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SKIN TOXICITY WITH CHEMOTHERAPEUTIC AGENTS

Oncology

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ABSTRACT

Newer chemotherapeutic agents are associated with a range of cutaneous reactions. Reactions range from common non-specific exanthematous eruptions to rare but distinctive cutaneous lesions affecting the patient's quality of life. The differential diagnosis of a cutaneous reaction in a cancer patient receiving antineoplastic therapy includes a broad range of aetiologies. A physician's knowledge and familiarity with the scope and patterns of adverse reactions caused due to these various agents is important for an accurate diagnosis. It is important for the physician to be familiar with the patterns of cutaneous reactions caused due to various chemotherapeutic agents. Accurate diagnosis of the aetiology will pave the way for effective management of these toxicities. This review will focus on the cutaneous side effects of the newer classes of chemotherapy drugs, including targeted monoclonal antibody therapy and small molecule inhibitors.

KEYWORDS

cutaneous toxicity, chemotherapy drugs, targeted therapy, drug adverse reaction.

INTRODUCTION:

Chemotherapy is a crucial component of all cancer management. Over the last few decades, novel antineoplastic strategies have been introduced that target the molecular abnormalities in certain types of cancers. New chemotherapeutic agents include drugs and monoclonal antibodies targeting epidermal growth factor receptor (EGFR), other therapeutic monoclonal antibodies, biologically active cytokines and small molecule tyrosine kinase inhibitors.[1,2] Though these agents significantly improve survival rates, toxic effects on the skin are pronounced.[3-5] Skin toxicities can reduce quality of life and result in poor compliance or disruptions to therapy.[1,6] Physicians need to be aware of these adverse effects in order to devise effective management strategies.

In this article, we will review the dermatologic toxicities seen with several classes of biologic and molecularly-targeted agents.

Cutaneous Reaction Patterns To Chemotherapy

Cutaneous reactions to various chemotherapeutic agents involve the skin, hair, nails, and mucous membranes. Many of these reactions are non-specific, such as alopecia, mucositis and onychodystrophy. Some cutaneous reactions to conventional chemotherapeutic agents have been noted in the table (Table 1).[7]

Table 1. Cutaneous Reaction Patterns to Chemotherapy with Conventional Agents

Cutaneous reaction	Definition	Causative Drugs
Acral erythrodysaesthesia	Painful erythematous plaques on the palms and soles. Heals with prominent desquamation	Cytarabine Doxorubicin 5-fluorouracil Bleomycin Lomustine Hydroxyurea Methotrexate 6-mercaptopurine Interleukin-2 Etoposide
Photosensitivity	An increased sensitivity to ultraviolet (UV) light exposure, which can manifest in a number of ways	Dacarbazine 5-fluorouracil Methotrexate Mitomycin C Vinblastine
Radiation recall	Reactivation of inflammatory dermatitis at a site of prior radiation therapy months to years later	Methotrexate Cytarabine Dactinomycin Bleomycin Lomustine Cyclophosphamide Doxorubicin Etoposide 5-fluorouracil Hydroxyurea Melphalan Vinblastine
Neutrophilic eccrine hidradenitis	Erythematous, edematous plaques in patients with malignancy (with or without chemotherapy), infections, or receiving a variety of chemotherapeutic agents	Cytarabine Doxorubicin Bleomycin Lomustine Chlorambucil Cyclophosphamide Mitoxantrone
Eccrine squamous syringometaplasia	Asymptomatic erythematous papules on trunk/extremities; self-limited; pathology demonstrates squamous metaplasia of eccrine gland epithelium	Busulfan Carmustine Cytarabine Cisplatin Cyclophosphamide Doxorubicin Etoposide 5-fluorouracil Methotrexate Mitoxantrone Thiotepa
Leg ulcers	Painful lesions located on the leg	Hydroxyurea
Sweet's syndrome Or acute febrile neutrophilic dermatosis-	A skin disease characterized by the sudden onset of fever, an elevated white blood cell count, and tender, red, well-demarcated papules and plaques that show dense infiltrates by neutrophil granulocytes on histologic examination	Filgrastim (G-CSF) Sargramostrin (GM-CSF)
Onychodystrophy/Onycholysis	Alteration in nail morphology which may manifest as misshapen, damaged, infected or discoloured nails/Inflammation in the nail bed, which	Bleomycin Cyclophoshamide Doxorubicin 5-fluorouracil Hydroxyurea

	leads to detachment of the overlying nail	
Pigmentary changes	Pigmentary changes involving the skin, nails, and mucous membranes; enhanced pigmentation may be localised or diffuse	Diffuse: Busulfan Cyclophosphamide Hydroxyurea Methotrexate Flagellate: Bleomycin Supravenous serpentine: Fotemustine Vincristine Nails: Bleomycin Cyclophosphamide Doxorubicin Hydroxyurea Teeth: Cyclophosphamide
Worsening of psoriasis	Increase in psoriasis symptoms such as exfoliative dermatitis on long-term treatment with chemotherapeutic agents	Interferon Interleukin-2

Adapted From: Payne et al, 2006[7]

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Some targeted therapies like epidermal growth factor inhibitors, multikinase inhibitors and proteasome inhibitors cause different types of skin reactions. A detailed description of the cutaneous reactions caused by these newer agents is given below.

Taxanes: Docetaxel and Paclitaxel

Docetaxel and Paclitaxel exert their anticancer activity by stabilising microtubules.[7] The incidence of cutaneous side effects in patients treated with these drugs is estimated to be as high as 81%. Nail changes such as onycholysis, discoloration, subungual hyperkeratosis and acute exudative paronychia are seen in up to 41% of patients.[8] Acral erythrodysaesthesia is a common reaction seen to docetaxel and paclitaxel. Skin biopsies may show features of syringo-squamous metaplasia and eccrine neutrophilic hidradenitis suggesting local toxicity of the drug in eccrine sweat glands. Cases may be mild and asymptomatic to confluent and even erosive.[9]

Sometimes lesions exhibiting mixed features of acral erythrodysaesthesia and fixed drug eruption (FDE) are observed with taxane therapy. Fixed drug eruption is characterised by the appearance of a dusky, well demarcated plaque or patch within a few hours after ingestion of the drug.[10] A partially reversible scleroderma-like reaction is also observed with taxane therapy.[11] Docetaxel and paclitaxel are also associated with the development of subacute cutaneous lupus erythematosus.[12] Severe local skin and soft-tissue necrosis can result due to extravasation injury with taxanes (Fig 1). Extravasation recall phenomena - painful and inflamed tissues on repeat treatment at sites of prior paclitaxel extravasation or soft tissue exposure are known to occur.[13] A distinctive pattern of hyperpigmentation called serpentine supravenous hyperpigmentation has been noted with docetaxel infusion.[14]

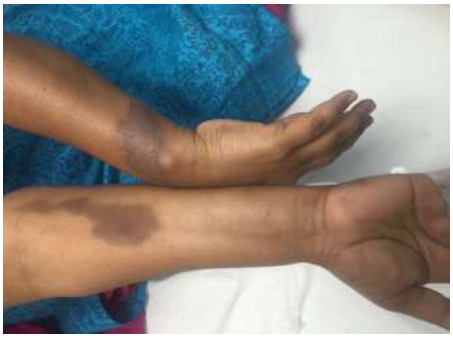


Figure 1: Extravasation injury with docetaxel.

Anthracyclines: Polyethylene Glycol-Coated Liposomal Doxorubicin

Doxorubicin directly binds to DNA. The antitumor effect of doxorubicin is likely through direct inhibition of DNA synthesis and/or induction of DNA mutagenesis and chromosomal aberrations.[15] Historically, doxorubicin has been associated with significant side effects. The polyethylene glycol-coated liposomal formulation of doxorubicin however exhibits a lower rate of hematologic and cardiac side effects than its nonencapsulated form. Dose-limiting mucocutaneous toxicities can however still occur (Fig 2).[7]

Acral erythrodysaesthesia is a common dose-limiting side effect that can occur with liposomal doxorubicin. Reported incidences are variable with 2% to 50% of treated patients being affected.[16,17] Other cutaneous reaction patterns associated with the drug include potentially severe and dose-limiting stomatitis, new development of melanotic macules, mild folliculocentric scaly erythema and sunburn/radiation recall.[7]

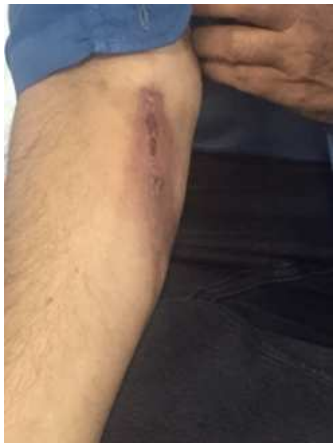


Figure 2: Hyperpigmentation - 5FU and anthracycline toxicity.

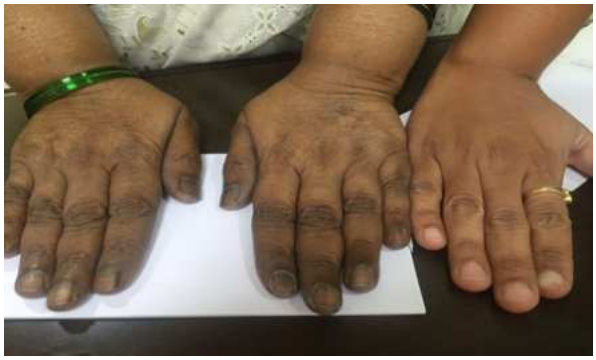
Antimetabolites: Gemcitabine, Capecitabine and Pemetrexed

Gemcitabine (a deoxycytidine analogue) and capecitabine [a prodrug of 5-flurouracil (5-FU)] are nucleoside analogues that interfere with DNA replication, while pemetrexed depletes folate pools and inhibits de novo purine biosynthesis.[7]

Cutaneous side effects associated with gemcitabine include macular xanthema seen in about 39% of patients.[18,19] This drug is also associated with recurring fixed erythrodysaesthesia plaques as seen with taxane therapy.[20,21] In addition, pseudolymphomatous reaction of the skin has been noted.[22] Reactions with capecitabine include nail changes such as onycholysis and onychomadaesis.[23]

Inflammation and partial clearing of actinic keratosis is also associated with capecitabine treatment.[24] Radiation recall is a notable reaction with both gemcitabine and capecitabine.[25,26] Acral erythrodysaesthesia is more commonly associated with capecitabine than with gemcitabine. More than 50% of patients receiving capecitabine-docetaxel combination chemotherapy show this reaction.[27] Almost 100% of patients treated with Pemetrexed develop some form of cutaneous toxicity such as pruritic rash.[28]

Other cutaneous side effects associated with antimetabolites include hyperpigmentation (Fig 3a and 3b).



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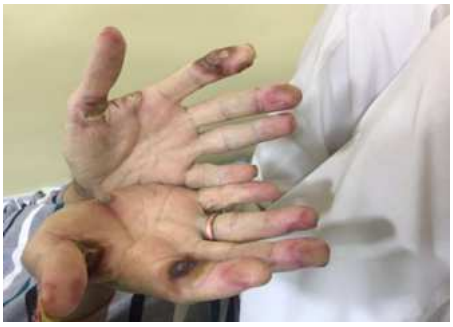


(b)

Figure 3 (a,b): Hyperpigmentation with fluorouracil.

Small Molecule Signal Transduction Inhibitors: Imatinib Mesylate

Imatinib mesylate is a protein- tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and c-kit tyrosine kinases.[7]

Use of imatinib shows a diverse pattern of cutaneous adverse events with rash being reported in 22% of patients and oedema in up to 60% of patients in clinical trials (Fig 4).[7] The frequency of rash was dose-dependent, with the incidence increasing up to 93% at a daily dose of 600 mg or higher.[29] Common rash morphology is exanthematous macular and papular eruption. Acute generalized exanthematous pustulosis (AGEP), consisting of high fever, leukocytosis, and a sterile follicular pustular eruption, as well as Sweet's syndrome (acute febrile neutrophilic dermatosis), classically consisting of fever, leukocytosis, and an acute onset of erythematous plaques have been described after imatinib therapy.[30,31] Severe reactions such as Stevens-Johnson syndrome are associated with higher initial doses of imatinib therapy.[32]Photosensitivity and pigmentary changes have also been noted in clinical trials (Fig 3).[29,33]

Figure 4: Rash with imatinib mesylate in renal cell carcinoma (RCC)

Epidermal Growth Factor Pathway Inhibitors: Monoclonal antibody and Tyrosine kinase inhibitors

The EGF signalling pathway regulates growth, survival, proliferation and differentiation in mammalian cells.[34] An array of antineoplastic drugs has been developed that target this pathway. Therapeutic monoclonal antibodies to the EGF receptor include cetuximab, panitumumab, necitumumab and nimotuzumab. Orally active small molecule tyrosine kinase inhibitors include gefitinib, erlotinib, lapatinib, afatinib, osimertinib and sorafenib.[2]

A common cutaneous reaction noted with the EGF pathway inhibitors is diffuse papulopustular (rash) acneiform eruption. It is noted in about two-thirds of patients receiving these drugs. The reaction is often dose-dependent and consists of erythematous lesions occurring on the face, trunk and extremities (Fig 5).[35] The reaction may often be accompanied by pruritus, sometimes severe.[36]

Skin xerosis (dryness) is present in up to 35% of patients receiving EGFR pathway inhibitor therapy.[37,38]The reaction is more commonly seen with gefitinib.[39] The typical presentation is dry, itchy, scaly skin. Areas simultaneously or previously affected with papulopustular eruption are more prone. Xerosis can evolve to chronic eczema, with erythema and worsening of pruritus.[36]

About 10%-20% of patients undergoing EGFR inhibitor therapy may show nail and periungual toxicity weeks to months after therapy. This may manifest as acute paronychia, oozing, bleeding, and pyogenic granuloma-like lesions. Nail changes are common and include pitting, discoloration, and onycholysis. Nail or paronychial toxicities may be accompanied by follicular eruption (Fig 6).[40] Hair impairment is seen in up to 50% of patients treated with EGFR inhibitors. Patients may present with either excess growth of facial hair, or curly, wavy, and brittle texture of hair.[37]

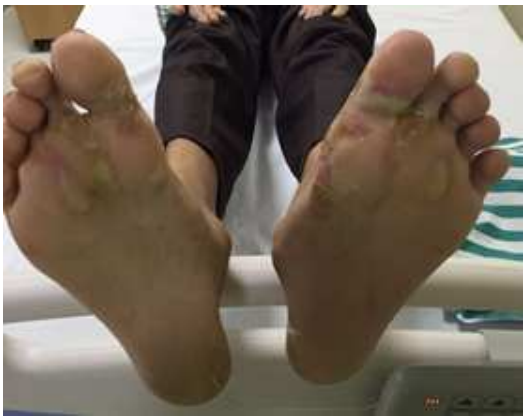


Fig 5. Hand-foot syndrome (acral erythrodysaesthesia) with sorafenib in renal cell carcinoma.

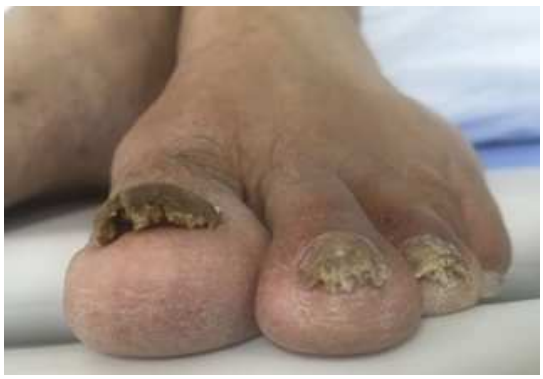


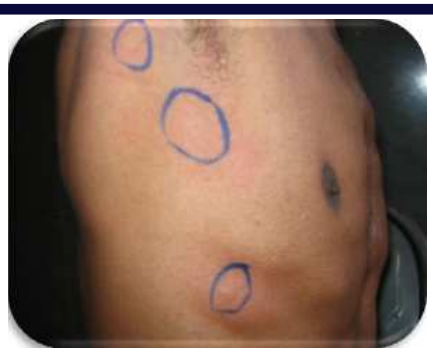
Figure 6: Hypertrophic nails with erlotinib in pancreatic cancer.

Is Nimotuzumab Safer Compared to Cetuximab?

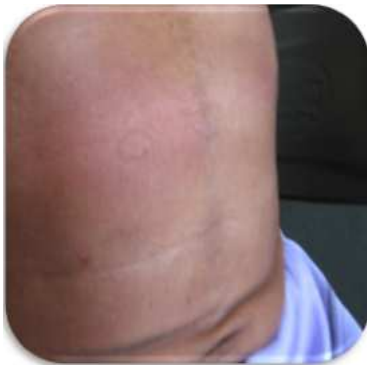
Nimotuzumab is a humanized monoclonal antibody to EGFR. Studies support the use of nimotuzumab with chemoradiation therapy (CRT)/radiation therapy (RT) as a viable therapeutic option in patients with inoperable, locally advanced squamous cell carcinoma of the head and neck. A striking outcome of these studies is the almost complete absence of severe adverse events. Unlike most anti-EGFR drugs, nimotuzumab caused minimal skin rash (Fig 7a and 7b). As per a 5-year randomised, open-label, phase II study in Indian patients (BEST Trial), concurrent use of nimotuzumab with CRT/RT is safe and provides survival benefit. No incidences of debilitating skin rashes, hypomagnesaemia and negligible incidences of classical EGFR inhibition related toxicities were reported (2 out of 46 patients showed minimal skin rashes).[41,42]

Pharmacodynamic studies show that nimotuzumab as a single agent inhibits EGFR phosphorylation in both skin and tumour cells. However, EGFR downstream effects were not observed in skin whereas they were observed in tumour cells.[43] This effect of nimotuzumab can be attributed to the fact that the drug requires bivalent binding for stable attachment. This leads to increased binding in cells and tissues which express moderate to high levels of EGFR such as tumour cells. In normal tissues such as skin, the EGFR density is low, causing transient monovalent interaction. This leads to sparing of healthy tissues and avoidance of severe toxicities.[41]

In contrast, cetuximab can be added to RT, but cannot be added to CTRT because of SAEs noted in clinical trials. Cetuximab attaches with monovalent binding and binds specifically to EGFR on both normal and tumour cells.[44] Skin rash is a result of action on normal cells (Fig 8).



(a)



(b)

Figure 7 (a,b): Minimal skin rashes with Nimotuzumab

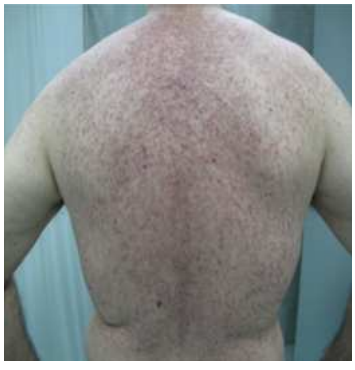


Figure 8. Follicular rash with cetuximab.

Skin Toxicity With Other Chemotherapy Agents

Majority of monoclonal antibody therapies such as rituximab and trastuzumab are well tolerated cutaneously. Adverse reactions reported include infusion reactions and serum sickness.[7]

Cutaneous reactions with topoisomerase I inhibitors such as topotecan and irinotecan are mostly mild to moderate in severity and do not require specific treatment. Cases of morbilliform rash have been reported in 6% to 21% of patients on monotherapy with either of the two drugs, while cellulitis-like fixed drug eruptions have been associated with topotecan therapy.[45]

Thalidomide acts as an anti-inflammatory, immunomodulatory, and anti-angiogenic agent. Cutaneous toxicity is mostly limited to xerosis and rash with morbilliform, maculopapular and erythrodermic morphologies. Additionally cases of exfoliative erythroderma and/or toxic epidermal necrolysis (TEN) have been associated with the drug.[46]

The vinca alkaloids such as vinorelbine exhibit local and potentially severe skin necrosis with extravasation injury. Acral erythrodysaesthesia has also been noted in some patients.[47]

The proteasome inhibitor bortezomib acts by inhibiting intracellular protein degradation pathways. It is currently approved for the treatment of multiple myeloma. About 8% to 15% of patients suffer from mild cutaneous adverse effects in clinical trials.[48]

Prevention and Management of Dermatologic Toxicities with Chemotherapeutic Agents

Prevention and management of mucocutaneous toxicities is essential to maintain the patients' health-related quality of life and dose-intensity of antineoplastic regimens.

Many chemotherapy induced skin reactions are mild to moderate and do not require any alteration in protocol.[7] Some reactions such as Stevens-Johnson syndrome are dose-limiting and can be effectively managed with decreased dosing regimens. Others require preventive/prophylactic or treatment/reactive management.

Due to the high frequency of papulopustular (acneiform) rash in EGFR inhibitor treated patients, prophylactic management of these patients is recommended. Based on randomised data, a combination of sunscreen, moisturizer, hydrocortisone 1% and doxycycline 100 mg bid for the first 6 weeks is recommended. Prophylactic minocycline 100 mg daily may also be effective in regions with a high UV index.

Based on in vitro studies, reactive use of medium- to high-potency topical corticosteroids is also recommended.[49]Reports suggest that pyridoxine at a dose of 50 mg three times daily may be effective for palmar-plantar erythrodysaesthesia due to taxane therapy.[50]Localised treatment such as hypothermia was also found to be successful in some cases. A trial was conducted using glycerin-containing Elasto-Gel thermal glove cooled to -25°C and worn on the hands just before, during and after docetaxel infusion. The incidence of onycholysis, pigmentation and acral erythrodysaesthesia was found to significantly decrease with this treatment.[51]

SUMMARY AND DISCUSSION:

Multiple chemotherapy agents may be associated with a given cutaneous reaction. The advent of multi agent regimens has therefore made it increasingly difficult to attribute drug reactions to a single agent. These diagnostic uncertainties can often be clarified by rechallenge. However, the physicians' knowledge and familiarity with various drug toxicities is very important for accurate diagnosis.

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