Abstract

Background: The diagnosis of cutaneous adversities in the cancer patient is especially difficult, given the complexity of their illness and combination protocols used for the treatment. The present study was undertaken to know the spectrum of cutaneous adversities in patients undergoing chemotherapy and the drug(s) most commonly associated with it.

Materials and Methods: A total of 1000 patients with malignancies under chemotherapy in the oncology ward and outpatient department were screened in this observational study from January 2013 to February 2015. Relevant investigations for diagnosis of malignancies under chemotherapy and dermatological disorders were carried out. Results: Three hundred and eighty-four patients presented with cutaneous adversities of chemotherapy. The most common was anagen effluvium (78.6%), followed by xerosis (4.4%), thrombophlebitis (3.1%), generalised pruritus (2.9%), melanonychia (2.9%), hand-foot syndrome (2.6%), extravasation reactions (1.8%), flagellate dermatosis (1.3%), prurigo nodularis (0.8%), exfoliation (0.5%), ichthyosis (0.5%), papulopustular rash (0.3%), bullous photodermatitis (0.3%), and Sweet's syndrome (0.3%). Chemotherapeutic drugs were mostly given in combinations. Most common drugs to cause anagen effluvium were alkylating agents in combinations, hand-foot syndrome by taxanes (docetaxel), flagellate dermatoses by antitumour antibiotics (bleomycin), and exfoliation by antimitabolites (methotrexate). The limitation of this study was to imply a specific drug as the causation of the cutaneous adversities since the chemotherapy mostly consisted of combination protocols. Therefore, we have tried to associate the drug combination itself. Conclusion: Chemotherapeutic drugs produce a range of cutaneous adversities, certain specific adversities pertaining to drugs, and their combinations have been implicated which should be looked for and managed accordingly. Knowledge of the adverse effects of anticancer drugs will help reduce the psychological trauma and improve the quality of life.

Key Words: Adverse reactions, anagen effluvium, chemotherapy, drug reactions, hand-foot syndrome

Introduction

New chemotherapeutic agents have been used for the treatment of cancer.[1] This increased use has led to rise in the incidence of cutaneous side effects and worsening of the quality of life. The most common cutaneous adverse manifestations are anagen effluvium, hyperpigmentation, hand-foot syndrome, radiation recall, hypersensitivity, extravasation injuries, and nail dystrophies. They are rarely fatal but may result in significant morbidity, cosmetic disfigurement, and psychological distress.[2] The aim of our study is to find the spectrum of cutaneous adversities and frequency of association with the chemotherapeutic agent(s).

Materials and Methods

An observational study was conducted at our centre, after obtaining ethical committee clearance. All cancer patients starting from January 2013 to February 2015 were screened. After excluding patients on concurrent radiotherapy, cutaneous adversities due to internal malignancies, and who already had cutaneous symptoms from the Department of Dermatology, Venereology and Leprosy, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, Department of Dermatology, Venereology and Leprosy, S. P. Medical College, Bikaner, Rajasthan, India.

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before the initiation of chemotherapy, 1000 consecutive cancer patients, who received chemotherapy in the oncology department, were included in the study.

In all patients, epidemiological data, malignancy, dermatological complaints, cutaneous and systemic examination, and chemotherapy treatment details were recorded. Cutaneous lesions were diagnosed on the basis of typical clinical manifestations. Skin biopsies for histopathology were done in relevant cases.

Results

Out of 1000 cancer patients studied, 295 (29.5%) were male and 705 (70.5%) were female. The mean age was 46.8 ± 16.1 years (range: 4–80 years). They had 67 different types of malignancies, out of which the most common was genitourinary malignancy in 241 (24.1%) patients, followed by breast carcinoma in 147 (14.7%) patients. There were 384 patients who presented with 14 different types of dermatological manifestations [Table 1], out of which anagen effluvium was most common, found in 302 (78.6%) patients. The various cutaneous adversities of chemotherapeutic agent(s) and their frequency distribution are depicted in Table 2.

Discussion

Chemotherapeutic agents individually or in combination have cutaneous side effects that worsen patient’s quality of life. Appropriate management is, therefore, necessary to improve the quality of life and to better the clinical outcome.

In our study, among the patients who presented with dermatological side effects, anagen effluvium was the most common lesion found in 302 (78.6%) patients followed by xerosis in 17 (4.4%), thrombophlebitis in 12 (3.1%), and melanonychia and generalised pruritus in 11 (2.9%) patients each [Table 1]. Mucositis is a known common adversity, but surprisingly, in our observation, none of the patients had it. This might be due to the proper care taken by the patients.

Trueb RM observed that chemotherapy-induced hair loss [Figure 1] occurred with an estimated incidence of 65%.[3] It occurs in >80% of patients treated with antimicrotubule agents; 60 to 100% with topoisomerase inhibitors; >60% with alkylating agents and 10 to 50% with antimetabolite which was similar to a study by Hussein.[4] In our study, the incidence is 30.2% among all patients on chemotherapy. We found that anagen effluvium was seen in all of the patients receiving adriamycin + dacarbazine, carboplatin + docetaxel, paclitaxel + mitomycin + 5-fluorouracil (5-FU) followed by 84.7% of patients receiving ifosfamide + etoposide and 78% of patients receiving oxaliplatin + cyclophosphamide + adriamycin. Hair loss was seen in 85 (8.5%) patients after 1st cycle and in 88 (8.8%) patients after the 2nd cycle.

In our study, we observed xerosis in 17 (4.4%) patients. Xerosis was reported with cetuximab, paclitaxel, and gemcitabine + carboplatin.[5] We observed xerosis with temozolomide, 5-FU + adriamycin + cyclophosphamide, and cisplatin + 5-FU.

In a retrospective study, 44 of 2186 (2.01%) patients under chemotherapy had Hand-foot syndrome [Figure 2]. Most commonly implicated drugs were cytarabine, 5-FU, docetaxel, and doxorubicin.[6] Pavey et al observed it in a patient who received sorafenib.[5] In our study, hand-foot syndrome was found in 10 patients receiving docetaxel, sunitinib, cytarabine and cisplatin + paclitaxel + 5-FU [Table 2].

Docetaxel-induced subacute cutaneous lupus erythematosus in 4 cases was observed by Chen et al.[7] We encountered 1 patient under docetaxel of bullous photodermatitis [Figure 3] which was not reported earlier.

| Table 1: Various cutaneous adverse reactions of chemotherapy drug(s) |
|---------------------------------------------------------------|
| Cutaneous adverse reaction | Number of patients (%) |
| Anagen effluvium | 302 (78.6) |
| Xerosis | 17 (4.4) |
| Thrombophlebitis | 12 (3.1) |
| Melanonychia | 11 (2.9) |
| Generalised pruritus | 11 (2.9) |
| Hand-foot syndrome | 10 (2.6) |
| Extravasation reaction | 7 (1.8) |
| Flagellate dermatosis | 5 (1.3) |
| Prurigo nodularis | 3 (0.8) |
| Ichthyosis | 2 (0.5) |
| Exfoliation | 2 (0.5) |
| Sweet’s syndrome | 1 (0.3) |
| Folliculitis | 1 (0.3) |
| Bullous photodermatitis | 1 (0.3) |

One patient given cisplatin + bleomycin + etoposide regimen developed alopecia as well as flagellate dermatosis.

Figure 1: Anagen effluvium
Table 2: Frequency distribution of cutaneous adverse reactions to various drug protocols

| Cutaneous adverse reaction | Drug(s) protocol | Number of patients with cutaneous adverse reaction | Total number of patients receiving the drug(s) (%) |
|----------------------------|------------------|---------------------------------------------------|-------------------------------------------------|
| Anagen effluvium           | Adriamycin + dacarbazine  | 4                                                  | 4 (100)                                          |
|                            | Carboplatin + docetaxel   | 4                                                  | 4 (100)                                          |
|                            | Paclitaxel + mitomycin + 5-FU | 2                                                  | 2 (100)                                          |
|                            | Ifosfamide + etoposide    | 6                                                  | 7 (84.7)                                         |
|                            | Oxaliplatin + cyclophosphamide + adriamycin | 6                                                  | 8 (75.0)                                         |
|                            | Cisplatin + doxorubicin    | 9                                                  | 14 (64.2)                                        |
|                            | Carboplatin              | 5                                                  | 8 (62.5)                                          |
|                            | Cisplatin + bleomycin      | 4                                                  | 7 (57.1)                                          |
|                            | Cisplatin + bleomycin + etoposide | 8                                                  | 14 (57.1)                                        |
|                            | Cisplatin + paclitaxel + 5-FU | 20                                                | 36 (55.5)                                        |
|                            | Cisplatin + paclitaxel     | 80                                                 | 145 (55.1)                                       |
|                            | Cisplatin + etoposide      | 10                                                 | 19 (52.6)                                        |
|                            | Cisplatin + cyclophosphamide | 11                                              | 22 (50.0)                                        |
|                            | Paclitaxel + mitomycin + methotrexate + mitoxantrone | 4                                                  | 8 (50.0)                                         |
|                            | Cisplatin                | 16                                                 | 34 (47.0)                                        |
|                            | Paclitaxel + 5-FU         | 9                                                  | 20 (45.0)                                        |
|                            | 5-FU + adriamycin         | 4                                                  | 11 (36.3)                                        |
|                            | Paclitaxel + carboplatin  | 70                                                 | 120 (33.3)                                       |
|                            | Adriamycin + etoposide    | 2                                                  | 7 (28.5)                                          |
|                            | Paclitaxel               | 4                                                  | 14 (28.5)                                        |
|                            | 5-FU + oxaliplatin        | 13                                                 | 57 (22.8)                                        |
|                            | Cisplatin + 5-FU          | 11                                                 | 141 (7.8)                                        |
| Xerosis                    | Temozolomide              | 7                                                  | 7 (100)                                           |
|                            | 5-FU + adriamycin + cyclophosphamide | 3                                                  | 25 (12.0)                                        |
|                            | Cisplatin + 5-FU          | 7                                                  | 141 (4.9)                                        |
| Thrombophlebitis           | Carboplatin + 5-FU        | 4                                                  | 4 (100)                                           |
|                            | Cytarabine + daunorubicin | 3                                                  | 3 (100)                                           |
|                            | 5-FU + oxaliplatin        | 5                                                  | 57 (8.7)                                          |
| Generalised pruritus        | 5-FU + cyclophosphamide + epirubicin | 5                                                  | 9 (55.5)                                          |
|                            | Cisplatin + 5-FU          | 6                                                  | 141 (4.2)                                        |
| Melanonychia               | Cisplatin + paclitaxel    | 11                                                 | 145 (7.5)                                        |
| Hand-foot syndrome          | Docetaxel                 | 2                                                  | 3 (66.6)                                          |
|                            | Sunitinib                 | 2                                                  | 4 (50)                                            |
|                            | Cytarabine                | 4                                                  | 9 (44.4)                                          |
|                            | Cisplatin + paclitaxel + 5-FU | 2                                                  | 36 (5.5)                                          |
| Extravasation reaction      | Cisplatin + 5-FU          | 5                                                  | 141 (3.5)                                        |
|                            | 5-FU + oxaliplatin        | 2                                                  | 57 (3.5)                                          |
| Flagellate dermatosis       | Paclitaxel + carboplatin + bleomycin | 1                                                  | 1 (100)                                           |
|                            | Bleomycin                 | 2                                                  | 2 (100)                                           |
|                            | Cisplatin + bleomycin + etoposide | 2                                                  | 14 (14.2)                                         |
| Prurigo nodularis           | Paclitaxel + carboplatin  | 3                                                  | 120 (2.5)                                        |
| Ichthyosis                  | Methotrexate              | 2                                                  | 5 (40.0)                                          |
| Exfoliation                 | Methotrexate              | 2                                                  | 4 (50)                                            |
| Sweet's syndrome            | Imatinib                  | 1                                                  | 1 (100)                                           |
| Foliculitis                 | 5-FU + oxaliplatin        | 1                                                  | 57 (1.7)                                          |
| Bullous photodermatitis     | Docetaxel                 | 1                                                  | 3 (33.3)                                          |

5-FU: 5-fluorouracil

Melanonychia was reported with cisplatin, paclitaxel + carboplatin, vincristine + daunorubicin, and cyclophosphamide + doxorubicin therapy.\[^5\] We observed melanonychia in 11 (7.5%) patients receiving cisplatin + paclitaxel regimen. It was already known that cisplatin causes melanonychia and Muehrcke lines in a case report.\[^8\]

[^5]: Biswal and Mehta: Cutaneous adverse reactions of chemotherapy in cancer patients
[^8]: Indian Journal of Dermatology | Volume 63 | Issue 1 | January - February 2018
Each of the major classes of antineoplastic agents (alkylating agents, antimetabolites, antibiotics, plant alkaloids, nitrosoureas, and enzymes) includes drugs capable of producing cutaneous reactions including pruritus. Patients receiving antineoplastic drugs frequently report dry skin and scaling thought to be related to effects on sebaceous and sweat glands. In our study, generalised pruritus was seen in 11 (2.9%) patients on chemotherapy. It was seen in 55.5% of patients on 5-FU + cyclophosphamide + epirubicin therapy and in 4.2% having cisplatin + 5-FU therapy. Prurigo nodularis was found in 3 (2.5%) patients receiving paclitaxel + carboplatin therapy.

Pavey et al encountered extravasation reaction in 1 patient with paclitaxel + carboplatin therapy. In our present study, it occurred in 3.5% of patients treated with cisplatin + 5-FU and 5-FU + oxaliplatin therapy [Figure 4].

Ziemer et al observed that flagellate dermatitis [Figure 5] and subsequent hyperpigmentation in the skin were fairly common among patients receiving bleomycin, with reported incidence between 8% and 22% whereas Júlio César Gomes Silveira et al observed its occurrence was variable, as it was described in a percent range from 8% to 66% of cases in different studies. In our study, it was seen in 5 cases. Two patients with bleomycin and 1 patient with paclitaxel + carboplatin + bleomycin therapy showed flagellate dermatosis.

Exfoliation and ichthyosis were found in 2 cases each treated with methotrexate [Figure 6]. Jetton and Eby also observed ichthyosis associated with methotrexate therapy.

Papulopustular rash was reported with gefitinib, cetuximab, and ABVD regimen. We observed it in a case with 5-FU + oxaliplatin therapy.

Phlebitis is an inflammatory response to intravenously injected chemotherapy drugs that may last for weeks or months and leads to various types of vein damage including pain, erythema and swelling, and thickening of injection area and finally, fever. Thrombophlebitis was seen in 12 patients treated with cytarabine + daunorubicin, carboplatin + 5-FU, and 5-FU + oxaliplatin in our study. Chemotherapy-induced phlebitis incidence has been reported as 70%; it increases the probability of embolism affecting the health of the patients.

It has been reported that Sweet’s syndrome developed secondary to administration of imatinib mesylate for
In our study also one patient who received imatinib, developed Sweet's syndrome.

In our study, we found cisplatin + paclitaxel caused cutaneous side effects as anagen effluvium in 55.55% and melanonychia in 7.58% of the patients. The main side effects of this combination regimen were myelosuppression, gastrointestinal reactions, and peripheral neuropathy in a study by Zhao et al.[16]

In 141 patients who received Cisplatin + 5-FU regimen cutaneous adversities seen were anagen effluvium in 7.8%, xerosis in 4.96%, generalised pruritus in 4.25%, and extravasation reactions in 3.54%. This is similar to a study by the Christie NHS Foundation Trust.[17]

Similarly, therapy with paclitaxel + carboplatin led to anagen effluvium in 33.33% and prurigo nodularis in 2.5% of 120 patients. A diffuse rash had been reported after the administration of this combination therapy.[18]

Cisplatin + paclitaxel + 5-FU regimen showed anagen effluvium in 55.55% and hand-foot syndrome in 5.55% of 36 patients treated with this as compared to Hitt et al who found that peripheral neuropathy (Grade 2–3, 14%) and catheter-associated venous thrombosis (7%) were main toxicities of cisplatin + paclitaxel + 5-FU regimen in 70 patients.[19]

The limitation of this study was the inability of pinpointing a single drug responsible for a particular dermatological adverse since the chemotherapy mostly constituted of combination protocol. Therefore, we have tried to associate the drug combination itself.

**Conclusion**

We conclude that 78.6% of the patients having dermatological adversities presented with anagen effluvium most commonly by alkylating agents, cytotoxic agents, and taxanes in various combinations. Similarly, bleomycin was found to be the most probable cause of flagellate dermatoses in combinations. Alkylating agents and antimetabolites were most frequently implicated in xerosis, thrombophlebitis, generalised pruritus, extravasation reactions, and papulopustular rash. Hand-foot syndrome was associated most commonly with taxanes followed by epidermal growth factor receptor antagonist (sunitinib) and antimetabolites. Melanonychia, bullous photodermatitis, and prurigo nodularis were seen mostly by alkylating agents and their various combinations. Similarly, exfoliation and ichthyosis were caused by methotrexate while Sweet’s syndrome by tyrosine kinase inhibitor imatinib.

These reactions occur in varying degrees of frequency and severity within each class of chemotherapeutic drugs which may result in significant morbidity, obliging physicians to suspend therapy. Proper treatment may allow achievement of ideal durations of chemotherapy administration, as well as the optimization of response rates. It is stressed that counseling of the patients and their attendants before initiation of chemotherapy may reduce the psychological trauma of the cosmetically unacceptable adversities and hence improvise the lifestyle management. Cooperation between oncologist and dermatologist is also fundamental to make the best decision for the patients and to implement preventive measures.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**What is New?**

Here, we have taken a large sample of 1000 cancer patients under chemotherapy having cutaneous adversities in 394 patients and studied not only about the cutaneous adverse drug reactions of the various combination protocols and single cancer chemotherapy drugs but also their frequency of association.

**References**

1. Alley E, Green R, Schuchter L. Cutaneous toxicities of cancer therapy. Curr Opin Oncol 2002;14:212-6.
2. Berthelot C, Kunishige JH, Apisarnthanarax N, Duvic MM. Dermatologic complications of cancer chemotherapy. In: Cancer Medicine. 8th ed. Hamilton, ON: B.C. Decker; c2010. p. 1779-87.
3. Trüeb RM. Chemotherapy-induced hair loss. Skin Therapy Lett 2010;15:5-7.
4. Hussein AM. Chemotherapy-induced alopecia: New developments. South Med J 1993;86:489-96.
5. Pavey RA, Kambil SM, Bhat RM. Dermatological adverse reactions to cancer chemotherapy. Indian J Dermatol Venereol Leprol 2015;81:434.
6. Hueso L, Sanmartín O, Nagore E, Botella-Estrada R, Requena C, Llombart B, et al. Chemotherapy-induced acral erythema: A clinical and histopathologic study of 44 cases. Actas Dermosifiliogr 2008;99:281-90.
7. Chen M, Crowson AN, Woofter M, Luca MB, Magro CM. Docetaxel (taxotere) induced subacute cutaneous lupus erythematosus: Report of 4 cases. J Rheumatol 2004;31:818-20.
8. Monteagudo B, Cabanillas M, Suárez-Amor O, Martínez-Calvo L, Graña-Suárez B. Muehrcke’s lines on nails after docetaxel/
cisplatin/fluorouracil. Gastroenterol Hepatol 2009;32:381-2.
9. Dunagin WG. Clinical toxicity of chemotherapeutic agents: Dermatologic toxicity. Semin Oncol 1982;9:14-22.
10. Ziemer M, Goetz S, Juhasz K, Elsner P. Flagellate dermatitis as a bleomycin-specific adverse effect of cytostatic therapy: A clinical-histopathologic correlation. Am J Clin Dermatol 2011;12:68-76.
11. Silveira JC, Cunha BM, Estrella RR. Bleomycin- induced flagellate dermatitis. Ann Bras Dermatol 2006;81:83-5.
12. Jetton RL, Eby CS. Ichthyosis and methotrexate: A word of caution. Pediatrics 1971;47:911-3.
13. Mermel LA. Prevention of intravascular catheter-related infections. Ann Intern Med 2000;132:391-402.
14. Tagalakis V, Kahn SR, Libman M, Blostein M. The epidemiology of peripheral vein infusion thrombophlebitis: A critical review. Am J Med 2002;113:146-51.
15. Ayirookuzhi SJ, Ma L, Ramshesh P, Mills G. Imatinib-induced Sweet syndrome in a patient with chronic myeloid leukemia. Arch Dermatol 2005;141:368-70.
16. Zhao Y, Wang SM, Zhang J. [Combination chemotherapy with taxol and cisplatin for 57 patients with non-small cell lung cancer by intraartery and intravenous infusion]. Ai Zheng 2002;21:1365-7.
17. The Christie NHS Foundation Trust. Cisplatin and 5-Fluorouracil (Urology); 2014. Available from: http://www.christie.nhs.uk/booklets/707.pdf. [Last accessed on 2015 Jan 27].
18. Hazan E, Santa E, Sahu J. Diffuse rash after the administration of carboplatin and paclitaxel. Am J Dermatopathol 2016;38:365.
19. Hitt R, Paz-Ares L, Brandáriz A, Castellano D, Peña C, Millán JM, et al. Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: Long-term results of a phase II trial. Ann Oncol 2002;13:1665-73.