

Review Article

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 includes: 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 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 now 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 drug related skin manifestations may be due to chemotherapy or targeted
59 therapy. Many chemotherapeutic drugs cause nonspecific dermatological toxicities
60 including alopecia, mucositis and onchodystrophy. Some targeted therapies like epidermal
61 growth factor inhibitors, multikinase inhibitors and proteosome inhibitors cause different
62 type skin reactions. Some specific dermatological complications may occur like radiation
63 recall reactions, toxic erythema and skin hyperpigmentation.

64 **Common toxicities:** It includes mucositis, alopecia, onychodystrophy, extravasation and
65 hypersensitive reactions.

66 1) Mucositis: Mucositis: Inflammation of the mucosal surfaces of the mouth and
67 gastrointestinal tract may occur due to high cell regeneration and growth rate [6]. It
68 occurs in 5-20% of patients receiving chemotherapy for solid tumours, whereas, 60-
69 100% of patients receiving myloablative regimens prior to stem cell transfusion [7]. It
70 may presents with erythema of the mouth followed by erosion and ulceration. Due
71 to involvement of GI tract diarrhoea may occur. Most of the chemotherapeutic
72 agents cause mucositis, particularly affecting DNA synthesis and s-phase specific
73 agents. Concurrent use of radiotherapy along with chemotherapy potentiates the
74 chemotherapy induced oral mucositis. Alkylating agents are more responsible for
75 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 preventive measures for patients requiring conditioning chemotherapy for stem 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 analgesias 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 viscus lidocaine is used for relief of symptoms, but, severe mucositis requires systemic opioid analgesias [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 taxane 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 upregulate 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 vincristin [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. It is seen in 0.1-6% adults treated with CT. Severity of it depends upon

volume, concentration and type of the drugs administered. Extravasation results in pain, erythema, ulceration and tissue necrosis in severe cases [14,15]. Drugs causing extravasations are divided into non-irritating, irritating and vesicant drugs. Non-irritants provoke edema at the site of extravasations without tissue damage. Irritants are drugs with milder inflammatory response leading to erythema, edema, pain and tissue damage without necrosis, and symptoms are usually short-course and leave on sequelae. While vesicants are drugs which may cause more severe long-lasting tissue damage resulting blistering 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, vinblastin)
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 edema 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 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 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 threatening reactions may occur due to chemotherapy administration.

Some Specific complications: It includes radiation and UV recall reaction, 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 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 persistant of residual hyperpigmentation for the months or years. Discontinuation of the drug, application of physical sunscreens, cold compresses, systemic antihistaminics, use of topical or oral corticosteroids, and Minimizing exposure to sun is 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 pohototoxicity [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 [21]. Acral erythema/palmar-plantar erythrodysethesia/hand-foot syndrome/palmar-plantar erythema/Burgdorf's reaction: Hand-Foot Syndrome: 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) postinflammatory 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) of the palms and soles, with or without presence of bullae is the most common manifestations. Sensation of the skin may be altered (dysaesthesia) and may be severe affecting daily activities. Usual course of the early lesions is desquamation followed by re-epithelialization. It rarely occurs on knee, elbows, and elsewhere. It usually occurs after chemotherapy use and rarely caused by sickle-cell disease, bone marrow transplant patients. The symptoms can occur 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 week after discontinuation of the drug. 5-FU, capecitabine, doxorubicin, vincristine, vinblastin, cytarabine, etoposide, taxane, liposomal doxorubicin, sorafenib, sunitinib and cabozanitinib are the agents may that 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, diffused 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 Addition-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 supravenuous hyperpigmentation) [18]

249 - Platinum-based agents and thiotepa (localized hyperpigmentation in areas of
250 trauma, pressure, or occlusion) [9]

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

270 Different types of hyperpigmentation due to chemotherapy are given in table-1.

271

272 **Others:**

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

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

289 Treatment of vasculitis includes discontinuing the drug and use of systemic corticosteroids.

290

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

Inflammatory changes in pre-existing keratoses: Systemic use of 5-FU, cytarabine, and capecitabine result in such type of inflammation [36]. Actinic keratoses and seborrheic lesions may become inflamed, erythematous and pruriginous in the first week following CT, and regression occurs 1-4 week after discontinuation of 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 pain.

Intertriginous like eruption/ cutaneous dysmaturation: It is the erythema with maceration often complicated by bacterial or candidal infections resulting bullae formation. Liposomal doxorubicin and dactinomycin causes such side effect [37]. Astringent compresses and topical corticosteroids with antibiotics and antifungal medications are 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 use of gemcitabine [41].

Eosinophilic pustular folliculitis: There is repeated occurrence of crops of pruritic follicular papulopustules mainly on the scalp, face, trunk 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 reaction [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 [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 care, use of cold or heat packs is 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. Nitrogens mustards, anthracyclins 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 Hand-Foot syndrome. 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

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. Skin toxicities due to antiEGFRs are more often pharmacological effect. Gefitinib causes expressive thinning of 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 first two weeks of treatment causing extremely irritating pruritus and may 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 rashes and increase in tumour response. EGFR inhibitors may cause frequent nail changes and the mechanism is unknown. Paronychia and periungal abscess usually begins after 2 months of beginning of therapy. The lesion first affect 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 necessary. Asteatosis may occur due to gefitinib.

Multikinase inhibitors such as Sorafinib and sunitinib are used for liver and kidney cancers. These agents may cause inflammatory actinic keratoses [68,69]. Sunitinib causes Hand-foot syndrome and bullous manifestation [70]. Imatinib, Dasatinib and Nilotonib 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 use of such drug. C-KIT signalling pathway plays a role in melanogenesis and this pathway is inhibited by imatinib resulting possible reason for hyperpigmentation of skin [72].

Targeted therapy induced skin manifestations are given in tabule-2.

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. Pretreatment 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 therapies 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.

References

1. Jatoi A, Nguyen PL. Do patients die from rashes from epidermal growth factor receptor inhibitors? A systematic review to help counsel patients about holding therapy. *Oncologist* 2008, 13:1201–1204.
2. Wagner LI, Lacouture ME. Dermatologic toxicities associated with EGFR inhibitors: the clinical psychologist's perspective. Impact on healthrelated quality of life and implications for clinical management of psychological sequelae. *Oncology (Williston Park)* 2007, 21:34–36.
3. Martin T, Hui LI. Severe cutaneous adverse drug reactions: a review on epidemiology, etiology, clinical manifestation and pathogenesis. *Chin Med J* 2008;121:756–61.

4. Atzori L, Pinna AL, Ferreli C, Aste N. Pityriasis rosea-like adverse reaction: Review of the literature and experience of an Italian drug-surveillance center. *Dermatol Online J* 2006;12:1.
5. Justiniano H, Berlingeri-Ramos AC, Sanchez JL. Pattern analysis of drug-induced skin diseases. *Am J Dermatopathol* 2008;30:352–69.
6. Martorell-Calatayud A, Sanmartín O, Botella-Estrada R, Balmer NN, Serra-Guillén C, Gomez-Moyano E, et al. Chemotherapy-related bilateral dermatitis associated with eccrine squamous syringometaplasia: reappraisal of epidemiological, clinical, and pathological features. *J Am Acad Dermatol*. 2011;64(6):1092-103.
7. Barasch A, Epstein JB. Management of cancer therapy-induced oral mucositis. *Dermatol Ther*. 2011;24(4):424-431.
8. Peterson DE, Ohn K, Bowen J, Flidner M, Lees J, Loprinzi C, et al. Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Support Care Cancer*. 2013;21(1):327-332.
9. Rachel LK, Milan JA. Dermatologic adverse events to chemotherapeutic agents, Part 1: cytotoxic agents, epidermal growth factor inhibitors, multikinase inhibitors, and proteasome inhibitors. *Seminars in Cutaneous Medicine and Surgery* 2014, 33.
10. Silva GB, Mendonça EF, Bariani C, Antunes HS, Silva MA. The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. *Photomed Laser Surg*. 2011;29(1):27-31.
11. Saunders DP, Epstein JB, Elad S, Allemano J, Bossi P, van de Wetering MD, et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3191-3207.
12. Palamaras I, Misciali C, Vincenzi C, Robles WS, Tosti A. Permanent chemotherapy-induced alopecia: a review. *J Am Acad Dermatol*. 2011;64(3):604-606.
13. van den Hurk CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - results of the Dutch Scalp Cooling Registry. *Acta Oncol*. 2012;51(4):497-504.
14. Langer SW. Extravasation of chemotherapy. *Curr Oncol Rep*. 2010;12(4):242-246.
15. Schulmeister L. Extravasation management: clinical update. *Semin Oncol Nurs*. 2011;27(1):82-90.
16. Hadaway L. Infiltration and extravasation. *Am J Nurs*. 2007;107:64-72.
17. Criado PR, Brandt HRC, Moure ERD, Pereira GLS, Sanches JA Jr. Adverse mucocutaneous reactions related to chemotherapeutic agents – Part II. *An Bras Dermatol*. 2010;85(5):591-608.
18. Huang V, Anadkat M. Dermatologic manifestations of cytotoxic therapy. *Dermatol Ther*. 2011;24(4):401-410.
19. Burris HA 3rd, Hurtig J. Radiation recall with anticancer agents. *Oncologist*. 2010;15(11):1227-1237.
20. Payne AS, James WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. *Semin Oncol*. 2006;33:86-97.
21. Corrie PG, Bulusu R, Wilson CB, Armstrong G, Bond S, Hardy R et al. A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. *Br J Cancer*. 2012;107(4):585-587.

22. Lokich JJ, Moore C. Chemotherapy associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984, 101:789-800.
23. Childress J, Lokich J. Cutaneous hand and foot toxicity associated with cancer chemotherapy. *Am J Clin Oncol* 2003;26:435-436.
24. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am J Clin Dermatol* 2001, 2:253–262.
25. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006, 355:2733–2743.
26. Lokich J. Phase I clinical trial of weekly combined paclitaxel plus docetaxel in patients with solid tumors. *Cancer* 2000, 89:2309-2314.
27. Degen A, Alter M, Schenck F, Satzger I, Völker B, Kapp A, et al. The hand-foot-syndrome associated with medical tumor therapy - classification and management. *J Dtsch Dermatol Ges.* 2010;8(9):652-661.
28. Balagula E, Lacouture ME. Dermatologic toxicities. The MASCC textbook of cancer supportive care and survivorship. Springer, 2011, 361–380.
29. Chittari K, Tagboto S, Tan BB. Cyclophosphamide-induced nail discoloration and skin hyperpigmentation: a rare presentation. *Clin Exp Dermatol.* 2009;34(3):405-406.
30. vvanTienhoven G, Wilmink JW. A woman with palmar and plantar hyperpigmentation. *Ned Tijdschr Geneesk* 2011, 155:A4100.
31. Surjushe A, Vasani R, Medhekar S, Thakre M, Saple DG. Handfoot syndrome due to capecitabine. *Indian J Dermatol* 2009, 54:301–302.
32. Vasudevan B. An unusual case of capecitabine hyperpigmentation: Is hyperpigmentation a part of hand-foot syndrome or a separate entity? *Indian J Pharmacol* 2010, 42:326–328.
33. Leonard R, Hennessy BT, Blum JL, O'Shaughnessy J. Doseadjusting capecitabine minimizes adverse effects while maintaining efficacy: a retrospective review of capecitabine for metastatic breast cancer. *Clin Breast Cancer* 2011, 11:349–356.
34. Paravar T, Hymes SR. Longitudinal melanonychia induced by capecitabine. *Dermatol Online J* 2009, 15:11.
35. Syrigou E, Syrigos K, Saif MW. Hypersensitivity reactions to oxaliplatin and other antineoplastic agents. *Curr Allergy Asthma Rep.* 2008;8:56-62.
36. Serrao VV, Feio AB. Inflammation of actinic keratoses with capecitabine therapy for colon cancer. *Eur J Dermatol.* 2008;18:200.
37. Sanchez Henarejos P, Ros Martinez S, Marin Zafra GR, Alonso Romero JL, Navarrete Montoya A. Intertrigo-like eruption caused by pegylated liposomal doxorubicin (PLD). *Clin Transl Oncol.* 2009;11:486-7.
38. Webber KA, Kos L, Holland KE, Margolis DA, Drolet BA. Intertriginous eruption associated with chemotherapy in pediatric patients. *Arch Dermatol.* 2007;143:67-71.
39. Almagro BM, Steyls MC, Navarro NL, Domínguez EG, Herrera-Acosta E, Pérez MA, et al. Occurrence of subacute cutaneous lupus erythematosus after treatment with systemic fluorouracil. *J Clin Oncol.* 2011;29(20):e613-615.
40. Wiznia LE, Subtil A, Choi JN. Subacute cutaneous lupus erythematosus induced by chemotherapy: gemcitabine as a causative agent. *JAMA Dermatol.* 2013;149(9):1071-1075.
41. Bessis D, Guillot B, Legouffe E, Guilhaou JJ. Gemcitabine associated scleroderma-like changes of the lower extremities. *J Am Acad Dermatol.* 2004;51:S73-6.

42. Laing ME, Laing TA, Mulligan NJ, Keane FM. Eosinophilic pustular folliculitis induced by chemotherapy. *J Am Acad Dermatol* 2006;54:729–30.
43. Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis: a comprehensive review of treatment options. *Am J Clin Dermatol* 2004;5:189–97.
44. Ooi CG, Walker P, Sidhu SK, Gordon LA, Marshman G. Allopurinol induced generalized eosinophilic pustular folliculitis. *Austr J Dermatol* 2006;47:270–3.
45. Cleveland MG, Ajaikumar BS, Reganti R. Cutaneous fibrosis induced by docetaxel. A case report. *Cancer* 2000;88:1078–81.
46. Itoh M, Yanaba K, Kobayashi T, Nakagawa H. Taxane-induced scleroderma. *Br J Dermatol* 2007;156:363–7.
47. Kluger N, Girard C, Bessis D, Guillot B. Methysergide-induced scleroderma-like changes of the legs. *Br J Dermatol* 2005;153:224–5.
48. DeWitt CA, Siroy AE, Stone SP. Acneiform eruptions associated with epidermal growth factor receptor-targeted chemotherapy. *J Am Acad Dermatol* 2007;56:500–5.
49. Journagan S, Obadiah J. An acneiform eruption due to erlotinib: Prognostic implications and management. *J Am Acad Dermatol* 2006;54:358–60.
50. Milano G, Etienne-Grimaldi MC, Marl M, Lasalle S, Formento JL, Francoual M, et al. Candidate mechanisms for capecitabine related hand-foot syndrome. *Br J Clin Pharmacol* 2008; 66:188–95.
51. Vasquez-Bayo C, Rodriguez-Bujaldon AL, Jimenez-Puya R, Galàn-Gutierrez M, Moreno-Gimenez JC. Capecitabine induced hyperpigmentation. *Actas Dermosifiliogr* 2007; 98:491–493.
52. Dave S, Thappa DM. Peculiar pattern of nail pigmentation following cyclophosphamide therapy. *Dermatol Online J* 2003; 9(3):14.
53. Kumar S, Dixit R, Karmakar S, Paul S. Unusual nail pigmentation following cyclophosphamide-containing chemotherapy regimen. *Indian J Pharmacol* August, 2010, 42(4):243–244.
54. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, Von Pawel J, et al. Randomized phase III trial of pemetrexed *versus* docetaxel in patients with non small cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004, 22: 1589-1597.
55. Scagliotti GV, Parikh P, Von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemo-naïve patients with advanced-stage nonsmall cell lung cancer. *J Clin Oncol* 2008, 26: 3543-3551.
56. Tummino C, Barlesie F, Tchouhadjian C, Tasei AM, Gaudy- Marqueste C, Richard MAS, et al. Toxicite cutanee grave apres pemetrexed en traitement de deuxieme ligne pour un cancer bronchique. *Revue des Maladies Respiratoires* 2007, 24(5): 635-638.
57. Bosch-Barrera J, Gaztanaga M, Ceballos J, Perez-Gracia JL, Lopez-Picazo JM, Garcia-Foncillas J, et al. Toxic epidermal necrolysis related to pemetrexed and carboplatin with vitamin B12 and folic acid supplementation for advanced non-small cell lung cancer. *Onkologie* 2009, 32(10): 580-584.
58. Scagliotti GV, Shin DM, Kindler HL, Vasconcelles MJ, Keppler U, Manegold C, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. *J Clin Oncol* 2003, 21: 1556-1561.

59. Dasanu CA, Wiernik PH, Vaillant J and Alexandrescu DT. A complex pattern of melanonychia and onycholysis after treatment with pemetrexed for lung cancer. *Skin Med* 2007, 6(2): 95-96.
60. Al-Khenaizan S, Al-Berouti B. Flagellate pigmentation: a unique adverse effect of bleomycin therapy. *Eur J Dermatol* 2011;21:146.
61. Abess A, Keel DM, Graham BS. Flagellate hyperpigmentation following intralesional bleomycin treatment of verruca plantaris. *Arch Dermatol* 2003;139:337–9.
62. Ibrahimi OA, Anderson RR. Images in clinical medicine. Bleomycin-induced flagellate hyperpigmentation. *N Eng J Med* 2010;363:e36.
63. Silveira JC, Cunha BM, Estrella RR. Dermate flagelada induzida pela bleomicina. *Ann Bras Dermatol* 2006;81:83–5.
64. Ziemer M, Goetze S, Juhasz K, Elsner P. Flagellate dermatitis as a bleomycin-specific adverse effect of cytostatic therapy. *Am J Clin Dermatol* 2011;12:68-76.
65. Mowad CM, Nguyen TV, Elenitsas R, Leyden JJ. Bleomycin-induced flagellate dermatitis: a clinical and histopathological review. *Br J Dermatol* 1994;131:700-2.
66. Tianhong L, Roman P. Skin toxicities associated with epidermal growth factor receptor inhibitors. *Targ Oncol* 2009; 4:107–119.
67. Galimont-Collen AFS, Vos LE, Lavrijsen APM, Ouwerkerk J, Gelderblomb H. Classification and management of skin, hair and nail and mucosal side effects of epidermal growth factor receptor (EGFR) inhibitors. *Eur J Cancer* 2007; 43:845–851.
68. Vincenzi B, Santini D, Russo A, Addeo R, Giuliani F, Montella L, et al. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with Sorafenib. *The Oncologist* 2010; 15:85–92.
69. Williams V, Cohen P, Stewart D. Sorafenib-induced premalignant and malignant skin lesions. *Int J Dermatol* 2011; 50(4):396–402.
70. Jain L, Sissung TM, Danesi R, Kohn EC, Dahut WL, Kummar S, et al. Hypertension and hand-foot skin reaction related to VEGFR2 genotype and improved clinical outcome following bevacizumab and sorafenib. *J Exp Clin Cancer Res* 2010; 29:95.
71. Noushin H, Haley N, Susan B. Chemiotherapeutic agents and the skin: an update. *J Am Acad Dermatol* 2008; 58:545–570.
72. Alexandrescu DT, Dasanu CA, Farzanmehr H and Kauffman CL. Persistent cutaneous hyperpigmentation after tyrosine kinase inhibition with imatinib for GIST. *Dermatology Online J* 2008, 14(7): 7; July 15.

Tables

Table-1

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

Targeted therapy agents	Skin manifestations
Gefitinib	Acneiform rash, paronychia, onchocryptosis, 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

627

628