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Drug eruptions associated with tumor therapy: Great imitators

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Abstract Many studies have investigated cutaneous reactions to antitumor drugs and found them to be quite numerous. We describe drug eruptions that may be associated with different therapies by class: antimetabolite chemotherapeutics, genotoxic agents, spindle inhibitors, signal transduction inhibitors, and immunotherapies. Methotrexate is most often associated with mucocutaneous reactions, alkylating antimetabolite agents with hyperpigmentation, and platinum antimetabolite agents with type I IgE-mediated hypersensitivity reactions. Anthracycline derivatives can induce the hand-foot syndrome in patients, and bleomycin is associated with a bleomycin-induced flagellate erythema. Taxane spindle inhibitors can result in acneiform eruptions, which may also be seen with use of epidermal growth factor receptor inhibitors. Imatinib and its derivatives can cause a truncal maculopapular eruption, whereas multikinase inhibitors can produce a hand-foot-skin reaction. Vemurafenib can result in squamous cell carcinomas and photosensitivity. First-generation mammalian target of rapamycin inhibitors may cause a maculopapular eruption initially involving the face and neck. Programmed death (PD)-1-ligand and receptor inhibitors are associated with bullous pemphigoid. Ipilimumab, targeting Cytotoxic -T- Lymphocyte- associated (CTLA-4) receptors, can cause a morbilliform reaction, whereas Interleukin -2 (IL-2) analogs can create the capillary leak syndrome. Chemotherapeutic drug eruptions classically can manifest in the aforementioned ways; however, it is important to understand that they are associated with myriad cutaneous adverse effects, which may be mistaken for organic skin disease. Oncologists prescribing these medications should be familiar with the cutaneous side effects of these medications, and so they may counsel patients to be on the lookout for them.

Introduction

The advancement of cancer screening and detection, along with the development of chemotherapeutic agents, has resulted in an increased incidence of adverse cutaneous reactions. These untoward events range from mild to life-threatening and may often be difficult to distinguish from common skin lesions. We describe drug eruptions that may be associated with various antitumor therapies that we have classified according to class: antimetabolite chemotherapeutics, genotoxic agents, spindle inhibitors, signal transduction inhibitors, and immunotherapies (Table 1).

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Table 1 Drugs used for cancer treatment that are notably associated with cutaneous eruptions

Category of antitumor drug	Name of drug	Mechanism of action	References
Antimetabolites	Methotrexate	Folate antagonist	1–25
Genotoxic agents	Cyclophosphamide	DNA alkylation	26–36
	Ifosfamide		
	Bendamustine		
	Estramustine		
	Temozolomide		
	Busulfan		
	Thiotepa		
	Cisplatin	Crosslink DNA	37–40
	Carboplatin		
	Oxaliplatin		
	Doxorubicin	DNA intercalation and topoisomerase II inhibition	27,38,41–55
	Daunorubicin		
	Bleomycin	DNA double-stranded break inducer	26,27,56,57
	Topotecan	Topoisomerase I inhibition	26,27,38,56,58,59
	Irinotecan		
Spindle inhibitors	Docetaxel	Mitotic inhibitors	60–62
	Paclitaxel		
Signal transduction inhibitors	Erlotinib	Epidermal growth factor receptor tyrosine kinase inhibition	63–65
	Cetuximab		
	Genitimab		
	Imatinib	Tyrosine kinase inhibition	66–68
	Dasatinib		
	Nilotinib		
	Sorafenib	Multikinase inhibition	69–72
	Sunitinib		
	Vemurafenib	$BRAF^{V600}$ inhibition	73–75
	Everolimus	mTOR inhibition	76–78
	Temsirolimus		
	Ridaforolimus		
Immunotherapies	Pembrolizumab	PDL-1 receptor inhibition	79–83
	Nivolumab		
	Atezolizumab	PDL-1 inhibition	79,82
	Durvalumab		
	Denileukin	IL-2 analogs	84–87
	Aldesleukin	Promote T cell differentiation	
	Ipilimumab	Anti CTLA-4 receptor Promotes T-cell activation	79

Antimetabolites

Antimetabolite chemotherapeutic agents include folic acid, pyrimidine, and purine analogs that prevent nucleic acid synthesis by interfering with the production of nucleotide metabolites or substituting for a natural metabolite. These agents are cytotoxic and disrupt the cell cycle of normal cells. Many frequently used chemotherapeutic agents in this class have been reported to cause cutaneous eruptions that may be difficult to distinguish from common cutaneous lesions.

Methotrexate is a folate antagonist used in the treatment of many hematologic and solid malignancies. The mucocutaneous reactions associated with methotrexate include acral erythema, alopecia, cutaneous ulceration directed at the plaques of psoriasis or mycosis fungoides, erythema multiforme, photosensitive induced lesions, pseudolymphoma, radiation recall dermatitis, Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and vasculitis.[1]

There have been reports of acral erythema after the initiation of methotrexate. Acral erythema, also known as palmar-plantar erythrodysesthesia, is a rare cutaneous reaction associated with various chemotherapeutic agents. Acral erythema is a symmetric, painful plantar and palmar erythema of the palms with a prodrome of paresthesia and sometimes bullous formation with desquamation.[2] Clinical manifestations often begin 1 day to 3 weeks after initiation and resolve within 1 to 2 weeks after discontinuation of therapy.[2,3] Although the majority of reported cases have been in adults receiving moderate- to high-dose intravenous methotrexate,[4,5] there have been recent reports of this cutaneous reaction occurring in patients

receiving low-dose oral methotrexate.[6] One study found that standard-dose oral methotrexate induces acral erythema in a pediatric patient with acute lymphoblastic leukemia.[7] Treatment is often supportive and includes compresses and general wound care. Pyridoxine has been associated with decreased pain in acral erythema.[8] There have been variable results with the use of systemic and topical corticosteroids to treat this side effect of methotrexate.[9,10]

There have been several reports of methotrexate-induced cutaneous ulceration, one of which noted four patients with erythrodermic mycosis fungoides who developed cutaneous ulceration as a manifestation of methotrexate toxicity.[11] Cutaneous ulceration has been noted most often as a side effect of methotrexate therapy in the treatment of psoriasis.[12–19] As in patients with psoriasis, cutaneous ulceration may be the first sign of methotrexate toxicity in patients with erythrodermic mycosis fungoides[11]; notably, this side effect is rare in patients without underlying skin disease.[20,21]

Methotrexate has been reported to cause erythema multiforme, where it gives a classic presentation of a pruritic papular dermatitis over the extensor surface of extremities. Methotrexate-induced erythema multiforme has been reported in the treatment of patients with acute T-cell lymphocytic leukemia,[22] nonmetastatic gestational trophoblastic neoplasia,[23] and rheumatoid arthritis.[24]

SJS and TEN are life-threatening cutaneous reactions that have been associated with methotrexate. A 2018 meta-analysis of English literature from the year 1950 to 2017 reported two cases of SJS and three cases of TEN, with two reported mortalities.[25]

Genotoxic agents

Genotoxic chemotherapeutic agents damage DNA within the nucleus and are classified according to the mechanisms by which they cause damage. These drugs include the DNA alkylating agents, DNA cross-linking agents, DNA intercalators, strand-break inducing agents, and topoisomerase inhibitors.[26] All of these agents may cause unique cutaneous eruptions.

DNA alkylating agents add an alkyl group to guanine bases and are used to treat a variety of hematologic malignancies, sarcomas, and carcinomas of the lung, breast, and ovaries.[27] A number of cutaneous toxicities have been attributed to the use of DNA alkylating agents in the aforementioned malignancies. Cyclophosphamide, ifosfamide, bendamustine, temozolomide, busulfan, and thiotepa are commonly used alkylating agents used to treat malignancies and autoimmune diseases.[27,28]

The toxic effects of cyclophosphamide are extensively documented and include myelotoxicity, gonadotoxicity, risk of infection, hemorrhagic cystitis, and marked increased risk for bladder cancer.[27,28] The most common reactions of the skin and mucous membranes to cyclophosphamide therapy include anagen effluvium, mucositis, and hyperpigmentation.[28] Hyperpigmentation is most often seen on the palmar and plantar surfaces, nails, and teeth and less commonly on the gums.[29] Melanonychia subsequent to cyclophosphamide therapy ranges from dark brown to black in color and fully covers the nail plate.[30] A rare case of diffuse reticulated pigmentation after cyclophosphamide therapy has been described with involvement of the face, trunk, arms, and leg.[31] In a combined busulfan, cyclophosphamide, and thiotepa treatment regimen, hyperpigmentation was more commonly seen in the intertriginous areas.[32]

Hyperpigmentation has also been found with ifosfamide use and is commonly seen in the axillae, groin, and underneath occlusive dressings.[26] A severe, acute reaction to ifosfamide characterized by malaise, redness, swelling, exfoliative dermatitis, and stomatitis has also been described.[33]

Twenty-one percent of patients on bendamustine develop stomatitis, and 14% develop an infusion reaction characterized by fever, chills, pruritus, dermatitis, hypotension, and swelling that is severe enough to discontinue treatment in one patient.[34] Adverse skin events have also been reported with estramustine and temozolomide, with varying degrees of xerosis, pruritus, and maculopapular eruptions.[35,36]

Platinum-based drugs, cisplatin, carboplatin, and oxaliplatin, are frequently used to treat testicular and ovarian cancers, as well as malignancies of the head and neck, bladder, colon, rectum, pancreas, esophagus, stomach, biliary tract, and lung.[26,37,38] These drugs act in a similar manner to alkylating agents, covalently linking purine bases to the platinum-containing molecule to form strand crosslinks and inhibit replication. The toxicity profiles may be severe in the case of cisplatin and somewhat less so for carboplatin and oxaliplatin. Cisplatin toxicity includes nausea and vomiting, neurotoxicity, nephrotoxicity, and ototoxicity. The major toxicity from carboplatin therapy is thrombocytopenia and myelosuppression in general. Oxaliplatin may cause neutropenia, emesis, diarrhea, and dose-limiting sensory neuropathy.[37,38]

Hypersensitivity reactions to platinum-based drugs are a well documented adverse effect of therapy. The reactions often occur after multiple infusions, suggesting that they are type I, IgE-mediated reactions. There is evidence for type IV, T-cell–mediated hypersensitivity as well. These reactions can appear from minutes to days after infusion of the drug, often beginning as a mild dermatitis with urticaria, flushing, palmar and plantar pruritus, burning, edema, abdominal cramping, diarrhea, and back pain. It may progress to more severe clinical manifestations such as wheezing, bronchospasm, seizures, chest pain and tightness, or anaphylaxis in about half of the patients.[37,38] Mild-to-moderate reactions may be adequately controlled with antihistamines and low-dose corticosteroids and do not warrant cessation of therapy.[37]

Other dermatologic toxicities to platinum-based chemotherapeutics include radiation recall dermatitis, mucositis, alopecia, urticaria, and Raynaud syndrome.[37–40] Up to 90% of patients undergoing cisplatin-based chemoradiotherapy develop significant oral mucositis that impedes nutrition and may be severely detrimental to quality of life.[40]

The *Streptomyces*-derived anthracyclines, doxorubicin and daunorubicin, intercalate between DNA nucleotides and inhibit replication, transcription, and the actions of topoisomerase II.[27,38] Both medications are used in the treatment of hematologic malignancies, whereas doxorubicin has additional efficacy in the treatment of solid tumors.[38] Doxorubicin is classically associated with cardiotoxicity; however, the use of the PEGylated-liposomal doxorubicin (PLD) dramatically improves cardiotoxicity at the expense of increased mucocutaneous toxicity.[41] It is hypothesized that the lipid-soluble liposomal preparation of doxorubicin collects in mucocutaneous tissues for extended periods and leads to the development of dermatologic toxicities.[42]

A characteristic and serious dermatologic toxicity associated with PLD is hand-foot syndrome (HFS), also known as acral erythema or palmar-plantar erythrodysesthesia (PPE).[43] HFS is characterized by painful, swollen, erythematous patches on the palmar and plantar surfaces that may develop bullae, desquamation, and ulceration in severe cases.[43,44] A meta-analysis of five trials in which single-agent PLD was used for the treatment of ovarian cancer found the incidence of HFS to be as high as 37.5%.[45] The accumulation of PLD in the skin predisposes patients to toxicity. Although the pathogenesis of HFS is incompletely understood, it is hypothesized that mechanical, subclinical trauma due to friction or pressure results in local inflammation and accumulation of PLD via increased blood flow.[41,43] PLD may also be carried by sweat into the stratum corneum, leading to generation of free radicals and subsequent HFS.[41] There are case reports of a rarer variant of HFS that affects the intertriginous areas, named "intertrigo-like dermatitis."[46] Areas of skin affected by a previous lesion may be more likely to develop HFS/PPE/intertrigolike dermatitis, as observed in one patient with resolved prurigo nodularis who developed a bullous, PPE-like eruption in the same area after treatment with PLD.[47]

Anthracyclines are also commonly associated with radiation-recall dermatitis that presents as drug-induced cutaneous eruption developing about a week after radiation therapy. It is characterized by painful, violaceous erythematous patches with vesicles, desquamation, ulceration, necrosis, and hemorrhage.[42,48] PLD may be associated with an increased risk of radiation-recall dermatitis due to the drug's tendency to collect in mucocutaneous tissues. Radiation-recall dermatitis with accompanying oral mucositis has been reported after the use of PLD.[42,49]

Other cutaneous toxicities associated with the anthracyclines include facial flushing with or without accompanying acute hypersensitivity reaction,[41] stomatitis,[38] mucocutaneous hyperpigmentation characterized by darkening of the lips and tongue, melanonychia,[50–52] local urticaria at the site of injection,[53] inflammation of existing actinic keratoses,[54] and alopecia.[55]

Chemotherapeutic agents that induce double-stranded breaks in DNA, such as bleomycin, are among the most cytotoxic treatments available.[26] Bleomycin is used to treat lymphomas, squamous cell carcinoma, germ cell malignancies, and malignant pleural effusion.[27,56] The toxicities associated with bleomycin are largely seen in the lungs and skin, as these tissues contain low concentrations of the enzyme bleomycin hydrolase, which is needed to inactivate the drug. Skin toxicity is less commonly seen compared with lung toxicity, but the adverse effects include hyperpigmentation, sclerosis, erythema multiforme, gangrenous changes, desquamation of the palms and soles, oral mucositis, alopecia, and the bleomycin characteristic flagellate erythema.[56]

The main clinical manifestation of bleomycin-induced flagellate erythema is pruritus. Pruritus may be followed by a closely grouped, linear arrangements of papules forming erythematous lines on the abdomen appearing as whiplike marks and leaving postinflammatory hyperpigmentation. As many as 22% of patients on bleomycin therapy experience flagellate erythema.[56,57]

Genotoxic chemotherapeutics that inhibit topoisomerase I interfere with enzyme's role in unwinding DNA for replication. They are related to an alkaloid derived from *Camptotheca acuminate,* a Chinese tree.[26,27,56] The topoisomerase I inhibitors topotecan and irinotecan are commonly used in the treatment of ovarian carcinoma, cervical cancer, small cell lung cancer, myelodysplastic syndrome, and metastatic colon cancer.[27,38] The primary toxicities from topotecan and irinotecan are hematologic and gastrointestinal, with neutropenia, thrombocytopenia, anemia, nausea, and diarrhea being commonly reported.[58] Topotecan is also commonly found to cause alopecia, affecting up to 77% of patients.[27,38] Other dermatologic side effects seen with topotecan and irinotecan include HFS, nail changes,[59] and a pruritic dermatitis.[58]

Spindle inhibitors

Taxane chemotherapeutic agents work by stabilizing microtubules and arresting mitosis. Docetaxel and paclitaxel are two drugs of this class, most commonly used to treat malignancies of the breast, ovary, and lung. They are effective against rapidly dividing cancer cells, but they also have similar effects on quickly replicating cells in the body such as keratinocytes.

Stabilization of the microtubules by taxane chemotherapeutic agents leads to disruption of replicating keratinocytes. Use of both docetaxel and paclitaxel has been found to induce cutaneous eruptions that show keratinocytic atypia on pathology. Skin eruptions after chemotherapeutic treatment with paclitaxel or docetaxel vary widely, ranging from erythematous plaques to pruritic papules. In contrast, histologic studies consistently show large keratinocytes with atypical mitoses.[60]

In these eruptions, atypical keratinocytes can mimic a neoplastic carcinoma in situ, strongly resembling a melanoma or squamous cell carcinoma,[61] but the atypical, apoptotic keratinocytes with multiple mitotic forms occur in the presence of preserved epidermal maturation and polarity. Histologic studies can differentiate these taxane-caused eruptions from a

true neoplasm and are indicated when the cutaneous eruptions occur in the context of taxane treatment of carcinoma.

Acneiform eruption has also been associated with docetaxel use. Taxane stabilization of microtubules can promote neutrophil migration into tissues, producing a neutrophilic infiltrate that resembles an infectious process but does not recede with antibiotics. One case illustrated a sterile pustular eruption occurring over the scalp after each chemotherapeutic dose of docetaxel administered for metastatic uterine leiomyosarcoma.[62]

Signal transduction inhibitors

Signal transduction inhibitors are an effective way of slowing the excessive growth that is characteristic of cancer cells. Dysregulation of pathways leading to cell growth often lead to malignancies, particularly when kinases are overactive in amplifying the upstream signals. Chemotherapy with signal transduction inhibitors can inhibit specific kinases and restore normal cell growth patterns.

Targeting the epidermal growth factor receptor tyrosine kinase with drugs such as erlotinib, cetuximab, and genitimab has been helpful for treating non–small cell lung cancer.[63] Skin toxicities, very common with epidermal growth factor receptor inhibitor use, may present as acneiform dermatitis, xeroderma, or paronychia. Erlotinib is often associated with cutaneous side effects, with secondary eruptions occurring in a majority of patients. Several studies have found that the development of dermatitis after erlotinib use was correlated with drug efficacy and actually indicated greater survival after therapy.[64] Paronychia amenable to adapalene applications may develop.[65]

Imatinib targets several tyrosine kinases—Abl, c-KIT, and PDGF-R and the notable translocation product BRC-ABL that is associated with chronic myeloid leukemia.[66] Imatinib and its second-generation successors dasatinib and nilotinib are found to cause cutaneous reactions. The largest study of chronic myeloid leukemia treatment studied 532 patients with late chronic-phase chronic myeloid leukemia who were treated with 400.0 mg imatinib daily; 60% of them developed superficial edema, 32% developed a dermatitis, and 9% developed generalized pruritis.[67] Another study of the use of imatinib for gastrointestinal stromal tumor found that, of 620 patients, 148 patients developed an erythematous maculopapular eruption starting on the trunk and arms, and 42 of these affected patients had dermatitis covering $\geq$50% of the body.[68]

Multikinase inhibitors capitalize on the structural homology of ATP-binding sites on kinases to increase potency by having multiple targets, and also reducing the possibility of drug resistance developing.[69] Sorafenib and sunitinib are two such multikinase inhibitors. Sorafenib and sunitinib target VEGF receptors and PDGF-β receptors, and sorafenib also inhibits the Raf kinase of the Raf/MEK/ERK signaling pathway.[70]

Sorafenib is often effective against hepatocellular and renal cell carcinomas that are unresectable or metastatic. The European Advanced Renal Cell Carcinoma Sorafenib Expanded Access Study found that the most common adverse effect in 56.3% of the 1,145 patients included, was hand-foot-skin reaction. Hand-foot-skin reaction usually begins with paresthesias, tingling, and burning sensations on the palms and soles that precede cutaneous lesions. Hand-foot-skin reaction is visualized as symmetric acral hyperkeratotic plaques surrounded by edema and erythematous halo.[71] Sunitinib is also used to treat metastatic renal cell carcinomas. The most common side effect of sunitinib is hypertension. A study comparing use of sunitinib to pazopanib for treatment of advanced renal cell carcinomas found that 50.18% of 553 patients using sunitinib experienced hand-foot-skin reaction as a side effect.[72] Facial redness, scalp dysesthesia, alopecia, and subungual splinter hemorrhages have also been documented along with changes in hair color, alopecia, and dry skin.[71,72]

Vemurafenib is a $BRAF^{V600}$ inhibitor targeting only those BRAF kinases with a V600E mutation present. This abnormal V600E BRAF kinase is usually found in melanomas. Vemurafenib is effective in treating advanced melanomas. Many of the side effects of this anticancer drug are also cutaneous. Patients can develop multiple squamous cell carcinomas, benign verrucous keratosis, and eruptions that histopathologically are acantholytic dyskeratosis. Diffuse keratosis pilarislike eruption may occur after a few weeks of treatment with the drug.[73,74] Another toxic effect of vemurafenib is increased photosensitivity. A study determined that exposure to UVA radiation as low as 10.0 to 49.0 J/cm^2 elicited pain and burning sensations, and later intense erythema and pronounced edema developed in those areas.[75]

Mammalian target of rapamycin (mTOR) inhibitors were classically used as immunosuppressive drugs. Sirolimus was approved for prevention of transplant rejection, but the first-generation mTOR inhibitors everolimus, temsirolimus, and ridaforolimus are chemically stable for dosing in cancer patients and have become a drug of choice for treating renal[76] and gynecologic[77] cancers by targeting the P13K/AKT/mTOR signaling pathway. Their use is commonly associated with development of mild dermatitis and reported to affect 27.3% of 2725 patients treated with either everolimus or temsirolimus for various cancers.[78] This dermatitis is primarily a maculopapular or acneiform eruption on the face and neck, often appearing within the first few weeks of treatment with everolimus, temsirolimus, or ridaforolimus.[88]

Immunotherapies

Chemotherapeutic agents that take advantage of the host's own immune system to seek out and destroy tumor cells present an exciting new development in the field of cancer treatment. IL-2–based agents have been effective in the treatment

of melanoma, cutaneous T-cell lymphoma, and renal cell carcinoma.[84] The checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, durvalumab, and ipilimumab target receptors and ligands involved in the inhibition of T cells and have been shown to improve survival in patients with solid tumors. Autoimmune damage from uninhibited T cells likely leads to the development of dermatologic adverse events that should be identified and treated.

Pembrolizumab and nivolumab target the PD-1 receptor found on T cells and prevent it from binding to the PD-1-ligand expressed on tumor cells that inhibits T-cell activity. The loss of inhibition facilitates the development of an effective adaptive immune response against the tumor.[80] Up to 39% of patients treated with pembrolizumab may develop cutaneous adverse effects.[81] In a study of 83 patients placed on pembrolizumab therapy for various solid malignancies, 35 suffered some form of skin toxicity, most commonly a maculopapular eruption (29%), followed by pruritus (10%) and hypopigmentation (8%).[80] Bullous pemphigoid may also occur with PD-1 and PD-L-1 inhibitors. In a study of 21 patients in whom bullous pemphigoid developed after treatment with a PD-1 or PD-L-1 inhibitor, almost half of the patients developed bullous pemphigoid subsequent to nivolumab and pembrolizumab therapy, respectively. Twelve of the 21 cases were preceded by pruritus.[82] Case reports of bullous pemphigoid after nivolumab therapy have described the eruptions beginning as pink or erythematous pruritic patches that develop tense bullae and vesicles occasionally accompanied by crusting.[83]

The PD-L-1 inhibitors atezolizumab and durvalumab have similar mechanisms of action to the PD-1 inhibitors. They target the PD-1-ligand found on tumor cells directly with the same goal of removing inhibition against T cells and allowing a proper adaptive immune response. The cutaneous toxicity of PD-L-1 inhibitors is similar to that of the PD-1-inhibitors, with dermatitis, pruritus, and vitiligo being the most common adverse events. Two of the 21 case reports of bullous pemphigoid after checkpoint therapy developed after the use of atezolizumab and durvalumab.[82]

Ipilimumab is a monoclonal IgG antibody that targets the inhibitory CTLA-4 receptor on T cells. Normally, the CTLA-4 receptor on T cells interacts with the B7 receptor on dendritic cells to promote inhibition against self-antigens. Direct inhibition of the CTLA-4 receptor by ipilimumab therefore facilitates activation of the T cell. Cutaneous adverse effects due to anti–CTLA-4 therapy are almost twice as common as those due to anti–PD-1 or anti-PD-L-1 therapy at 68% to 38%, respectively. Cutaneous toxicity to ipilimumab generally occurs within 3 to 6 weeks after administration and most commonly presents as a morbilliform eruption covering the trunk and extremities (68% of cases). Other dermatologic adverse events include acneiform dermatitis, acute generalized exanthematous pustules, CD30 lymphomatoid reaction, dermatomyositis, DRESS, lichenoid reaction, photosensitivity reaction, pyoderma gangrenosum, radiation dermatitis, Sweet syndrome, SJS/TEN, dermatitis herpetiformis, Grover disease, prurigo nodularis, regression of melanocytic nevi, tumoral melanosis, and vitiligo.[79]

IL-2 analogs such as denileukin and aldesleukin have been shown to be effective for melanoma and renal cell carcinoma. IL-2 stimulates the activation of T cells and differentiation into CD4 helper and CD8 cytotoxic cell lines. The most well documented adverse effect to IL-2 therapy is capillary leak syndrome, in which IL-2 increases vascular permeability and fluid extravasation into tissue.[84] Skin reactions are less commonly documented with IL-2 therapy compared with other immunotherapies, but adverse events may include facial flushing,[85] acute hypersensitivity reaction accompanied by dermatitis,[86] exfoliative dermatitis, and generalized, morbilliform, or vesicular dermatitis. In general, around 14% of patients treated with denileukin diftitox developed dermatitis and 9% developed pruritus.[87] Erythema and pruritus have been documented with the use of aldesleukin and were managed effectively with the use of emollient creams.[84]

Conclusions

Cutaneous drug reactions range in intensity from mild eruptions to life-threatening conditions, including SJS-TEN. Eruptions are also incredibly diverse with different types of lesions sometimes presenting simultaneously within the same patient and often occurring in more than half of the patients. There are classic cutaneous drug reactions associated with chemotherapeutics as well as other skin reactions that may be more difficult to separate from organic skin disease. The pathogenesis of these reactions is varied:

- Hypersensitivity reactions may be seen with the use of platinum drugs.
- Anthracycline derivatives can exert direct toxic effects.
- Nonspecific dermatitis or alopecia can be seen.

When an organic skin disease may not fully explain a cutaneous eruption, a drug-induced reaction should be kept in the differential and carefully considered in patients receiving chemotherapeutics.

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