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Original Research Article

Cutaneous adverse effects of chemotherapy in cancer patients: A clinico epidemiological study

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ABSTRACT

Background: With chemotherapy being the major modality of treatment, cutaneous and systemic side effects have been a concern for not only the patients, but also the treating clinicians. Because chemotherapy target not only the cancer cells, but also the other rapidly proliferating cells, skin and skin appendages like hair and nails are most commonly affected.
Objectives: To study the cutaneous adverse events associated with the commonly used cancer chemotherapy drugs.
Materials and Methods: 120 patients of clinically diagnosed cancer who underwent chemotherapy and satisfied the inclusion and exclusion criteria were included in this observational study. Photographic images of skin, hair and nails were taken before and after every cycle of chemotherapy were collected. Data were analysed using SPSS version 16.0.
Results: 120 patients including 72 females and 48 males were included in this study with majority (56%) belonging to age group of 55-70 years. The common indications for chemotherapy were carcinoma breast (34%), carcinoma oropharynx (22%) and carcinoma stomach (12%).Hair changes were the most common presentation, reported in 38 patients, skin changes in 35 cases, nail changes in 15 cases. Xerosis (46%) and hyperpigmentation (22%) were the most commonly observed adverse event affecting skin.
Conclusion: Since all cancer chemotherapy agents are not target based, adverse effects of skin and appendages become inevitable. However, early detection of such adverse effects can help them managed effectively and thereby reducing the morbidity and increasing the quality of life of cancer patients.

1. Introduction

There has been an ever-rising trend in incidence of various types of cancers over the last decade. With chemotherapy being the major modality of treatment, cutaneous and systemic side effects have been a concern for not only the patients, but also the treating clinicians.

Cancer is a leading cause of mortality and morbidity in both developed and developing parts of the world with the disease burden projected to grow exponentially in the future. International Agency for Research on Cancer, which is the specialized cancer agency of World Health Organization (WHO), reported 14.1 million new cancer cases and 8.2 million cancer-related deaths in 2012. Indian data reported 1.14 million new cases and 0.7 million cancer-related deaths in 2012.[1]

Chemotherapy is the administration of powerful cytotoxic drugs to destroy cancer cells. It usually works by keeping the cancer cells from growing, dividing, and making more cells. Because cancer cells usually grow and divide faster than normal cells, chemotherapy has more of an effect on cancer cells. However, the drugs used for

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chemotherapy are powerful, and they can still cause damage to healthy cells. This damage causes the side effects that are linked with chemotherapy.

Because chemotherapy target not only the cancer cells, but also the other rapidly proliferating cells, skin and skin appendages like hair and nails are most commonly affected. Adverse reactions can range from minor skin changes such as paronychia, *Acneiform* eruption, and alopecia to life-threatening severe cutaneous adverse reactions (SCARs) such as SJS and TEN.

These drug eruptions are usually immunologically mediated reactions that are termed type B adverse reaction. Most drug eruptions appear to result from T-cell mediated delayed hypersensitivity. The secondary activation of different cascades of cytokines, may contribute to the heterogeneity of clinical presentation.[2]

2. Materials and Methods

120 patients of clinically diagnosed cancer who underwent chemotherapy were included in this Observational study after due approval institutional ethical clearance and patient consent.

2.1. *Exclusion criteria*

1. De novo cutaneous presentations of internal malignancies
2. Patients undergoing radiotherapy
3. Pre-existing dermatoses

Photographic images of skin, hair and nails were taken before and after every cycle of chemotherapy were collected. Cutaneous adverse effect were graded as per criteria for adverse effects version 4.0 of National Cancer Institute.[3]

Data were analysed using SPSS version 16.0

3. Results

Out of 120 patients, 72 females and 48 males were found to have adverse effects with (72%) belonging to age group of 50 to 70 years.

Table 1: Agedistribution

Age in years	Number of patients
40 – 50	8
50 – 60	38
60 – 70	49
70 – 80	25

Common indications for chemotherapy include carcinoma breast (34%), oropharynx (22%) and stomach (12%).[2]

The most commonly used chemotherapy drugs were Alkylating agents (Cyclophosphamide, Busulfan), Antimetabolites (5FU, Capecitabine, Gemcitabine), Antitumor Antibiotics (Dactinomycin, Bleomycin, Doxorubicin, Daunorubicin) and others (Etoposide, Irinotecan, Paclitaxel, etc.)

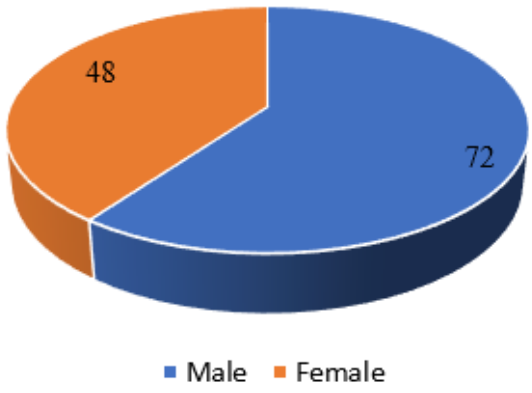

Fig. 1: Gender distribution

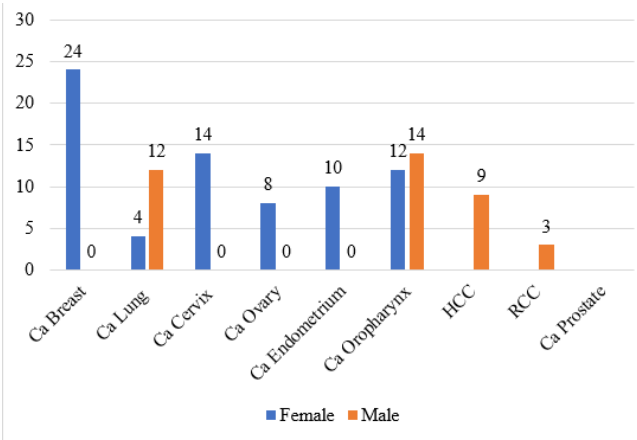

Fig. 2: Gender distribution of cancer

Chemotherapeutic agents with narrow therapeutic index are toxic to rapidly proliferating cells of skin, hair nails at therapeutic doses resulting in multifarious side effects.[4,5]

Anagen effluvium - most common presentation found in 66 cases, skin changes in 45 cases, nail changes in 12 cases. Alopecia is psychologically distressing with 58 % rated alopecia secondary to chemotherapy as the most traumatic side effects and 8% discontinued chemotherapy because of fear of hair loss.[5–7] The cessation of mitotic activity in the hair matrix results in a narrow weakened portion of the hair shaft known as Pohl-Pinkus constriction which is prone to fracture.[8]

Xerosis (46%) and Hyperpigmentation (22%) were commonly observed. Xerosis occurred due to abnormal keratinocyte differentiation which leads to an impaired sebaceous gland function and loss of ability to retain water.[9]

Table 2:

S.No.	Cutaneous adverse effects	Drugs incriminated
1.	Anagen effluvium	Alkylating agents, Antimetabolites, Taxanes
2.	Xerosis	Cyclophosphamide, Adriamycin, cisplatin 5-FU
3.	Prurigo nodularis	Paclitaxel, carboplatin
4.	Hand foot syndrome	Capecitabine , 5-FU
5.	Flagellate dermatosis	Bleomycin
6.	Acneiform eruption	EGFR ihibitors, ABL Tk inhibitors
7.	Melanonychia/nail changes	Taxanes, Cyclophosphamide, Capecitabine,
8.	Diffuse pigmentation/ dyspigmentation	Busulfan, Methotrexate, Procarbazine, Capecitabine

Hyperpigmentation is due to post inflammatory hyperpigmentation, stimulation of melanin synthesis by the increased action of adrenocorticotrophic hormone, or due to hypersensitivity reactions.[10]

Acneiform eruption was seen in 8 cases. Hand and foot syndrome was seen in 5 cases. Melanonychia was seen in 3 cases. Prurigo nodularis was seen in 4% cases and flagellate pigmentation in 3 cases.

Single case of Bullous photodermatitis was reported.

4. Discussion

The major cutaneous adverse effects observed in our study are described as below.

Acneiform eruptions or papulopustular rash occur mainly on the seborrheic areas such as the face, scalp and chest associated with Epidermal growth factor receptor inhibitors.[11] These drug alters signaling pathways causing in keratinocyte growth arrest, apoptosis, decreased cell migration and increased differentiation and elicits an inflammatory response mediated by various cytokines.[12] 7 patients on these drugs had an itchy papulo-pustular rash in this study. Such Acneiform eruption was seen in 9% cases by Ashok et al[13] 10% cases by Pavey et al[12] and 11% cases by Biswal et al.[14]

Hair changes were the most commonly noted followed by skin, nail, and mucosal changes in our study. Table 2 summarizes the comparison of different cutaneous findings reported by Biswal et al.,[14] Kirthi et al.,[15] Pavey et al.,[12] Chiewchanvit et al.,[16] and in our study, Anagen effluvium was seen in 76% cases as compared to 37 % by Pavey et al,78% in Biswal et al and 70.3 % by Fabbrocinni et al.[17]

Xerosis found in 46% cases. Majority (53.9%) noticed skin lesions by 4–6^{th} week of therapy. Pavey et al. reported a similar incidence of xerosis (22%) but the onset of lesions was earlier at 2-4 weeks. Xerosis was seen in 26% by Ashok et al.

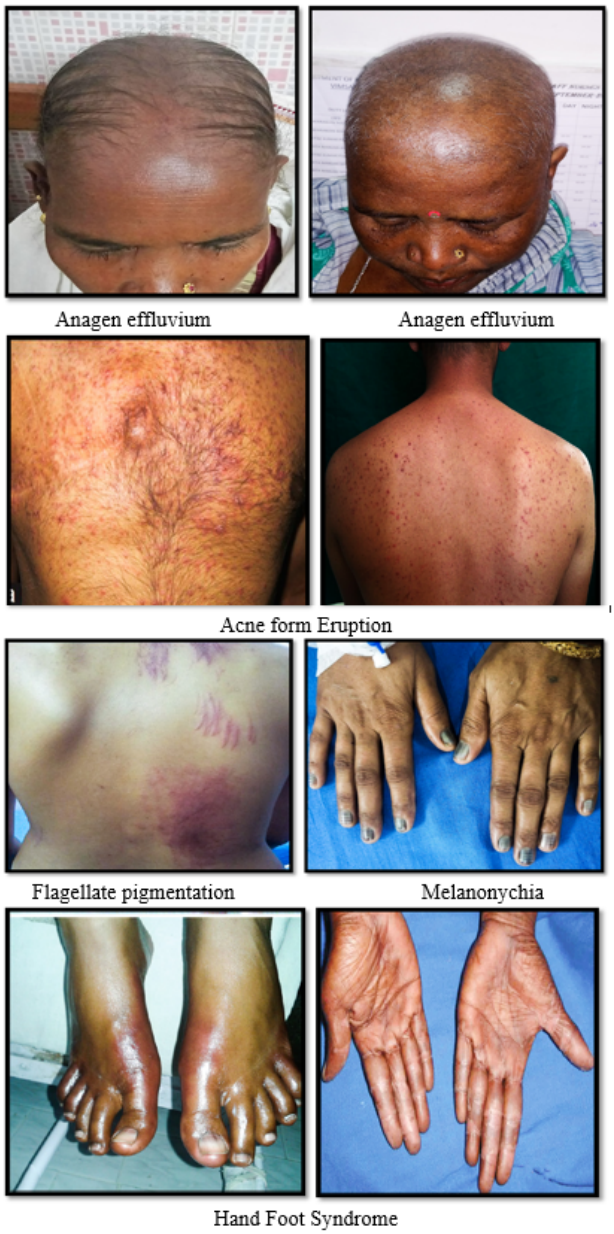

Fig. 3:

Hyperpigmentation was the next most common adverse reaction observed in 22 (22%) patients in this study. The sites most commonly involved were dorsum of hands, feet, and periungual region. Diffuse hyperpigmentation seen in 3% patients. Pavey et al. and Chiewchanvit et al. observed a frequency of 22.2% and 31.3% of hyperpigmentation in their respective studies.[12,16] 5-fluorouracil, cyclophosphamide, cisplatin, doxorubicin, gemcitabine, and ifosfamide are the drugs found to cause hyperpigmentation in this study.

Melanonychia or pigmentation of nail matrix was seen in 12.5 % cases in our study. Such changes were seen in 29% cases by Fabbrocini et al, 49%cases by Pavey et al and 15% cases by Ashok et al.

Hand foot dermatitis was seen in 2.2% cases as compared to 2.6% cases by Biswal et al and 1.5% cases by Ashok et al.

Flagellate pigmentation was seen in 2 patients as compared to 1.5% cases by Ashok et al 1.2% cases by Pavey et al and 0.3% cases by Biswal et al.

Table 3: Comparative studies on various adverse effects

Cutaneous finding	Fabbrocini et al	Biswal et al	Pave et al	Ashok et al	Present study
Anagen effluvium	70.3%	78.6%	37%	68%	76%
Xerosis	38%	4.4%	22.2%	26%	46%
Dyspigmentation			22.2%	22%	14%
Hand Foot Syndrome		2.6%	0.1%	1.5%	2.2%
Prurigo nodularis	3%	5%	4%	6%	4%
Flagellate dermatosis	1.5%	0.3%	1.2	1.5	0.08
Acneiform eruotion	8.5%	11%	10%	9%	7.5%
Melanonychia/Nail changes	29.4%	2.9%	49%	15%	12.5%
Bullous photo dermatitis	0.3%	0.6%		0.4%	0.08%

5. Conclusion

Since all cancer chemotherapy agents are not target based, adverse effects of skin and appendages become inevitable.

Adverse reaction occur in varying degrees of frequency and severity within each class of chemotherapeutic drugs resulting in significant physical and psychological morbidity.

Counselling of patients and attendants play a major part as many adverse reactions are reversible with end of chemotherapy.

Thus, early detection of such adverse effects can help them managed effectively and thereby reducing the morbidity and increasing the quality of life of cancer patients.

Need of the hour is conglomeration of expert Dermatology care along with chemotherapy in order to assuage the psychosocial trauma out of cutaneous reactions of chemotherapy.

6. Source of Funding

None.

7. Conflict of Interest

None.

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