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Mucocutaneous Side Effects of Antineoplastic Drugs Used in Cancer Therapy in Erbil

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Abstract

Background and objectives: Mucocutaneous side effects of antineoplastic drugs can produce both local and systemic mucocutaneous adverse reactions that sometimes misinterpreted with other cancer related dermatological manifestations such as infection, paraneoplastic diseases, and nutritional deficiency. The aim of the study was to identify the most common mucocutaneous side effects associated with antineoplastic drugs to be looked for and managed properly. **Methods:** A study was conducted on patients receiving anti-cancer therapy. Data were collected from 109 patients, of which 87 were females and 22 were males, with biopsy proven malignancies. Forty one patients were on single chemotherapy and 68 were on combined chemotherapy. Seventy seven patients were on conventional chemotherapy, 29 on hormonal therapy and 13 on immune target therapy. Detailed history was obtained from the patients. Afterwards each patient subjected to full dermatological examination involving skin, mucosa, hair and nail. **Results:** Hair changes were the most common adverse effect noticed in (31.71%) of the patients with anagen effluvium being the most common (68 cases), followed by skin changes in (28.29%). Nail changes were observed in (20.49%) of the cases and the most common changes were melanonychia that was noticed in 22.The mucosal changes accounted for (19.51%) of the cases and 36 patients complained of apthus ulcer. **Conclusions:** This study showed that adverse effects of antineoplastic drugs can cause a great degree of morbidity to cancer patients on chemotherapy although most of the complications subsided with cessation of the therapy without causing permanent damage.

Keywords: Antineoplastic; Adverse effects; cutaneous; Alopecia.

Introduction

In the last decades the emergence of new antineoplastic drugs increased the survival rate among cancer patients[1]. These drugs targets rapidly proliferating malignant as well as normal cells including the skin, its appendages and mucus membrane[1,2]. A dermatologist should have a proper knowledge about the side effects, their accurate diagnosis and appropriate treatment to improve the patient's quality of life[3]. Alopecia considered the most common adverse cutaneous reaction of antineoplastic agents[4]. The drugs cause alopecia by causing a sudden termination of mitosis in matrix cells and resulting in anagen effluvium[3]. Anagen effluvium, usually starts about 2 weeks from initiation of the therapy[1,5]. The hair loss caused by antineoplastic drugs is almost always reversible after cessation of the drug. Topical agents like minoxidil 2% solution are not useful in preventing the antineoplastic drug induced alopecia[6]. Cutaneous hyperpigmentation is a common side effect of antineoplastic drugs. It may develop as a result of direct effect on melanocytes and induction of melanin production[4].

The pattern of presentation may vary from diffuse to localized or drug specific pattern[3]. The diffuse pattern is most commonly seen in patients receiving hydroxyurea[4] and serpinginous configuration[7] by actinomycin.. An acneiform eruption is most commonly occurs in association of epidermal growth factor inhibitors[8].The eruption appears within 7 days of initiation of the therapy in seborrhic distribution[9], they affect the signaling pathway causing hyperkeratosis by inducing cell apoptosis, reduce cell migration, inflammation and cytokine release[10]. Acral Erythema also known as hand-foot syndrome[11,12]. Most commonly occur in patients receiving cytarabine, doxorubicine[1]. The patient might have a prodome of pain and palmoplanter dysthesia, few days later an edematous erythema of the lateral aspects of the palms and less frequently the

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soles5. After discontinuation of the culprit drug the symptoms will decrease within 2 weeks[13]. Xerosis can be caused many drugs and has a negative impact on quality of life. The pathogenesis involve an altered keratinocyte differentiation and a decrease in water retention and subsequently disruption of stratum corneum. Protective measures such as emollients, bath with lukewarm water and gentle soap may prevent further deterioration[14]. Extravasation of chemotherapeutic agent begins as burning sensation, redness and itchiness at site of injection and along the veins, followed by edema that resolve[4]. Elevation of the limb and applying cold packs may reduce the local reaction except for vinca alkaloid drugs in which case the cold pack should be avoided to prevent ulceration[4,3]. Nail matrix cells are in continuous proliferating state that makes them a common target for chemotherapeutic[15]. Most frequent nail change is horizontal depressed line called Beau lines that represent a sudden cessation of nail growth[4]. Diffuse or band like hyperpigmentation of the nails is another common presentation which is thought to be due to altered melanin distribution from the matrix to nail plate[1]. Muehrck's lines, a pair of white transverse bands caused by vascular bed abnormality, can be seen in patients receiving chemotherapy[15]. Stomatitis considered a common dose-limiting complication of antineoplastic drugs[3]. Usually it develops within the first week of initiation of the therapy as a painful edema and redness of oral mucosa followed by a small patch of ulceration, spontaneous healing, without scarring, occurs within 3-4 weeks after the treatment ceased[16]. Prophylactic measures to maintain proper oral hygiene by brushing, flossing and sodium bicarbonate mouth wash[17]. Granulocyte colony-stimulating factor may aid in correcting the neutropenia and promote ulcer healing[18]. The aim of the study was to identify the most common mucocutaneous side effects among patients receiving antineoplastic drugs in Erbil city.

Patients and methods

A cross sectional study was conducted on patients receiving anti-cancer therapy attending oncology outpatient department in Nanakali Teaching Hospital in Erbil city during the period from March 2017 to February 2018. Data were collected from 109 patients, of which 87 were females and 22 were males, with biopsy proven malignancies. All the enrolled patients had solid tumor with breast cancer being the most common one followed by colon-rectal, lung, brain , ovarian and prostate cancer. Forty one patients were on single chemotherapy and 68 were on combined chemotherapy. Seventy seven patients were on conventional chemotherapy, 29 were on hormonal therapy and 13 were on immune target therapy. The most commonly drugs used were (Bleomycine, Capsetabine , Carboplatin, Cisplatine, Cyclophosphomide, Cyclosporine, Docetaxel, Doxorubicin, Epirubicin, Etoposide, Everolimus, Gemsitabine, Irinotecan, Methotrexate, Oxaliplatin, Paclitaxel, Pemetrexed, Sfluloruracil, Tamoxefin, Zoladex, Anastrazole, Letrozole, Imatinib, Trastuzumab, Bevacizumab) . We included patients of both genders, aged more than 18, who developed side effects after the first administration of the drug/drugs. Patients under 18 years of age, patients on radiation therapy, unconscious patients, those who are in medically critical settings and patients who had mucocutaneous symptoms prior to initiation of the therapy were excluded from the study. Each patient was asked about the type of the symptom, its time of onset, their severity, whether if its localized or generalized, relieving and aggravating factors, how long it last and if they had response to the treatment. Afterwards each patient subjected to full dermatological examination involving skin, mucosa, hair and nail. The Common Terminology Criteria of Adverse Events (CTCAE) v4.0 was applied. In skin examination we searched for signs of dryness, how much of total body surface was involved, any local injection site reactions, hyperpigmentation, wheals for urticaria, any acneiform reactions, edema, erythema or any signs of infection. Suspected fungal infections were excluded by skin scrapping and KHO examination. Hair examination involved whether the hair loss involves more than 50% or less of the scalp, if the shredded hairs were in anagen or telogen phase, any signs of atrophy or scales. The nails were examined to differentiate between true and apparent leukonychia, if it's tender melanonychia or not, nail clipping and KHO examination was done to exclude onychomycosis. Informed verbal consent was obtained from each patient who enrolled in the study after a detailed explanation about the aim of

the study was given. The statistical package for social science SPSS version 24 used for data analysis. The study was approved by ethical committee of the Kurdistan Board of Medical Specialties.

Results

Among the 109 patients that's enrolled in the study, hair changes were the most common adverse effect noticed in (31.71%) of the patients, followed by skin in (28.29%), nail changes in (20.49%) and mucosal changes in (19.51%) of the cases. The skin changes were xerosis which was seen in 41 patients, pruritus in 18,pigmentary changes in form of hyperpigmentation was seen in 10, injection site reactions (ecchymosis and bruising) in 10, skin peeling in 9, erythema in 4 and other changes like flushing and edema in 7 patients, Figure 1 and Figure 2.

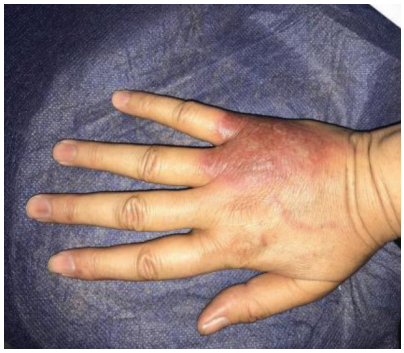

Figure (1):A patient with injection site reaction.

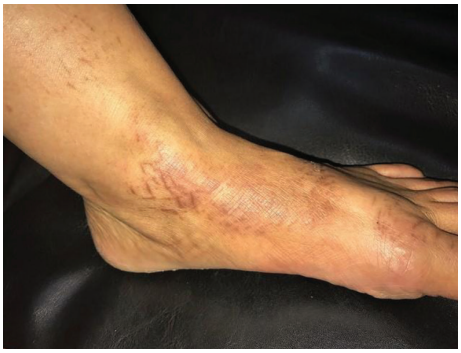

Figure (2):A patient with flagellate erythema.

The most common hair changes were anagen effluvium which was observed in 68, body hair loss in 28 cases and only 1 case suffered from brittle hair, the changes started, within 2-20 days after administration of the drugs, with majority of the patients the hair fall recorded with the first week, Figure 3.

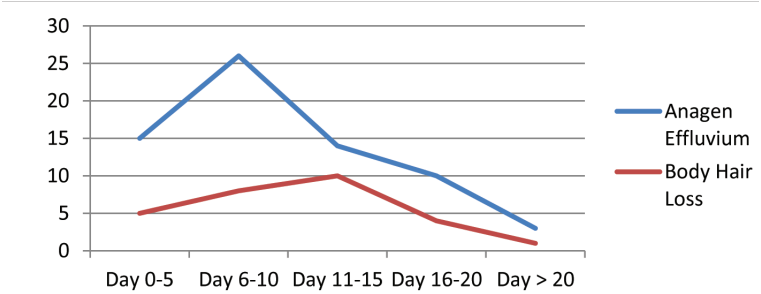

Figure (3): Time of onset of the hair changes among the study patients.

Among the nail changes melanonychia (either diffuse or longitudinal type) was the most common finding seen in 22 patients, onychorrhexis in 11, followed by Muherck's lines in 6 cases and beau's line, paronychia, koilonychias, half and half nails and ridging. Only 1 patient had periungual pyogenic granuloma, Table 1, Figure 4 and Figure 5.

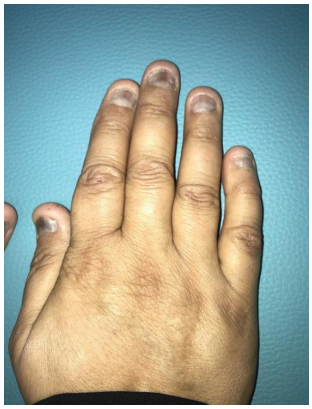

Figure (4):A patient with diffuse melanonychia.

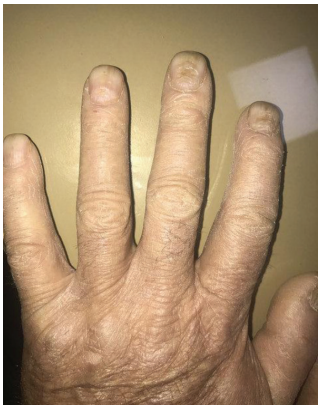

Figure (5):A patient with onychorrhexis.

Table (1): Nail changes in the study patients.

Nail Changes	No.(%)
Melanonychia	22 (20.18%)
Onychorrhexis	11 (10.09%)
Muehrck's lines	6 (5.50%)
Koilonychya	4 (3.66%)
Paronychia	3 (2.75%)
Beaus line	3 (2.75%)
Half and Half	3 (2.75%)
Ridging	2 (1.83%)
Mees line	0 (0.00%)

Table (2): Mucosal changes in the study.

Mucosal Changes	No.(%)
Apthus ulcer	36 (33.02%)
Oral candidiasis	4 (3.66%)
Oral erosions	2 (1.83%)
Conjunctivitis	2 (1.83%)
Herpes Labialis	1 (0.91%)
Gingivostomatitis	1 (0.91%)
Others	1 (0.91%)

Most common mucosal change was apthus ulcer which was observed in 36 patients followed by oral candidiasis in 4 cases.Two cases with oral erosions, 2 with conjunctivitis, and a case for each of gingivostomatitis and herpes labialis was observed in our study, Table 2, Figure 6 and Figure 7.

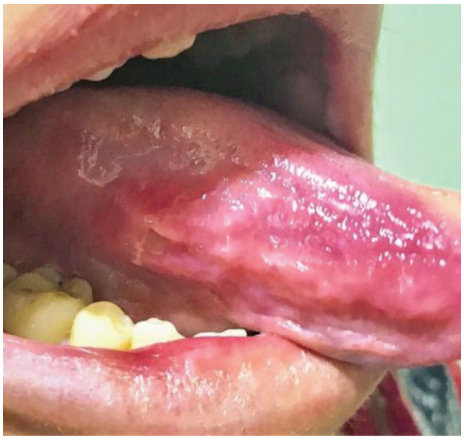

Figure (6): A patient with apthus ulcer.

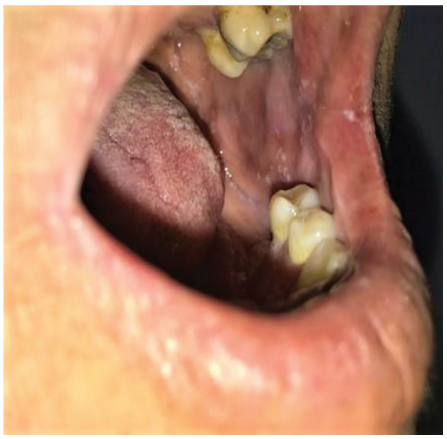

Figure (7): A patient with Candidiasis.

Discussion

Our study was conducted on 109 patients with biopsy proven malignancies receiving a single or a combination of chemotherapies. The group consisted of 87 females and 22 males with mean age (52.5 years ±). As it's predicted the most common mucocutaneous side effect observed in our study was alopecia, anagen effluvium, (68 cases), which is caused by sudden termination of mitosis in actively proliferating matrix cells and inhibition of hair production3 and it was comparable to studies done by Kamil et al.[2], Chiewchanvit et al.[19] and Chandah et al.[20] The result is also consistent to studies done earlier Susser et al.[3] Fitzpatrick et al.[21] However a studies done by Pavey et al.[1] and Rajashekar et al.[22] showed a lower incidence of alopecia which can be attributed to difference in age groups or the drugs used in the treatment. Only 1 patient had brittle hair in the study. Xerosis was the most common skin manifestation occurred in 41 patients that were similar to results of Cardoza-Torres et al[23] but higher than that of Kamil et al.[2] and Rajashekar et al.[22] which can be due to different sample size, male: female ration or combination of the drugs. Pruritus was second most common skin finding in our study observed in 18 patients which was higher than that of Kamil et al.[2] that can be explained by lower number of patients having xerosis, which cause stratum corneum disruption[14], in their study. Skin hyperpigmentation observed in 10 patients which in comparison to studies conducted earlier by Garg et al.[24] and Cardoza-Toress et al.[23] shows lower incidence, this can be attributed to variation in types and frequency of the drugs used. Injection site reaction was seen in 10 patients ranging from mild redness to necrosis needing discontinuation of the drug, this result was higher than that's reported by Pavey et al.[1] , and Kamil et al.[2] this is most probably due to larger study sample and

variations in drug administration route. Skin peeling documented in 9 patients enrolled in our study and it's comparable to results obtained by Rajashekar et al.[22] Flushing and edema were also reported in the current study. Variety of nail changes were observed in our study the most common abnormality was melanonychia, in the form of diffuse, longitudinal or transverse bands, that was reported in 22 patients and similar results were obtained by Rajashekar et al.[22] , Pavey et al.[1] and Kamil et al.[2] The second most common nail change seen in 11 cases was onychorrhexis, this result was much higher than Garg et al.[24] result that can be related to difference in the age groups. Muehrcke's lines was seen in 6 patients unlike the studies done by Rajashekar et al.[22] and Pavey et al.[1] and Chen et al.[15] were Muehrck's lines was the commonest finding, this can attributed to the age group as all the three studies were done on pediatric age group. Other nail findings observed in our study were koilonychias, paronychia, beau lines, half and half nails, similar findings were reported by Kamil et al.[2] Aphthus ulcer, the most common mucous finding, was reported in 36 patients, which was either due to direct cytotoxic effect of the drugs or due to myelosupression[5], followed by oral candidiasis in 4 patients, 2 patients for each of oral erosions and conjunctivitis, and single case of herpes labialis and gingivostomatitis. These results were similar to Garg et al.[24] and Rajashekar et al.[22] but slightly lower than that's reported by Cardoza-Toress et al.[23] this difference is related to the doses administered. All lesions healed without scar.

Conclusions

This study concluded that adverse effects of antineoplastic drugs can cause a great degree of morbidity to cancer patients on chemotherapy. Although most of the complications are subsided with cessation of the therapy without causing a permanent damage, the dermatologist in conjugation with oncologist should identify and provide the proper management to the patients, to maintain higher quality of psychological and physical health during their therapy.

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