis from docetaxel has been reported.[172]

Paclitaxel. Paclitaxel has received FDA approval for the treatment of ovarian carcinoma, metastatic breast cancer, NSCLC, and AIDS-related Kaposi's sarcoma. Neutropenia is the major dose-limiting toxicity, while mucositis is dose-limiting in leukemic patients and in those patients requiring prolonged infusions.[173] Paclitaxel doses of greater than 135 mg/m^2 commonly cause reversible alopecia, involving loss of hair in the axillary, pubic, eyebrow, eyelash, and scalp regions (recommended dose range, 135-175mg/m^2).[174] Other common clinical side effects include hypersensitivity reactions, peripheral neuropathy, and arrhythmias.

Initial clinical studies of paclitaxel were hampered by immediate hypersensitivity reactions that included dyspnea, hypotension, bronchospasm, urticaria, and erythema.[174] Prophylactic premedication with antihistamines and prolonging paclitaxel infusion time over 24 hours allowed a reduction of incidence in subsequent studies. Premedication with dexamethasone, diphenhydramine, or an H$_2$-blocker before drug infusion is now routinely recommended. It is unclear whether paclitaxel itself or its polyethoxylated castor oil vehicle (Cremophor EL; BASF, Florham Park, NJ) is responsible for this reaction. The latter agent is present in a higher concentration in the formulation of paclitaxel than other drugs and is known to induce histamine release from mast cells.[173]

Other cutaneous adverse events reported with paclitaxel therapy include radiation recall dermatitis,[175-177] erythema multiforme,[178] and onycholysis.[179] Only one case of acral erythema has been reported.[180] A single case of an AGEP-like generalized pustular dermatosis 5 days following the first treatment with paclitaxel in a patient with

Table VIII. Cutaneous effects of the antimetabolites (more than 1 case reported)

Cutaneous effect	Fludarabine	Cladribine	Capecitabine	Tegafur	Gemcitabine	Pemetrexed
Acral erythema			X		X	
Alopecia					X	
Erysipelas-like eruption					X	
Exanthem		X			X	X
Palmoplantar keratoderma				X		
Paraneoplastic pemphigus	X					
Photosensitization				X		
Radiation recall dermatitis					X	X
Stomatitis				X	X	

inflammatory breast cancer has been seen.[181] Bacterial culture of a pustule was negative. A biopsy revealed spongiform pustules and an increased number of eosinophils. Single cases of multiple fixed drug eruption[182] and inflammatory actinic keratoses have been documented in the literature.[183] A single case of SJS developing in a 63-year-old male treated with paclitaxel and carboplatin for advanced SCC of the lung has been described.[184] Cutaneous photosensitivity has also been described in a patient receiving both paclitaxel and trastuzumab therapy.[185]

A case similar to docetaxel-induced pseudoscleroderma has been described with paclitaxel. A patient with a primitive peritoneal cancer developed erythema and edema localized to her head, neck, and left arm 10 days after her first cycle of paclitaxel and paraplatin. This recurred after paclitaxel rechallenge and subsequently evolved into cutaneous sclerosis.[186] Subacute cutaneous lupus erythematosus has also been identified in one patient.[170]

Paclitaxel has also been shown to induce erythema, tenderness, and discomfort along the course of an injected vein and inflammation in areas of drug extravasation.[174] True necrosis has not been described.

Vinca alkaloids

Vincristine and vinblastine are well established vinca alkaloids that are effective in a wide range of lymphoproliferative malignancies and solid tumors.

Vinorelbine is a new semisynthetic vinca alkaloid that is structurally similar to vinblastine.[187] It is currently approved by the FDA for use as a single agent or in combination with cisplatin for first-line treatment of advanced, unresectable NSCLC. Common toxicities include leukopenia, mild to moderate peripheral neuropathy, phlebitis, nausea, and constipation. Moderate to severe alopecia is noted in approximately 8% of vinorelbine-treated patients.[187]

Other dermatologic effects of vinorelbine include acral erythema (seen with high-dose regimens) and severe extravasation reactions. Four of 60 patients who received high-dose vinorelbine in a continuous infusion over 4 days for the treatment of metastatic breast cancer developed acral erythema.[188] This has not been observed with the FDA-approved, lower vinorelbine doses for the treatment of NSCLC. As with other vinca alkaloids, vinorelbine has both irritant and vesicant properties.[1] Phlebitis occurs in up to 10% of patients and skin necrosis after extravasation has been reported.[189] Early treatment of vinorelbine extravasation includes the immediate discontinuation of the infusion, infiltration of the affected area with 1500 IU hyaluronidase and subsequent flushing with normal saline through multiple incision sites in the affected area.[190]

ANTIMETABOLITES

Antimetabolites interfere with enzymes that are required in the process of DNA synthesis. Their cutaneous effects are summarized in Table VIII.

Fludarabine

As a purine analog, fludarabine is a potent inhibitor of RNA and DNA synthesis via the inhibition of ribonucleotide reductase and DNA polymerase. It is approved in the United States for the palliative treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or have progressed during treatment with at least one standard alkylating agent-containing regimen. Its efficacy has been demonstrated in low-grade non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, and other low-grade lymphoid malignancies.[191] The most common adverse effect observed in phase I and II studies is dose-related myelosuppression. Toxicities seen at the recommended dose include somnolence, metabolic acidosis, confusion, fatigue, nausea, vomiting, and an increase in serum creatinine and aminotransferase

concentrations.[192] Reported, but uncommon, dermatologic adverse events in trials include macular and papular rash, stomatitis, and acral erythema.[193,194] Oral fludarabine has a relatively similar clinical efficacy and safety profile to the intravenous formulation; it causes more gastrointestinal toxicity but improved insomnia in patients.[195] An increased frequency of autoimmune phenomena has been observed with fludarabine, including hemolytic anemia, aplastic anemia, pure red-cell aplasia, thrombocytopenia, and transfusion-associated graft-versus-host disease.[196-199] A blistering disorder resembling erythema multiforme and toxic epidermal necrolysis that was subsequently recognized as paraneoplastic pemphigus (PNP) has also been reported in association with fludarabine.[197,200-203] Three patients with longstanding CLL developed PNP within 1 week of completion of treatment of fludarabine.[202] While hematologic malignancy itself, specifically non-Hodgkin's lymphoma and CLL, is associated with PNP, the above cases were thought to be linked to the drug, not the disease, because both the skin and mucous membrane involvement improved markedly upon withdrawal of fludarabine and delivery of immunosuppressive therapy in all three patients. This finding contrasts to neoplasia-induced PNP, in which the mucosal lesions are notoriously resistant to therapy.[204]

Cladribine

Cladribine (2-chlorodeoxyadenosine; 2-CdA) is a purine analog that has activity in a variety of lymphoproliferative disorders, including hairy cell leukemia, CLL, Waldenstrom's macroglobulinemia, cutaneous T-cell lymphoma, and indolent non-Hodgkin's lymphoma.[205] It was approved by the FDA for the treatment of hairy cell leukemia in 1993. Common adverse events are myelosuppression, fever, chills, fatigue, and headache.

Three papers address the cutaneous manifestations of 50 patients who received cladribine. Twelve patients developed an exanthem and 2 developed toxic epidermal necrolysis (TEN). Only 2 of the 12 patients who developed an exanthem received no other medication: 5 received an antibiotic, either a sulfonamide or amoxicillin, and 6 received allopurinol. Of the 2 patients who developed TEN, one received a sulfonamide and one received both allopurinol and a sulfonamide. The causal relationship between cladribine and these eruptions is therefore questionable.[206-208]

Capecitabine

Capecitabine is a novel antineoplastic agent that was first approved by the FDA in 1998 and is used in the treatment of metastatic colon and breast cancers. It is a prodrug of 5-fluorouracil (5-FU) that is converted by a cascade of three enzymes that are found in the liver and tumor tissue to 5-FU. The latter enzyme of this pathway has its highest activity in tumor tissue, so that active 5-FU will be concentrated in tumors rather than in the plasma or adjacent tissues. As a result, systemic toxicity of 5-FU, specifically gastrointestinal side effects, are lowered.[209] The metabolites of 5-FU are incorporated into DNA and RNA as false bases, and inhibit thymidylate synthetase thereby impairing DNA synthesis.[160] Capecitabine is administered orally. In clinical trials, the most common side effects noted were diarrhea, stomatitis, acral erythema, and nausea.[210]

Acral erythema associated with capecitabine therapy is well described in the literature,[211-215] occurring in 45% to 56% of treated patients.[211] In 41 patients with metastatic colorectal cancer who received capecitabine in the recommended doses, 28 (68%) developed acral erythema. Of these, 5 patients (18%) experienced mild changes (numbness, dysesthesia, paresthesia, tingling, painless swelling, or erythema and discomfort that did not disrupt normal activities); 20 patients (71%) developed moderate changes (painful erythema and swelling of the hands and/or feet that resulted in discomfort affecting the patient's activities of daily living); and 3 patients (11%) experienced more severe changes (moist desquamation, ulceration, blistering, and severe pain of the hands and/or feet that resulted in severe discomfort, limiting ability to work or perform activities of daily living). Of patients who developed acral erythema, 92.9% of them did so within the first two cycles of therapy. Recurrence with each cycle was the rule. While treatment was not discontinued secondary to this syndrome, dosage reductions were necessary in 16 patients.[211] Narasimhan et al[214] reported specific findings of this syndrome in patients of color. Marked hyperpigmentation and palmoplantar keratoderma were seen in 3 of 5 dark-skinned patients in this study. Acral hyperpigmentation was observed in one of our patients receiving capecitabine (Fig 8).

Piguet et al[216] described a case of capecitabine-induced pyogenic granulomas in an 81-year-old male with metastatic colorectal cancer. Pyogenic granulomas developed periungually in 8 of 10 toes during the fourth month of capecitabine treatment. The mechanism of induction of these remains obscure.

Inflammation of actinic keratoses as a result of systemic treatment with oral capecitabine has been reported, occurring 12 days after treatment initiation (Fig 9). Chemotherapy-induced inflammation of actinic keratoses was first described in 1962 with

Fig 8. Hyperpigmentation of the dorsal surface of the hands from capecitabine.

the use of systemic fluorouracil, but had never before been linked to capecitabine therapy.[217]

Other capecitabine-induced cutaneous adverse events described in single case reports include cutaneous and mucosal hyperpigmentation, spotty, "leopard-like" repigmentation of vitiligo in sun-exposed sites,[218] radiation recall dermatitis, onycholysis, and onychomadesis.[210,219]

Tegafur

Tegafur is a prodrug of 5-FU that is given orally. The drug is not available in the United States, but is employed elsewhere in the treatment of advanced gastrointestinal neoplasms. Acral erythema has rarely been reported.[160,220,221] A unique reaction to continued tegafur therapy is the development of palmoplantar keratoderma within areas initially affected by acral erythema.[222-226] Acral hyperpigmentation, particularly along the crease lines, longitudinal melanonychia of the fingernail plates, and brittle changes of the toenail plates have also been noted in these and other cases.[227,228] A case of keratoderma with knuckle pads is reported.[225] These changes of palms and soles have been seen to resolve spontaneously with discontinuation of tegafur. Photoallergic and photolichenoid eruptions to tegafur are also reported.[226,227,229]

One case of Mucha–Habermann syndrome in a patient receiving tegafur is also reported. A 59-year-old male noticed a papulonecrotic eruption on his trunk and extremities after approximately 200 days of daily tegafur use. Histology revealed "epidermal necrosis surrounded by spongiosis, perivascular inflammatory infiltrations composed of lymphocytes and erythrocytes, and endothelial swelling."[230]

Fig 9. Inflammation of actinic keratoses from capecitabine. (Photo courtesy of Benjamin N. Rosenberg, MD.)

Gemcitabine

Gemcitabine is an analogue of deoxycytidine. After phosphorylation, it is inserted into DNA in the deoxycytidine sites and acts as a chain terminator.[231] Gemcitabine has demonstrated efficacy in a variety of solid tumors, including NSCLC, ovarian, breast, head and neck, and pancreatic carcinomas.[232] It is approved in the United States for use in cases of advanced pancreatic cancer and advanced NSCLC in combination with cisplatin.

Gemcitabine is administered as single agent or combination therapy and is relatively well tolerated. Common and significant adverse events include myelosuppression (primarily leukopenia, which may be dose-limiting), nausea, emesis, general fatigue, flu-like symptoms, stomatitis, and elevation in transaminases.[233] Dermatologic adverse effects caused by gemcitabine occurred in 25.7% to 39% of patients: the most common is alopecia (15%) followed by mild to moderate rash (5-32%).[234] The latter is characterized by a macular or macular and papular pruritic eruption of mild-to-moderate severity involving the trunk and extremities.

Gemcitabine has also been reported to cause radiation recall dermatitis.[235-241] A case of linear IgA bullous dermatosis that was related to gemcitabine was reported in a patient with squamous cell carcinoma of the lung treated with cisplatin, vinorelbine, and gemcitabine.[242] Gemcitabine was discontinued with resolution of the eruption. There was no recurrence despite continued therapy with cisplatin and vinorelbine.

Recently, a pseudosclerodermatous reaction similar to that seen with the taxanes was reported secondary to gemcitabine after a preceding edematous phase.[243] The drug has also been postulated to induce venous endothelial injury in a patient with chronic venous stasis, causing an acute lipodermatosclerosis change with edema of the medial calves

followed by dermal fibroplasia.[234] It is conceivable that the latter case represents a more localized manifestation of the former.

Erythema resembling erysipelas developed on the lower extremities in one patient[244] and in preexisting lymphedema in three patients.[245] In another case, localized erythematous plaques also resembling erysipelas developed over elbow and knee joints and recurred on subsequent cycles.[246] A case of gemcitabine-induced pseudolymphoma in a patient with NSCLC has been reported.[247] Biopsies in this case revealed a widespread infiltrate of CD30^{+} cells. The eruption disappeared 20 days after cessation of therapy and the patient was not rechallenged with the drug. It is possible, however, that the "multiple erythematous lesions…that evolved to a microvesicular eruption" should more accurately be defined as lymphomatoid papulosis based on the clinical and histopathologic description of the lesions rendered in this paper.[247] A case of SJS has been reported in the setting of gemcitabine and radiation therapy.[248] Finally, a case of fixed erythrodysesthesia plaque has been reported in a patient who received gemcitabine and epirubicin, though it is unclear which of these agents was responsible.[249]

Pemetrexed

Pemetrexed is a novel agent that in 2004 was approved by the FDA for the first-line treatment of primary unresectable mesothelioma in combination with cisplatin. It was subsequently approved for the first-line treatment for advanced NSCLC and has also demonstrated activity in breast cancer and head and neck tumors. It is a folate analog that suppresses tumor growth by inhibiting multiple folate-dependent enzymes that are active in purine biosynthesis, including thymidylate synthetase, dihydrofolate reductase, and formyltransferase ribonucleotide glycinamide.[153] Myelosupression is the most commonly encountered toxicity of pemetrexed; neutropenia may be dose-limiting. "Rash" was the most common nonhematologic adverse effect reported, developing in 66% of 39 patients in one phase II study.[250] This is an exanthema, which is of mild to moderate severity in most cases.[251] In a subsequent phase III study, reduction in the rate of rash to 17% of 265 patients was seen with the use of dexamethasone given on 3 consecutive days (with chemotherapy given on day 2).[252] Prophylactic dexamethasone is therefore routinely recommended.

Two cases of radiation recall dermatitis from pemetrexed have been reported. The first case occurred in a patient with a pleural mesothelioma who received cisplatin and pemetrexed 19 days after completion of chest wall radiation therapy. Twelve days later, pruritic confluent erythema developed.[253] This is an important side effect to be aware of, because radiation therapy often accompanies chemotherapy in the treatment of mesothelioma. The second case developed in a patient who had been treated with radiation therapy for breast cancer 27 years earlier. She developed a radiation recall dermatitis in the irradiated field 3 days after pemetrexed therapy initiation for NSCLC.[254]

A case of urticarial vasculitis secondary to pemetrexed therapy has been reported. A biopsy of persistent erythematous plaque on the shin that had been treated as a cellulitis confirmed the diagnosis. The rash responded to and resolved quickly with prednisone therapy.[255]

GENOTOXIC AGENTS

Platinum agents, anthracycline antibiotics, and topoisomerase I inhibitors are all directly toxic to DNA through distinct mechanisms of action.

Platinum agents

Platinum agents, including carboplatin and oxaliplatin, are considered to be one of the major classes of drugs for first-line treatment and platinum-sensitive recurrence of ovarian carcinoma. They are alkylating agents that form reactive platinum complexes, which inhibit DNA synthesis by causing inter- and intrastrand cross-linking of DNA molecules. They are cell cycle—phase nonspecific. Cisplatin is an older platinum agent that is employed in the treatment of a wide variety of solid tumors.

Carboplatin. As a second-generation platinum compound, carboplatin is structurally related to cisplatin. It was developed initially with the hope that it could improve the therapeutic activity of cisplatin as well as diminish the dose-limiting adverse effects of its parent compound. Indeed, carboplatin demonstrates less nephrotoxicity, neurotoxicity, ototoxicity, and emesis induction than carboplatin.[256] The drug is approved by the FDA as the first-line therapy for ovarian cancer in combination with other drugs, as well as for recurrent disease.

The dose-limiting toxicity of carboplatin is myelosuppression, predominantly thrombocytopenia.[257] Other common and significant nondermatologic adverse reactions include nausea, vomiting, electrolyte abnormalities, and an increase in blood urea nitrogen, creatinine, and transaminases. Alopecia is the most common dermatologic adverse effect. When carboplatin is administered alone, alopecia is milder than if it is continued for more than three cycles or is used in combination with other chemotherapeutic agents.[257]

A hypersensitivity reaction, as seen with paclitaxel, occurs in around 2% of patients. It typically occurs well into the course of treatment, rising from 0 reactions at 5 treatments in a series of 205 patients to 27% after 8 treatments.[258] A spectrum of clinical severity is seen: just over half of the aforementioned patients experienced severe reactions with erythroderma, tachycardia, chest tightness, wheezing, facial swelling, dyspnea, and hypo- or hypertension.[258] The remainder of the patients reported itching or erythema, particularly of the palms and soles, or facial flushing only.[259] In contrast to paclitaxel, carboplatin itself, rather than its vehicle, is thought to be the inciting compound. In refinery workers, platinum salts are known to be highly allergenic and are a well-known cause of occupational asthma.[260] The reaction is IgE-mediated. The delayed onset of this reaction after carboplatin exposure is thought to be related to the very low concentrations of free platinum.[261] Intradermal skin tests with varying concentrations of carboplatin can be used to confirm a suspected reaction.[262] Management of hypersensitivity reactions is tailored to the severity of the reaction. Antihistamines suffice for milder reactions, whereas discontinuation of carboplatin has been advised for more severe reactions involving respiratory compromise, because desensitization or premedication with corticosteroids and antihistamines were deemed rarely successful.[259,263] A recent study suggests that that premedication with H_1 and H_2 antagonists may prevent hypersensitivity reactions.[264] Another recent study describes a successful 6-hour desensitization protocol that allows for ongoing drug treatment in previously sensitized patients.[265] Interestingly, cisplatin has also been safely administered to 13 carboplatin-sensitive patients without reaction.[266,267]

Oxaliplatin. Oxaliplatin is a third-generation platinum analogue that received approval for the treatment of recurrent or progressive metastatic colon and rectal carcinoma in combination with 5-FU and leucovorin. Its mechanism of action is similar to carboplatin, and common adverse effects include neutropenia, nausea, vomiting, diarrhea, and sensory neuropathy, which may be dose-limiting.[268]

After many courses of therapy, oxaliplatin, like carboplatin, causes a hypersensitivity reaction, including skin rashes, pruritus, dizziness, dyspnea, and anaphylaxis.[269-271] The rate of oxaliplatin hypersensitivity reactions is estimated to be between 2% and 12%.[269] Hypersensitivity reactions can be controlled with antihistamines or glucocorticoids after treatment cessation. Intradermal testing with 0.1 ml of oxaliplatin, 3 mg/ml in 5% glucose, was found to have an 80% positive predictive value, indicating that

this test can be used to identify which drug in a multidrug regimen is responsible for a hypersensitivity reaction.[269]

Cisplatin has both irritant and vesicant properties.[1] While oxaliplatin is generally causes irritant extravasation reactions, tissue necrosis has rarely been reported.[272-276] There are single case reports in the literature of oxaliplatin-induced radiation recall dermatitis[277] and delayed urticaria.[278]

Anthracyclines

Anthracyclines are directly toxic to DNA and RNA. They are intercalating agents that insert themselves in between nucleotides, thereby interfering with replication and transcription. They also inhibit topoisomerase II, thereby causing the formation of reactive oxygen species that damage DNA and cell membranes. Doxorubicin and daunorubicin are both well established antineoplastic agents; the former has efficacy in the treatment of solid tumors as well as hematologic malignancies and the latter is the cornerstone of treatment for many hematologic malignancies.

Liposomal doxorubicin. The use of doxorubicin is accompanied by substantial toxicity, including severe neutropenia and cardiotoxicity. The drug is also a well-known cause of mucocutaneous effects, including acral erythema, radiation recall and enhancement, neutrophilic eccrine hidradenitis, and, less commonly, hyperpigmentation, including that with a blue-gray color.[1] Furthermore, alopecia and stomatitis may be seen at standard doses.

The liposomal-encapsulated form of doxorubicin has the advantages of enhancing therapeutic efficacy as well as reducing toxicity.[279] The liposome prolongs the half-life of the drug in the circulation and alters its biodistribution pattern allowing increased deposition of drug in tumor tissue and an overall decrease in normal tissues. Pegylation, the coating of the liposome with polyethylene glycol, further enhances these effects and has been shown to confer greater cardiac safety than the nonpegylated formulation.[280] However, skin uptake of pegylated liposomal doxorubicin (PLD) is preserved in nude mice: this finding may explain the persistence of mucocutaneous toxicities, which are the primary adverse effects of this formulation.[281]

PLD is approved for the treatment of AIDS-related Kaposi's sarcoma and metastatic ovarian cancer in patients with disease refractory to previous combination treatment. The recommended dosage schedules are 20 mg/m^2 every 3 weeks for Kaposi's sarcoma and 50 mg/m^2 every 4 weeks for ovarian cancer. The most common adverse events are myelosuppression, acral erythema, stomatitis, and

nausea. Stomatitis is dose- and schedule-dependent, with reported incidences ranging from 3% to 21%.[282] Acral erythema is seen in as many as 50.6% of patients receiving the higher dosing schedule and up to 4% at the lower dose,[282] commonly occurring after 2 to 3 cycles. Severe reactions are rarely seen at both doses, but have necessitated dose reduction or interval prolongation.[283] Vitamin B6 and topical application of 99% dimethylsulfoxide have been successfully employed in the treatment of PLD-induced acral erythema.[284] Infusion hypersensitivity reactions are experienced with PLD in 3% to 25% of patients. Reactions occurring a few minutes into the first infusion of the drug can be aborted on interruption of infusion and do not occur when PLD is reinfused at a slower rate or on subsequent cycles. The prevailing hypothesis is that the liposomal component of the formulation induces this IgE-independent reaction, and that complement could be important in its pathogenesis.[285] A number of other cutaneous effects are more rarely encountered: exanthems, radiation, ultraviolet light recall,[286,287] and the formation of new melanotic macules on palms and soles unrelated to acral erythema have all been reported.[279,288] The rare intertrigo-like eruption and the scaly follicular eruption with lichenoid histopathology that have been reported require further characterization.[288] While doxorubicin is a known cause of both vesicant and irritant reactions, only irritant reactions to PLD have been reported.[1]

Liposomal daunorubicin. Liposomal daunorubicin is also approved for the treatment of Kaposi's sarcoma. Myelosuppression, alopecia, stomatitis, and infusion reactions are all seen. Acral erythema is not seen at the recommended doses but has been reported in 2 patients receiving high-dose treatment.[289]

Idarubicin. Idarubicin is an analog of daunorubicin that has been approved by the FDA in combination with other antileukemic agents (such as cytarabine) for the treatment of acute myelocytic leukemia and acute nonlymphocytic leukemia in adults. The cytotoxicity of idarubicin is attributed to its intercalation into DNA as well as the inhibition of topoisomerase II, resulting in double- and single-strand DNA breaks. Documented cutaneous toxicities associated with idarubicin include radiation recall dermatitis, alopecia, acral erythema, stomatitis, transverse pigmented bands of the nails, and potentially severe extravasation reactions.[1,290-292]

Topoisomerase I inhibitors

Topoisomerase I transiently breaks single-stranded DNA during replication, thereby preventing supercoiling of the molecule. The topoisomerase I inhibitors bind to the topoisomerase I-DNA complex, inhibiting rejoining of DNA and therefore its replication.[153,293] They are analogs of camptothecin, a cytotoxic alkaloid extracted from the Chinese tree *Camptotheca acuminata.*

Topotecan. Topotecan is a semisynthetic water-soluble derivative of camptothecin. FDA indications for topotecan use include treatment of metastatic ovarian carcinoma and small cell lung cancer after failure of first-line chemotherapy. It has also shown activity in the treatment of myelodysplastic syndrome. The most frequent adverse event associated with topotecan-based regimens is myelosuppression, with neutropenia being the most common dose-limiting toxicity.[294] Common cutaneous toxicities reported in phase trials include alopecia and maculopapular rash, occurring at approximate incidences of 77% and 6%, respectively.[1,295,296]

Neutrophilic eccrine hidradenitis (NEH) has also been reported in a patient who was treated with topotecan and colony-stimulating factor (CSF) for ovarian cancer.[297] Although NEH has been linked to CSF therapy,[298] topotecan was the most likely culprit here, because the eruption recurred after CSF cessation and ongoing topotecan administration. The lesions disappeared completely upon permanent termination of topotecan therapy.

Irinotecan. Irinotecan is another semisynthetic water-soluble derivative of camptothecin. It is approved in the United States for the first-line treatment of metastatic colon cancer (together with 5-FU and leucovorin) and for progressive or recurrent disease after 5-FU—based regimens. Irinotecan has also shown activity in NSCLC, small cell lung cancer, and hematologic malignancies.[294] The most common side effect of irinotecan is diarrhea, which may be severe and life-threatening. Neutropenia may also occur in regimens that employ the drug as a bolus every 3 weeks, as opposed to a divided weekly dose. Severe mucositis occurs in 5% to 10% of patients. Around 50% of patients experience alopecia.[299] A single case of a lichenoid eruption from irinotecan has been seen (Susan Burgin, MD, unpublished observation).

CONCLUSIONS

The mucocutaneous effects of the newer chemotherapeutic agents have been highlighted and particular emphasis placed on signal transduction inhibitors and the newer literature pertaining to previously described reactions. New cutaneous side effect clusters have emerged, particularly with EGFR inhibitors and multikinase inhibitors. Pathomechanistically, the cutaneous effects of these

agents occur as integral, pharmacologic effects of these drugs. Bortezomib is the first of a new class of proteasome inhibitors in use. Vasculitis, which may be a marker of response to the drug, is an important association. Spindle inhibitors, antimetabolites, and genotoxic agents have varied cutaneous toxicity patterns that also manifest a degree of specificity.

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