

Chemotherapy induced skin toxicities and review of literature

Abstract

Chemotherapeutic drugs have proven efficacy in the treatment of most of the cancers. Chemotherapy induced side effects are commonly seen in clinical oncology. The development of new chemotherapeutic drugs and various new protocols results in increase of many dermatological complications. The skin manifestations can be acute during drug administration, or may occur during the course of the drugs. The patterns of manifestations are characterized by spectrum of inflammatory disease patterns. Reaction pattern is not specific for a particular drug. The possible skin toxicities are alopecia, hyperpigmentation, extravasation, erythrodysesthesia, nail changes, radiation recall reactions and photosensitivity. These chemotherapy related skin toxicities affect the quality of life particularly in young female patients. Proper evaluation, early detection and management of such toxicities with counselling are necessary before, during and after chemotherapy administrations in order to make suitable drug administration, improvement in quality of life and better clinical outcome.

Keywords: Chemotherapy, management, skin manifestations, targeted therapies.

Introduction

Skin manifestations may be related either as a phenomenon related to cancer diagnosis or as a consequence of cancer related treatment. Chemotherapy mostly responsible for skin manifestation in cancer related treatment.

Improvement of management in the field of oncology requires knowledge regarding the primary disease, the efficacy and side effects of the various kind of treatment. Patient's general conditions and expected complications of chemotherapy or targeted therapy should be considered before planning of any chemotherapy/targeted therapy schedule. Chemotherapy drugs are used in many cancers in settings of radical, neoadjuvant, adjuvant and palliative intent. Chemotherapy related side effects range from common to rare things and get confused with many dermatological manifestations. Drug induced inflammatory disease patterns include: perivascular dermatitis, nodular and diffuse dermatitis, vesiculobullous lesions, pustular eruptions, sclerodermoid reactions, vasculitis, folliculitis/perifolliculitis and paniculitis.

Though skin toxicities are rarely life-threatening but worsen the quality of life. These agents generally target rapidly dividing cells resulting toxicity to organ systems such as bone marrow, hair, nails, skin, and the gastrointestinal (GI) mucosa. Skin and mucosal toxicities are commonly seen among most chemotherapeutic agents. The GI and bone marrow related toxicities are established in the literature, whereas, there is paucity regarding data and guidelines for the management of skin toxicities. These toxicities may interfere in chemotherapeutic managements resulting in dose reduction, discontinuation or change in chemotherapeutic agents [1,2].

40 Recently, targeted therapy increases the survival rate of many cancers like kidney, lung,
41 colorectal, breast and liver. Dermatological adverse effects due to targeted therapies were
42 reported in the literature.

43 Physicians should know about the adverse effect of the chemotherapeutic drugs and their
44 managements and prevention. The purpose of this article is to review the skin related
45 toxicities due to various chemotherapeutic agents and its management.

46 **Incidence**

47 In general, drug induced cutaneous adverse reactions are seen in 2-5% of hospitalised
48 patients with serious fatal disease [3]. It is more common in female. The incidence increases
49 with increase in age, number of drugs, and associated HIV infections or other
50 immunocompromised status [4,5].

51

52 **Mechanism of action in general**

53 Cytotoxic chemotherapeutic drugs act on tumour by interfering with DNA replication
54 process affecting normal healthy tissues including skin, hair, and mucosa as well as cancer
55 cells resulting in various common toxicities like alopecia, mucositis, onychodystrophy and
56 extravasations.

57 **Skin toxicity**

58 Antineoplastic drugs related skin manifestations may be due to chemotherapy or targeted
59 therapy. Many chemotherapeutic drugs cause nonspecific dermatological toxicities
60 including alopecia, mucositis and onychodystrophy. Some targeted therapies like epidermal
61 growth factor inhibitors, multikinase inhibitors and proteasome inhibitors cause different
62 types of skin reactions. Some specific dermatological complications may occur like radiation
63 recall reactions, toxic erythema and skin hyperpigmentations.

64 Various types of skin manifestations due to different chemotherapeutic drugs are
65 highlighted in table-1.

Drugs	Skin manifestations
Alkylating agents	Oral mucositis
Nitrogen mustard	Eccrine squamous metaplasia
mechlorethamine	Topical use-allergic contact dermatitis(type iv reaction)
cyclophosphamide	Mucositis oral mucositis, permanent alopecia (may cause), localised hyperpigmentation of palm, nail, soles, flushing, eosinophilic pustular folliculitis,black longitudinal pigmentation of nail
ifosphamide	Localised hyperpigmentation of palm, nail, soles
melphalan	Beau's line
ethylenimine (thiotepa)	Diffuse erythematous rash, localised hyperpigmentation on areas of trauma, pressure and occlusion

Alkyl sulfonate (busulfan)	Addisons like hyperpigmentation, flagellate hyperpigmentation, permanent alopecia (may cause)
triazine (dacarbazine)	photo sensitivity, flushing, phototoxicity
Methyl hydrazine (procarbazine)	Erythema vasculitis (type III hypersensitivity)
Platinum coordination complexes	Hypersensitivity, localized hyperpigmentation on areas of trauma, pressure, occlusion
cisplatin	Beau's line, flushing, livedo reticularis, Reynaud's phenomenon, distal necrosis, leg ulceration
carboplatin	Flushing
Antimetabolites	Eccrine squamous metaplasia
Folate antagonist	
methotrexate	Mucositis, tellogen effluvium (alopecia), Recall reaction, photosensitivity, flushing, leg ulceration, eosinophilic pustular folliculitis
pemetrexed	Prurigenous skin rash, melanochia, onycholysis
Pyrimidine antagonist	
5-flurouracil	Alopecia (tellogen effluvium-temporary), photo sensitivity, Hyperpigmentation of nail, skin and oral mucosa (serpentine supravenuous hyperpigmentation), flushing, phototoxicity (systemic and topical 5 FU), hand-foot syndrome (HFS) (in protracted infusion of 5 FU), inflammatory changes in pre-existing keratosis (systemic 5FU), sub acute cutaneous lupus, eosinoplic pustular folliculitis
capecitabine	Paronychia(<1%) , mucositis, hyperbillirubinemia, diarrhoea,myelosuppression, HFS, hyperpigmentation ,hyperpigmentation on tongue(rarely), nail changes(beau's line, periungual pyogenic granuloma, onycholysis, onychomadesis, melanochia), phototoxicity, inflammatory changes in pre-existing keratosis, sub acute cutaneous lupus
cytarabine	HFS, inflammatory changes in pre-existing keratosis, neutrophillic eccrine hidradenitis
gemcitabine	Recall reaction, livedo reticularis, Reynaud's phenomenon, distal necrosis, leg ulceration, periorbital edema, sub acute cutaneous lupus
Vinca alkaloids	Alopecia, dermatitis, recall reaction, extravasations, nail changes, sub acute cut. Lupus erythematosus
vincristine	Beau's line, HFS
vinblastine	Phototoxicity, HFS
vinorelbine	Hyperpigmentation of nail,skin and oral mucosa
Taxanes	Nail changes, sometimes permanent alopecia, hypersensitivity, PATEO, HFS, , dermatitis, recall reaction, extravasations, sub acute cut. Lupus erythematosus
paclitaxel	Alopecia (anagen effluvium), onycholysis
docetaxel	Alopecia (anagen effluvium), Beau's line, onycholysis, Recall reaction, schlederoid reaction
Epipodophyllotoxin/topoisomerase 2 inhibitors	Alopecia (anagen effluvium), hypersensitivity, Recall reaction, flushing, HFS

(etoposide)	
Camptothecin analogues / topoisomerase 1 inhibitors (irinotecan)	Alopecia (anagen effluvium), flushing
antibiotics	
dactinomycin	intertriginous like eruptions/cutaneous dysmaturation, Acneiferous drug eruptions (folliculitis)
doxorubicin	Alopecia (anagen effluvium-temporary), Beau's line, Recall reaction, flushing, HFS, intertriginous like eruptions/cutaneous dysmaturation (liposomal), longitudinal pigmentation of nail& local skin pigmentation
, daunorubicine	Hyperpigmentation of nail, skin and oral mucosa
epirubicine	Alopecia (anagen effluvium)
idarubicin	Alopecia (anagen effluvium)
Mitoxantrone	Alopecia (anagen effluvium), onycholysis
bleomycin	Beau's line, pruritus of trunk, flushing, livedo reticularis, Reynaud's phenomenon, distal necrosis, schlerodermoid reaction, neutrophilic eccrine hidradenitis, alopecia, stomatitis, nail changes, hyperpigmentations
miscellaneous	
hydroxyurea	nail changes, leg ulceration
asparaginase	Erythema vasculitis (type III hypersensitivity), flushing
anthracyclines	Mucositis, alopecia, nail changes, Eccrine squamous metaplasia
Hormonal agents (Tamoxifen, anastrozole, leuprolide, flutamide)	Flushing

66 Table-1 showing chemotherapy induced various skin manifestations

67 **Common toxicities:** It includes mucositis, alopecia, onychodystrophy, extravasation and
68 hypersensitive reactions.

69 1) Mucositis: Inflammation of the mucosal surfaces of the mouth and gastrointestinal
70 tract may occur due to high cell regeneration and growth rate [6]. It occurs in 5-20%
71 of patients receiving chemotherapy for solid tumours, whereas, 60-100% of patients
72 receiving myeloablative regimens prior to stem cell transfusion [7]. It may presents
73 with erythema of the mouth followed by erosion and ulceration. Due to involvement
74 of GI tract diarrhoea may occur. Most of the chemotherapeutic agents cause
75 mucositis, particularly affecting DNA synthesis and s-phase specific agents.
76 Concurrent use of radiotherapy along with chemotherapy potentiates the
77 chemotherapy induced oral mucositis. Alkylating agents are more responsible for
78 oral mucositis [8]. Methotrexate, anthracyclines and cyclophosphamide mostly
79 causes mucositis. Oral mucositis can be prevented by oral cryotherapy using oral ice
80 chips and popsicles before or during administration of chemotherapy [7]. Systemic
81 use of keratinocytic growth factors also reduces the chance of mucositis [9]. Local
82 low level oral laser therapy is also used as preventive measures for patients requiring
83 conditioning chemotherapy for stem cell transplantation [9,10]. It is rarely life

threatening. Severe form may require use of feeding tubes. Treatment is basically supportive care with symptom improvement. Routine oral care, mucosal coating agents and analgesics are the treatment options. Routine oral care: It includes removal of dentures, soft cleansing of the mouth and teeth, oral rinses with salt and baking soda. Mucosal coating agents: Topical kaolin/pectin, diphenhydramine, oral antacids and maltodextrin. Analgesia: Ice chips, topical local anaesthetic solutions, topical morphine sulphate in water, oral or intravenous analgesia with opioids. Topical viscous lidocaine is used for relief of symptoms, but, severe mucositis requires systemic opioid analgesics [11].

2) Alopecia: Hair loss is the most common side effect due to chemotherapy, usually temporary and resolves after stoppage of treatment. Telogen effluvium and anagen effluvium type of alopecias may occur due to chemotherapeutic drugs. 5-FU and methotrexate are mostly responsible for telogen effluvium, whereas, alkylating agents (doxorubicin, epirubicin, idarubicin and mitoxantrone), topoisomerase inhibitors and taxanes (paclitaxel and docetaxel) are responsible for anagen effluvium. Most of the alopecia induced by CT are reversible, but, some alkylating agents and taxanes induced alopecia rarely becomes permanent [12]. Busulphan and cyclophosphamide may cause permanent hair loss. It usually starts within 1-2 weeks. Taxanes and anthracyclines are mostly responsible for alopecia. Treatment includes cooling the scalp area, use of headband and immune treatment to up regulate cytokines. But all these treatments are not effective. EGFR inhibitors may cause slowing in growth of hair, brittle hair and thick hair. Scalp cooling may be used as prevention approach, but no widespread acceptance in United States [9,13]. Topical minoxidil is used after completion of CT helping in regrowth of hair [9].

3) Nail changes: Beau's line, onycholysis, onychomadesis, hyper- or hypo-pigmentation, nail pain with thickening or thinning and paronychia may occur. Anthracyclines, taxanes, hydroxyurea may cause nail changes. Paronychia occurs in 10-15% with anti-EGFR therapy and <1% with capecitabine therapy. Beau's line (transverse ridges across the nail) is associated with cytotoxic drugs like bleomycin, melphalan, doxorubicin, cisplatin, docetaxel and vincristine [9]. The Beau's line resolves after completion of chemotherapy. Onycholysis may occur due to cytotoxic drugs like mitoxantrone, docetaxel and prolonged use of paclitaxel [9]. Usually nail changes disappear with the replacement of the damaged nail with growth of new nails.

4) Extravasations: It is the unintentional leakage of the drugs through the canalised vessels into the surrounding interstitial tissues due to vascular rupture or by direct infiltration (figure-1). It is seen in 0.1-6% adults treated with CT. Severity of it depends upon volume, concentration and type of the drugs administered. Extravasations results in pain, erythema, ulceration and tissue necrosis in severe cases [14,15]. Drugs causing extravasations are divided into non-irritant, irritant and vesicant drugs. Non-irritants provoke oedema at the site of extravasations without tissue damage. Irritants are drugs with milder inflammatory response leading to

erythema, oedema, pain and tissue damage without necrosis, and symptoms are usually short-course and leave on sequel. Vesicants are drugs which may cause more severe long-lasting tissue damage resulting blister formation and tissue necrosis [15].

- a) Non-irritants: Cyclophosphamide, chlorambucil, methotrexate, hydroxyurea
- b) Irritants: 1) Platinum based alkylating agents
2) Taxanes
3) Topoisomerase inhibitors
(5-FU, carboplatin, cisplatin, bleomycin, mitomycin, dactinomycin, idarubicin, daunorubicin, dacarbazine, ifosfamide, cyclophosphamide, mechlorethamine, carmustine, mitoxantrone, paclitaxel, docetaxel, streptozocin, vinblastine, Vinorelbine and etoposide)
- c) Vesicants: 1) Anthracyclines (doxorubicin, dactinomycin)
2) Vinca alkaloids (vincristine, vinblastine)
3) Nitrogen mustards
(melphalan, bleomycin, mechlorethamine, carmustine, mitomycin, mitoxantrone, cisplatin, paclitaxel, dacarbazine, dactinomycin, daunorubicin, streptozocin, doxorubicin, epirubicin, vinblastine, vincristine, etoposide, vindesine and vinorelbine)

Proper venous assessment is important and indwelling catheter may be required. Infusion of 20 ml of saline just after completion of chemotherapy reduces the possibility of toxic residues. Duration of infusion of vesicant drugs should be less. In less involved case, the signs and symptoms will disappear after few weeks. Immediate cessation of infusion followed by aspiration of the drug should be done. Local application of heat results in vasodilatation and dilution of the drug. In extravasation due to drugs like etoposide, paclitaxel, vinblastin, vincristine and Vinorelbine, initial heat application done for 30 minutes, followed by ice application. Cold/ice application causes venous constriction resulting degradation of toxic metabolites, decreasing pain and inflammation [16]. Persistent erythema or oedema without ulceration or presence of extensive areas of necrotic tissue or skin ulceration may require surgery. In failure cases, ulcers may require debridement and grafting. Tendon, nerves and vessels may involve resulting contractures, neural deficits, nerve compression syndrome and reflex sympathetic dystrophy.



Figure-1 showing extravasations in forearm and arm due to doxorubicin

5) Hypersensitivity reactions: In general all chemotherapeutic drugs may cause hypersensitivity reactions. Majorities are type I (IgE-mediated) and presents with urticaria, pruritus, angioedema, and anaphylaxis within the first hour of chemotherapy. Circulating immunocomplexes due to procarbazine and L-asparaginase results in polymorphous erythema and vasculitis (type III reactions). Also, type IV reactions (allergic contact dermatitis) may occur due to topical use of nitrogen mustards mechlorethamine [17]. Taxanes, platinum-based compounds, epidophyllotoxins and procarbazine mostly responsible for hypersensitivity reactions [18]. Steven Johnson Syndrome, toxic epidermal necrolysis and exanthematous eruptions are severe life-threatening reactions may occur due to chemotherapy administration.

Some Specific complications: It includes radiation and UV recall reactions, toxic erythema, hyperpigmentation.

1) Recall reactions: It is the development of erythema in areas of previously quiescent sunburn or treated with radiotherapy at any time [19]. The mechanism is not clearly understood. Inflammatory rashes occur in the form of erythema to maculopapular eruption to desquamation. This reaction is drug dependant and occurs in 1.8% to 11.5% of cases [9]. These reactions are more intense in sun exposed areas of the skin. There may be persistence of residual hyperpigmentation for the months or years. Discontinuations of the drug, application of physical sunscreens, cold compresses, systemic antihistaminics, use of topical or oral corticosteroids, and minimizing exposure to sun are important options in the management [9]. Gemcitabine, methotrexate, docetaxel, etoposide, and doxorubicin are the possible agents causing such type of reactions. Drugs like methotrexate, 5-FU, dacarbazine have photosensitivity and results in sunburn even with minimal sun exposure. UV recall reaction is similar to radiation recall reaction. It occurs on exposure to drug in areas receiving prior UV ray therapy and pathological findings are similar to radiation recall reaction. Dacarbazine, systemic 5-FU, topical 5-FU, tegafur, capecitabine and vinblastine are the most possible agents responsible for phototoxicity [20].

2) Toxic erythema: It is the erythema often painful and begins 2-4 weeks after starting of chemotherapy and resolves after discontinuation of the drugs [9]. Three variants are seen such as Hand-foot syndrome, neutrophilic eccrine hidradenitis, and eccrine squamous syringometaplasia. Pyridoxine supplementation may reduce the incidence and severity of capecitabine induced Hand-foot syndrome (HFS) [21]. In 1984, Lokich and Moore first described it during protracted infusion of 5-FU [22]. The severity of syndrome increases with increasing the duration of exposure. It is seen in different forms and divided into grade-1, 2 and 3. Grade-1 consists of mild erythema with tingling and burning sensation but without affecting daily activities. In grade-2, lesions are painful causing difficult in daily activities and with intact skin surface. In grade-3, pain is severe and tissue breakdown occurs causing peeling of skin and blistering. Acral erythema occurs at dorsum of hand, around metacarpals involving thenar eminence and onycholysis may occur [23]. HFS is the most common

cutaneous side effect caused by capecitabine. It is mostly confined to palms and soles and more frequently occurs in dark-skinned patients. The classical presentation of HFS is initiation with bilateral numbness and tingling sensations of palms and soles with gradual development of erythema. Painful with various degrees of swelling may develop and may progress to blisters, desquamation and fissures. The possible mechanisms are: a) direct toxic effect on melanocytes, b) increased secretions of adrenocorticotrophic hormone and melanocyte stimulating hormone due to adrenal toxicity, c) deficiency in tyrosinase inhibitors, d) formation of stable drug-melanin complexes and e) post inflammatory pigmentation following toxicity [24]. The initial presentation is tingling and/or numbness over palms and/or soles followed by painful swelling red plaques and gradually peeling of the skin with resolution of the symptoms. Redness of the skin (painful erythema) over palms and soles, with or without presence of bullae is the most common manifestations. Sensation of the skin may be altered (dysesthesia) and may be severe affecting daily activities. Usual course of the early lesion is desquamation followed by re-epithelialisation. It rarely occurs on knees, elbows, and elsewhere. It usually occurs after chemotherapy use and rarely caused by sickle-cell disease, bone marrow transplant patients. The symptoms can occur at any point between days to months after drug administration and depends on dose and speed of drug administration. Exact mechanism is unknown. Pathophysiological mechanism of such syndrome is not established till date. Some theories may exist behind this such as: temperature differences, vascular anatomy, difference in the type of cells (rapidly dividing epidermal cells and eccrine glands). Reversible palmoplantar keratoderma may occur on long-term use of chemotherapy. The lesions typically disappear within a few weeks after discontinuation of the drug. 5-FU, capecitabine, doxorubicin, vincristine, vinblastine, cytarabine, etoposide, taxane, liposomal doxorubicin, sorafenib, sunitinib and cabozantinib are the agents that may cause the syndrome. Acral erythema caused by Tyrosine kinase inhibitors seems to be different from that induced by chemotherapeutic drugs. Grade III/IV HFS occurs in 11% of cases, whereas all grades are seen in 49% of patients using capecitabine [25]. Taxane induced syndrome is dose dependant and dose modification or treatment interruption or both is the option in the treatment [26].

There is no effective measure for prevention of it. Topical therapies can be tried. Cooling of hand and feet may help in prevention of such type of lesions. Treatments include drug interruption, dose reduction, discontinuation of the drug, use of corticosteroids, pyridoxine and symptomatic treatment (wound dressings, analgesia and cold compresses) [27].

PATEO (periarticular thenar erythema with onycholysis) syndrome may occur as a side effect of taxane and the pathophysiological mechanism is not established.

- 3) Hyperpigmentation: Cutaneous hyperpigmentation may occur after exposure to cytotoxic CT. It commonly affects skin, hair, nails and mucous membranes [17]. It may be localized or diffused [17]. Cutaneous hyperpigmentation can occur at any part of tegument (hair, nails and mucous membranes). It can be either localized, diffuse or a distinctive pattern [28]. The mechanism of CT induced

hyperpigmentation is still unclear. There is no existing specific treatment for hyperpigmentation. It resolves after months or years of chemotherapy completion.

- Busulfan (causes Addison-like hyperpigmentation) [29] (also causes flagellate hyperpigmentation, a self limiting and dose-dependent) [9]
- Cyclophosphamide, ifosfamide (localized hyperpigmentation of nails, palms, and soles) [29]
- 5-FU (causes serpentine supravascular hyperpigmentation) (figure-2) [18]
- Platinum-based agents and thiotepa (localized hyperpigmentation in areas of trauma, pressure, or occlusion) [9]



Figure-2 showing serpentine supravascular hyperpigmentation

Capecitabine induced hyperpigmentations (figure-3) is a confusion area as it is a self developed lesion or is an early manifestation of HFS. But, according to some literature, hyperpigmentations may be a manifestations associated with HFS [30,31]. Capecitabine induced hyperpigmentation over tongue (figure-4) can occur with rare chance [32]. Capecitabine is an oral antineoplastic drug and is used in most of the GI malignancies and metastatic breast cancers. Mucositis, hyperbilirubinemia, diarrhoea, myelosuppression and hand-foot syndrome are the dermatological manifestations caused by capecitabine. Capecitabine may cause hyperpigmentation over palms and soles, but pigmentation over tongue is an extremely rare entity. Drug interruptions and dose reduction may necessary. Dose reduction and starting with lower dose with subsequent escalation done according to tolerability without compromising efficacy [33]. Capecitabine may cause nail changes such as: periungual pyogenic granuloma like lesions, Beau's lines, onycholysis, onychomadesis and melanonychia [34]. Flagellated form is an unique pattern caused by bleomycin and presents as dark brown linear streaks nearly 10cm in length and criss-crossing one another (flagella appearance: whip-like structure of bacteria assisting in movement). Bleomycin causes pruritus of trunk causing scratch and results in local accumulation of the drug into the skin. 5-FU, Vinorelbine and daunorubicin can cause hyperpigmentation of skin, nails and oral mucosa (serpentine supravascular hyperpigmentation). Stoppage of the drug, use of oral antihistaminics and topical hydroquinone are various treatment options.



Figure-3 showing capecitabine induced hyperpigmentations over both palms and soles



Figure-4 showing capecitabine induced hyperpigmentations over tongue

Different types of hyperpigmentation due to chemotherapy are given in table-2.

Types of hyperpigmentation	Chemotherapeutic agents responsible
Acral	Capecitabine, tegafur
Patchy	5-FU
Diffuse	Busulphan, cyclophosphamide, hydroxyurea and methotrexate
Supervenous serpentine	Paclitaxel, docetaxel, Vinorelbine, vincristine
Transverse bands	Cyclophosphamide
Lentigo, eruptive naevi	Fluoropyridines
Flagellate	Bleomycin

Table-2 showing chemotherapy induced different types of skin hyperpigmentation

Others:

288 Flushing: It is a temporary erythema particularly seen in sites of face, neck, ears, upper chest
289 and upper abdomen. Transitory vasodilatation due to autonomic nervous system or the
290 direct effect of circulating substances on the vascular walls result in flushing. L-
291 asparaginase and bleomycin causes flushing soon after infusion [17]. Other agents causing
292 flushing includes irinotecan, topoisomerase I inhibitor, hormonal agents (tamoxifen,
293 anastrozole, leuprolide, flutamide, diethylstilbestrol), 5-FU, carboplatin, cisplatin,
294 cyclophosphamide, dacarbazine, doxorubicin, etoposide and methotrexate [17,35].

295 Other Vasomotor changes: Livedo, Raynaud's phenomenon, and distal necroses are caused
296 by bleomycin and cisplatin [17]. Vascular phenomenon: Raynaud phenomenon (exaggerated
297 response of blood vessels to cold temperature and emotional stress resulting demarcated
298 colour changes of skin of the digits) and vasculitis (inflammation of the blood vessel walls
299 compromising lumen may result in livedo reticularis, ischaemia, necrosis, ulceration,
300 thromboembolism). Bleomycin, cisplatin, gemcitabine and rituximab may cause such type
301 of vascular phenomenon. Raynaud phenomenon improves by discontinuing the drug,
302 avoiding exposure to cold, hand warmers, using protective clothing, and use of calcium
303 channel blockers and ACE inhibitors.

304 Treatment of vasculitis includes discontinuation of the drug and use of systemic
305 corticosteroids.

306

307 Leg ulcerations: Hydroxyurea, methotrexate, cisplatin, gemcitabine and rituximab are
308 responsible for leg ulcerations, but mechanism is unclear [17].

309 Inflammatory changes in pre-existing keratoses: Systemic use of 5-FU, cytarabine, and
310 capecitabine results in such type of inflammation [36]. Actinic keratoses and seborrheic
311 lesions may become inflamed, erythematous and pruriginous in the first week following CT,
312 and regression occurs 1-4 week after discontinuation of the drugs. But, the discontinuation
313 of the drug is not necessary as the lesion is self-limiting. Topical corticosteroids may be used
314 for local relief of the pain.

315 Intertriginous like eruption / cutaneous dysmaturation: It is the erythema with maceration
316 often complicated by bacterial or candidal infections resulting bullae formation. Liposomal
317 doxorubicin and dactinomycin causes such side effect [37]. Astringent compresses and
318 topical corticosteroids with antibiotics and antifungal medications are possible treatment
319 options [38]. Pegylated liposomal doxorubicin may cause intertriginous rash which may
320 associate with bullae formation [9].

321 Thiotepa causes diffuse erythematous rashes [9].

322 Bleomycin may cause fibrosis of the subcutis (Raynaud's syndrome) [17].

323 Subacute cutaneous lupus may be caused by antimetabolites (5-FU, capecitabine and
324 gemcitabine) [9,39,40]. Periorbital edema may occur due to use of gemcitabine [41].

Eosinophilic pustular folliculitis: There is repeated occurrence of crops of pruritic follicular papulopustules mainly on the scalp, face, trunk and extensor surfaces of the arms. Cyclophosphamide, methotrexate and 5-FU are the possible agents causing such type of reactions [42-44]. The pathogenesis is unknown. IL-5, COX-metabolites, intercellular adhesion molecule 1 and eosinophilic chemotactic factor may play role in the mechanism [42]. Drug withdrawal is the mainstay of treatment.

Sclerodermoid reaction: It is typified by cutaneous fibrosis and is heterogeneous [45]. Bleomycin and docetaxel may cause such reactions [46]. Excess amount of procollagen 1 and glycosaminoglycans, microvascular injury secondary to vasoconstrictive effects, and increased cytokine production may play role in the mechanism [45,47]. Sclerotic dermal reactions: Scar-like reactions occurs due to bleomycin and docetaxel. These are self-limiting agents.

Acneiform drug eruption: It is caused by EGFR inhibitors (gefitinib, erlotinib) and monoclonal antibodies (cetuximab, trastuzumab) [48]. Hyperkeratosis, abnormal desquamation, follicular plugging with bacterial overgrowths and acneiform lesions may occur [48,49].

Acneiform eruption (folliculitis): It occurs in three phases such as: erythema followed by papules and pustules. Face and upper trunks are the most common sites. Actinomycin D and EGFR inhibitors (gefitinib and cetuximab). Treatment options are oral doxycycline, topical antibiotics, topical retinoids and benzoyl peroxide.

Skin necrosis: Chemotherapeutic agents that delivered into veins and arteries may leak into subcutaneous tissue causing direct effect to skin resulting in necrosis of the tissue. Such type of reactions occurs either due to irritants (causing phlebitis and cellulitis) or due to vesicants (causing severe tissue necrosis, ulcers and scar formation). Local wound cares, use of cold or heat packs are treatment options. In case of doxorubicin induced skin extravasations, early plastic surgical intervention may require.

Neutrophilic eccrine hidradenitis: It appears as tendered papules, plaques or nodules. Trunk, face and ears are the most common sites. Pathologically neutrophils are seen surrounding eccrine glands. Secretions of high amount of chemotherapeutic drugs into the sweat glands are the possible mechanism. Bleomycin and cytarabine are the most common drugs implicated in such type of reactions. Lesion is self-limiting. Systemic steroids, non-steroidal analgesics and dapsone are used in symptomatic benefit.

Eccrine squamous metaplasia: It is also known as syringometaplasia affecting upper part of the eccrine sweat duct. It is a rare situation and red plaques or papules with crusted eruptions are clinical features. Nitrogen mustards, anthracyclines and antimetabolites cause such type of reactions. The lesion is self-limiting and may recur after reusing same chemotherapeutic agents.

Xerosis: Dry skin may occur due to use of EGFR inhibitors by arresting growth of keratinocytes and initiating terminal maturation. Mucosal surface of mouth, vagina and eyes are mostly affected.

Oedema: Use of multikinase inhibitors like imatinib causes oedema of the face, eyelids, ankles and forearms.

Hypopigmentation: Use of multikinase inhibitors may cause pale patches of skin more commonly in darker skin type patients. It is reversible on discontinuing the drug.

Other chemotherapy drugs causing skin toxicity:

Antimetabolites like 5-FU and capecitabine may cause HFS. Patient may present as mild symptoms like erythema, swelling, numbness and paraesthesia to severe symptoms like blister, ulceration and desquamation. The damage of the nerve fibres may cause neuropathic symptoms [50]. The lesions are seen in palms and soles. Capecitabine also causes hyperpigmentation. Cyclophosphamide and doxorubicin may cause black longitudinal pigmentation of the nail and local skin pigmentation [50-53].

Vinka alkaloids and taxanes are spindle inhibitors and their use may cause some skin manifestations like alopecia, dermatitis, radiation recall reaction, extravasations, nail changes and subacute cutaneous lupus erythematosus.

Novel antifolate agent pemetrexed is used in clinical field of non-small cell lung cancer and mesothelioma [54,55]. Pruriginous skin rash i.e. dermatitis is frequent with this drug and treated with antihistaminics and corticosteroids. Such type of dermatitis may cause life-threatening event like toxic epidermal necrolysis syndrome [56,57]. Prophylactic use of folic acid, vitamin B12 and corticosteroids as premedication has been recommended [58]. Asymptomatic hyperpigmentation of skin as a result of this drug particularly occurs at the site of hand and feet. The mechanism behind this remains unclear. Such type of toxicity is reversible after withdrawal of the drug and does not require any kind of pharmacological intervention. Melanonychia and onycholysis may occur with use of pemetrexed [59].

Bleomycin is a antitumour antibiotics (glycopeptides) and is used in pleurodesis, cutaneous warts, Hodgkin's lymphoma, squamous cell carcinoma, ovarian germ cell tumours and testicular cancers [60-62]. Bleomycin causes side effect to areas where the bleomycin hydrolase enzymes i.e. cysteine proteinase (drug metabolised by this enzyme) are low, particularly lung and skin [63-65]. Minor injury to the skin cause increase in local blood flow resulting local accumulation of the drug [64]. Bleomycin can cause alopecia, stomatitis, nail changes and hyperpigmentation [2]. Bleomycin induced hyperpigmentation may be diffuse, patchy and linear [62,63]. Flagellated dermatitis/hyperpigmentation occurs in 8-22% of cases and appears as linear or streaked pigmentation [60]. The lesions are self-limiting and resolves within six months of discontinuation of the drug [65]. Therefore, only treatment of trauma is necessary.

Targeted therapy related skin toxicity

409 **Skin manifestations due to EGFR/TK inhibitors:**

410 EGFR inhibitors are classified into two groups: parenteral monoclonal antibodies act as a
 411 ligand for EGF receptors and tyrosine kinase inhibitors that affects intracellular tyrosine
 412 kinase enzyme. Skin toxicities due to antiEGFRs are more often pharmacological effect.
 413 Gefitinib causes expressive thinning of stratum corneum layer with loss of normal basket-
 414 weave pattern.

415
 416 EGFR antagonists and multikinase inhibitors are Signal transduction inhibitors. These drugs
 417 may cause acneiform/papulo-pustular follicular rash and appears during first two weeks of
 418 treatment causing extremely irritating pruritus and may complicated by bacterial infections
 419 and are self-limiting [66,67]. Typical appearances of the rashes are acne with postules and
 420 inflammation on the face, scalp, and upper thorax. There are no preventive measures for
 421 the development of such type of rashes. There exists a co-relation between tumour
 422 response and severity of the rashes. Increase in dose lead to increase in severity of rashes
 423 and increase in tumour response. EGFR inhibitors may cause frequent nail changes and the
 424 mechanism is unknown. Paronychia and periungal abscess usually begins after 2 months of
 425 beginning of therapy. The lesion first affect great toe and present as a very painful
 426 erythema. In 10-15% of cetuximab and gefitinib users paronychia of fingers and toes may
 427 occur and treated with topical corticosteroids. Onychocryptosis may occur and temporary
 428 interruption of the drug and canthotomy may necessary. Asteatosis may occur due to
 429 gefitinib.

430 Multikinase inhibitors such as Sorafenib and sunitinib are used for liver and kidney cancers.
 431 These agents may cause inflammatory actinic keratoses [68,69]. Sunitinib causes HFS and
 432 bullous manifestation [70]. Imatinib, Dasatinib and Nilotonib are used in haematological
 433 malignancies and may associate with dermatitis particularly exfoliative [71].

434 Imatinib is used in CML and GISTs. Hyperpigmentation may be caused by use of such drug.
 435 C-KIT signalling pathway plays a role in melanogenesis and this pathway is inhibited by
 436 imatinib resulting possible reason for hyperpigmentation of skin [72].

437 Targeted therapy induced skin manifestations are given in table-3.

Targeted therapy agents	Skin manifestations
Gefitinib	Acneiform rash, paronychia, onychocryptosis, asteatosis
Cetuximab	Paronychia, acneiform rashes
Sorafenib	Inflammatory actinic keratoses
Sunitinib	Inflammatory actinic keratoses, hand-foot syndrome, bullous formation
Imatinib	Exfoliative dermatitis, hyperpigmentation, oedema of the face, eyelids, ankles and foot
Dasatinib	Exfoliative dermatitis
Nilotinib	Exfoliative dermatitis
Carbozanitinib	Hand-foot syndrome
Rituximab	livedo reticularis, Reynaud's phenomenon, distal necrosis, leg ulceration

Transtuzumab	Acneferous drug eruptions
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Table-3 showing various skin manifestations due to targeted therapies.

Conclusion

Proper diagnosis of the malignancy is necessary before selection of correct chemotherapeutic agents, so that drugs could be considered for possible changing due to dermatological severe complications. Pre-treatment assessment of patient's general condition is necessary before selection of the cytotoxic chemotherapy. Various chemotherapeutic drugs cause several types of nonspecific and specific dermatological reactions. Quality of life is affected by these reactions particularly in young women. Also, these reactions interfere with chemotherapy schedule and may cause reduction in dose schedule or change in chemotherapy drugs/regimen. Considering these two factors, clinicians should know about the details of chemotherapy related dermatological complications, the way of possible prevention from these complications and the management of these complications. Though chemotherapy related dermatological complications are known, but there is paucity of data regarding the details of it and needs further evaluation.

Recently targeted therapy increases the survival of many cancers, but dermatological manifestations caused due to this make physicians difficult to continue with these drugs. Therefore, further evaluation in this field is necessary to know the possibilities of preventing these side effects in order to enhance the effectiveness of therapies in cancer.

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