



Chemotherapy Induced Skin Toxicities and Review of Literature

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ABSTRACT

Chemotherapeutic drugs have proven efficacy in the treatment of most of the cancers. Chemotherapy induced side effects are commonly seen in clinical oncology. Development of new chemotherapeutic drugs and various new protocols results in increase of many dermatological complications. Skin manifestations can be acute during drug administration, or may occur during the course of the drugs. Patterns of manifestations are characterized by spectrum of the inflammatory disease patterns. Reaction pattern is not specific for a particular drug. Alopecia, hyperpigmentation, extravasation, erythrodysesthesia, nail changes, radiation recall reactions and photosensitivity are

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the possible skin toxicities. 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 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.

1. 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 manifestations 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 condition and expected complications of chemotherapy or targeted therapy should be considered before planning of any chemotherapy/targeted therapy schedule. Chemotherapy drugs may use in forms of radical, neoadjuvant, adjuvant and palliative intent in cancer patients. 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 panniculitis.

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 the 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 chemotherapeutic managements resulting in dose reduction, discontinuation or change in chemotherapeutic agents [1,2].

Recently, targeted therapy increases the survival rate of many cancers like kidney, lung, colorectal, breast and liver. Dermatological adverse effects

due to targeted therapies were reported in the literature.

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

2. INCIDENCE

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

3. MECHANISM OF ACTION IN GENERAL

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

4. SKIN TOXICITY

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

Various types of skin manifestations due to the different chemotherapeutic drugs are highlighted in Table 1.

Table 1. Showing chemotherapy induced various skin manifestations

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	Diffuse erythematous rash, localised hyperpigmentation on areas of
(Thiotepa)	trauma, pressure and occlusion
Alkyl sulfonate	Addisons like hyperpigmentation, flagellate hyperpigmentation,
(Busulfan)	permanent alopecia (may cause)
Triazine (dacarbazine)	photo sensitivity, flushing, phototoxicity
Methyl hydrazine	Erythema vasculitis (type III hypersensitivity)
(procarbazine)	
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, telogen effluvium (alopecia), Recall reaction, photosensitivity, flushing, leg ulceration, eosinophilic pustular folliculitis
Pemetrexed	Pruriginous skin rash, melanochia, onycholysis
Pyrimidine antagonist	
5-fluorouracil	Alopecia (telogen effluvium-temporary), photo sensitivity, Hyperpigmentation of nail, skin and oral mucosa (serpentine supragenous 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, eosinophilic pustular folliculitis
Capecitabine	Paronychia (<1%) , mucositis, hyperbilirubinemia, 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, neutrophilic 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, schlerdermoid reaction
Epipodophyllotoxin/	Alopecia (anagen effluvium), hypersensitivity, Recall reaction, flushing,

Drugs	Skin manifestations
topoisomerase 2 inhibitors (etoposide)	HFS
Camptothecin analogues / topoisomerase 1 inhibitors (irinotecan)	Alopecia (anagen effluvium), flushing
antibiotics	
dactinomycin	intertriginous like eruptions/cutaneous dysmaturation, Acneferous 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, schlerdermoid 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

4.1 Common Toxicities

It includes mucositis, alopecia, onychodystrophy, extravasation and hypersensitive reactions.

- 1) **Mucositis:** Inflammation of the mucosal surfaces of the mouth and gastrointestinal tract may occur due to high cell regeneration and growth rate [6]. It occurs in 5-20% of the patients receiving chemotherapy for solid tumours, whereas, 60-100% of the patients receiving myloablative regimens prior to stem cell transfusion [7]. It may presents with erythema of the mouth followed by erosion and ulceration. Due to involvement of the GI tract diarrhoea may occur. Most of the chemotherapeutic agents cause mucositis, particularly affecting DNA synthesis and s-phase specific agents. Concurrent use of radiotherapy along with chemotherapy potentiates the chemotherapy induced oral mucositis. Alkylating agents are more responsible for oral mucositis [8]. Methotrexate, anthracyclines and cyclophosphamide mostly causes mucositis. Oral mucositis can be prevented

by oral cryotherapy using oral ice chips and popsicles before or during administration of chemotherapy [7]. Systemic use of keratinocytic growth factors also reduces the chance of mucositis [9]. Local low level oral laser therapy is also used as a preventive measure for patients requiring conditioning chemotherapy for stem cell transplantation [9,10]. It is rarely life threatening. Severe form may require the 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 rises 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 the 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 the 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 the 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 slow growth of hair, brittle hair and thick hair. Scalp cooling may be used as preventive 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% of patients 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 by 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 (Fig. 1). It is seen in 0.1-6% adults treated with CT. Severity of it depends upon the volume, concentration

and type of the drugs administered. Extravasations result 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 causing 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 in 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 may require indwelling catheter. Infusion of 20 ml of saline just after the completion of chemotherapy reduces the possibility of toxic residues. Duration of vesicant drug infusion 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 the 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.

- 5) **Hypersensitivity reactions:** In general all the chemotherapeutic drugs may cause hypersensitivity reactions. The majority 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, the 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 the chemotherapy administration.

4.2 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 the cases [9]. It is 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 the important options in 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 the minimal sun exposure. UV recall reaction is similar to the radiation recall reaction. It occurs on exposure to drug in areas receiving prior UV ray therapy and pathological findings are similar to the 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 within 2-4 weeks after starting of chemotherapy and resolves after discontinuation of the drug [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]. Severity of the 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 the daily activities. In grade-2, the lesions are painful causing difficult in daily activities and with intact skin surface. In grade-3, the pain is severe and tissue breakdown occurs causing peeling of skin and blistering. Acral erythema occurs at the 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 the palms and soles and more frequently occurs in the dark-skinned patients. The classical presentation of HFS is initiation with bilateral numbness and tingling sensations of the palms and soles with gradual development of erythema. Painful with various degrees of swelling may develop and may progress to blisters,

desquamation and fissures. Possible mechanisms are: a) the 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 the 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 the daily activities. Usual course of the early lesion is desquamation followed by re-epithelialisation. It rarely occurs on the knees, elbows, and elsewhere. It usually occurs after chemotherapy use and rarely caused by the sickle-cell disease, bone marrow transplant patients. The symptoms can occur at any point between the days to months after drug administration and depends on the dose and speed of the drug administration. Exact mechanism is unknown. The 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). The 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 the tyrosine kinase inhibitors seems to be different from that induced by chemotherapeutic drugs. Grade III/IV HFS occurs in 11% of the cases, whereas all grades are seen in 49% of the patients using capecitabine [25]. The 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.



Fig. 1. Showing extravasations in forearm and arm due to doxorubicin

3) **Hyperpigmentation:** Cutaneous hyperpigmentation may occur after exposure to the cytotoxic CT. It commonly affects skin, hair, nails and mucous membranes [17]. It may be localized or diffuse [17]. Cutaneous hyperpigmentation can occur at any part of the 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 the 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 supavenous hyperpigmentation) (Fig. 2) [18]
- Platinum-based agents and thiotepa (localized hyperpigmentation in areas of trauma, pressure, or occlusion) [9]

Capecitabine induced hyperpigmentations (Fig. 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 (Fig. 4) can occur with the 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 the palms and soles, but the pigmentation over tongue is an extremely rare entity. Drug interruptions and dose reduction may necessary. Dose reduction and starting with lower dose followed by subsequent escalation should be done according to tolerability without compromising the efficacy [33]. Capecitabine may cause the nail changes such as: periungal pyogenic granuloma like lesions, Beau's lines, onycholysis, onychomadesis and melanonychia [34]. Flagellated form is an unique pattern caused by the 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 the skin, nails and oral mucosa (serpentine supavenous hyperpigmentation). Stoppage of drug, use of oral antihistaminics and topical hydroquinone are the various treatment options.

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



Fig. 2. Showing serpentine supavenous hyperpigmentation



Fig. 3. Showing capecitabine induced hyperpigmentations over both palms and soles



Fig. 4. Showing capecitabine induced hyperpigmentations over tongue

Table 2. Showing chemotherapy induced different types of skin hyperpigmentation

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

4.3 Others

Flushing: It is a temporary erythema particularly seen in the sites of face, neck, ears, upper chest and upper abdomen. Transitory vasodilatation

due to autonomic nervous system or the direct effect of circulating substances on the vascular walls result in flushing. L-asparaginase and bleomycin causes flushing soon after the infusion [17]. Other agents causing flushing includes

irinotecan, topoisomerase I inhibitor, hormonal agents (tamoxifen, anastrozole, leuprolide, flutamide, diethylstilbestrol), 5-FU, carboplatin, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, etoposide and methotrexate [17,35].

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

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

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

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

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

Thiotepa causes diffuse erythematous rashes [9].

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

Subacute cutaneous lupus may be caused by antimetabolites (5-FU, capecitabine and gemcitabine) [9,39,40]. Periorbital edema may occur due to the 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, transtuzumab) [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) may cause it. Treatment options are oral doxycycline, topical antibiotics, topical retinoids and benzoyl peroxide.

Skin necrosis: Chemotherapeutic agents that delivered into the 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 the treatment options.

In case of doxorubicin induced skin extravasations, early plastic surgical interventions 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 for 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 the 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 the 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.

4.4 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 the 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 the 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 cancers and mesotheliomas [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 events like toxic epidermal necrolysis syndromes [56,57]. Prophylactic use of folic acid, vitamin B12 and corticosteroids as premedication has been recommended [58]. Asymptomatic hyperpigmentation of the 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 the 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 the 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.

4.5 Targeted Therapy Related Skin Toxicity

4.5.1 Skin manifestations due to EGFR/TK inhibitors

EGFR inhibitors are classified into two groups: parenteral monoclonal antibodies act as a ligand for EGF receptors and tyrosine kinase inhibitors that affects intracellular tyrosine kinase enzyme.

Table 3. Showing various skin manifestations due to targeted therapies

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	Acneiform drug eruptions

Skin toxicities due to antiEGFRs are more often pharmacological effect. Gefitinib causes expressive thinning of the stratum corneum layer with loss of normal basket-weave pattern.

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

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

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

Targeted therapy induced skin manifestations are given in Table 3.

5. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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