Original Research Article

A Prospective Observational Study of Dermatological Adverse Effects of Chemotherapeutic Agents: Experience From A Tertiary Centre

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Abstract

Introduction: 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. **Materials and Methods:**A total of 106 patients attending the oncology outpatient department or those admitted in the oncology ward of GovtMedical College (GMC), Jammu, India between January 2020 and December 2020 were prospectively studied the cutaneous adverse effects related to chemotherapy were noted.We included patients ofboth sexes who suffered from mucocutaneous adverseeffects which began after initiation of the anti-cancer drug. Patient's developing cutaneous manifestations as a result of internal malignancies, patients who already had mucocutaneous symptoms at the start of therapy, and those on radiotherapy were excluded from the study. **Results:**Breast cancer was the most common cancer seen in 24 patients followed by ovarian cancer in 16 patients,Lung cancer in 14 patients and Acute Lymphocytic Leukemia in 12 patients. The remaining types are depictedin Figure 1.Of the 106 patients, 50 (47%) were males with a meanage of 46.9 years and 56 (53%) were females with amean age of 47.4 years. Nail changes were the mostcommon adverse effect noticed in 66 (62.2%) patients,followed by hair changes in 40 (37.7%), skin changes in 38(33.9%) and mucosal changes in 4 (3.7%) patients[Figure 2].**Conclusion:**Dermatological side effects related to chemotherapeutic agents is common but timely recognized, being a visible occurrence most of the times. Although this creates an alarming apprehension among the treating physician as well as the patients and their attendants, yet most of the times, the features are not of such serious nature as to warrant withdrawal or changeover of the therapy. But a thorough knowledge is essential to alleviate such an apprehension and avoid a wrong decision.

Keywords: Cancer, Chemotherapy, Skin, Mucosa ,Adverse effects.

Introduction

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. Over the last two decades, a number of new chemotherapeutic agents have been used for the treatment of cancer.These drugs may be classified according to their mechanism of action in: *Signal transduction inhibitors* (Epidermal growth factor receptor–EGFR- antagonists and Multikinase inhibitors), *Proteasome inhibitors, Spindle inhibitors* (Taxanes and Vinca alkaloids), *Antimetabolites* (Purine analogs and Pyrimidine analogs), *Genotoxic agents*[1-4]

Chemotherapeutic agents have significant side effects. Although skin toxicity is rarely life-threatening it often worsens the patients' quality of life.It is well known that, cytotoxic agents like Cyclophosphamide, Chlorambucil, Busulfan, Procarbazine can cause side-effects on hair and nails (alopecia, paronychia, melanonychia, and other abnormalities),on skin barrier (skin rash, skin dryness, hyperpigmentation) and on mucosa (Steven-Johnson Syndrome and toxic epidermionecrolysis).In recent years, targeted therapy has considerably increased survival rate in patients affected by important solid tumors of kidney, lungs, colon-rectum, breast and liver. Among the innovative therapeutic strategies in chemotherapy, the EGFR inhibitors (Cetuximab, Panitumumab, Erlotinib, Gefitinib) approved for lung and colon-rectum tumors showed an increasing skin toxicity, causing widespread skin dryness (in more than 90% of patients) and a follicular rash which can be complicated by pruritus, pain and infections.

Indian data reported 1.14 million new cases and 0.7 million cancer-related deaths in 2012.Latest data show that the 5-year survival of all cancers has increased from 50% to 66% over the past 20 years.WHO defines an adverse drug reaction as "any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis, or therapy."

Dermatological adverse effects are often reported as causes for discontinuation of therapy though they are seldom life-threatening events. This study aims at identifying the various cutaneous adverse events associated with cancer chemotherapy.

Materials and Methods

Study Design: A Prospective Study.

Study Location: Department of Radiotherapy, GovtMedical College (GMC), Jammu,India.

Study duration: January 2020 and December 2020.

A total of 106 patients attending the oncology outpatientdepartment or those admitted in the oncology ward ofGovtMedical College (GMC), Jammu,Indiabetween January 2020 and December 2020

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were prospectively studied the cutaneous adverse effects related o chemotherapy were noted.

Inclusion Criteria: We included patients of both sexes who suffered from mucocutaneous adverse effects which began after initiation of the anti-cancer drug.

Exclusion criteria: Patients developing cutaneous manifestations as a result of internal malignancies, patients who already had mucocutaneous symptoms at the start of therapy, and those on radiotherapy[5,6].

Results

Out of the 106 cancer patients studied, 38 patients were on a single chemotherapy drug and 68 were on combined chemotherapy.The various drugs used in thestudy were:cetuximab, geftinib, imatinib, sorafenib,paclitaxel,vincristine,vinblastine,6-mercaptopurine,5-fluorouracil,cytarabine,capecitabine,gemcitabine,cisplatin,carboplatin,oxaliplatin,etoposide,cyclophosphamide,doxorubicin,daunorubicin, epirubicin, hydroxyurea, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and ABVD(doxorubicin, bleomycin, vinblastine, dacarbazine)regimens.

Breast cancer was the most common cancer seen in 24 patients followed by ovarian cancer in 16 patients, Lung cancer in 14 patients and Acute Lymphocytic Leukemia in 12 patients. The remaining types are depicted in Figure 1.Of the 106 patients, 50 (47%) were males with a meanage of 46.9 years and 56 (53%) were females with amean age of 47.4 years. Nail changes were the most common adverse effect noticed in 66 (62.2%) patients,followed by hair changes in 40 (37.7%), skin changes in 38(33.9%) and mucosal changes in 4 (3.7%) patients[Figure 2].

The skin changes were acneiform (papulopustular) rash in 10 (27.7%) patients, xerosis in 8 (22.2%), hyperpigmentation in 8 (22.2%), and toxic epidermal necrolysis, hand foot syndrome, extravasation, erythema nodosum and supravenous hyperpigmentation in 2 patient each [Table 1].

The most common nail finding observed was melanonychia which was seen in 52 (78.7%) patients,followed by Muehrcke's lines, Mee's lines, and Beau's lines [Table 2].

Hair changes were mainly in the form of anagen effluvium seen in 40 (37.7%) patients. Mucosal changes included pigmentation of tongue and stomatitis [Table 3].

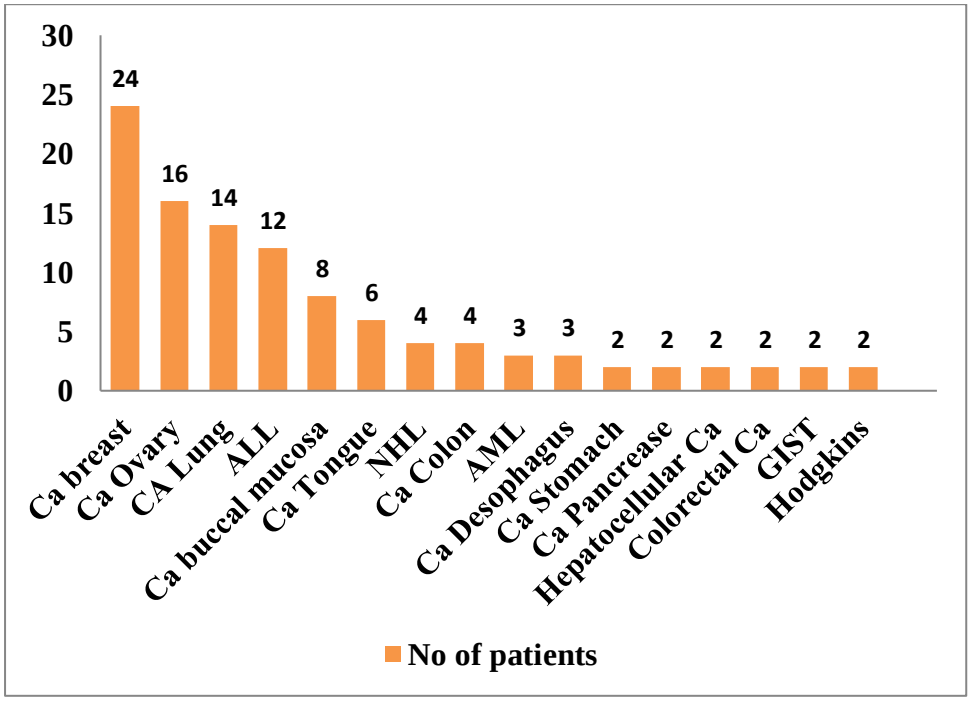

Fig 1: Types of cancer in the 106 patients (*N* = 106)

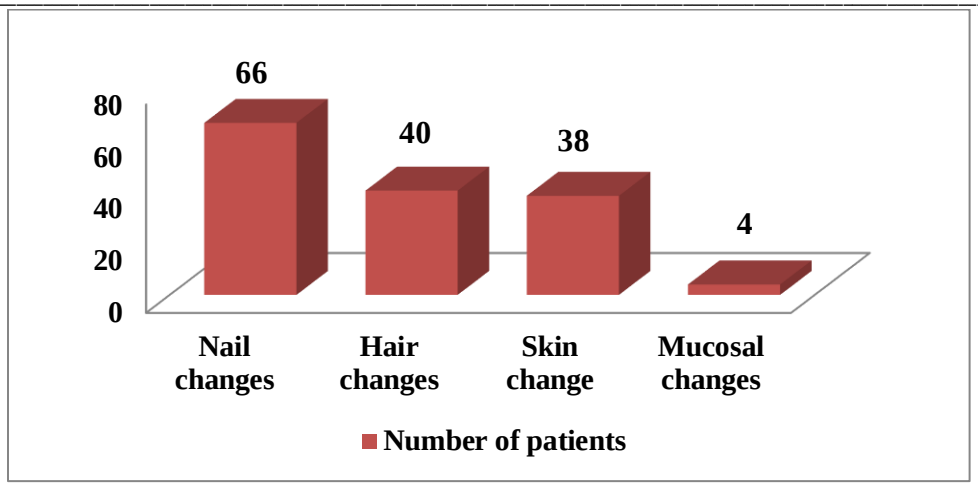

Fig 2: Frequency of adverse effects

Table 1: Skin Toxicity of Anticancer Drugs

S.No	Skin Toxicity	Number of cases	Causative Drugs
1	Papulopustular rash	10	Geftinib, cetuximab, ABVD regimen
2	Xerosis	8	Cetuximab, paclitaxel, gemcitabine,carboplatin
3	Hyper Pigmentation	8	Hydroxyurea, imatinib, etoposide,paclitaxel, capecitabine
4	Hand foot syndrome	2	Sorafenib
5	Toxic Epidermal Necrolysis	2	Capecitabine
6	Extravasation reaction	2	Paclitaxel,carboplatin
7	Erythema nodosum	2	6-mercaptopurine
8	Supravenous hyperpigmentation	2	ABVD regimen

Table 2: Nail toxicity of anticancer drugs

S.No	Nail Toxicity	Number of cases	Causative Drugs
1	Melanonychia	52	Cisplatin,paclitaxel,carboplatin,vincristine,daunorubicin,Cyclophosphamide,doxorubicin
2	Muehrcke's lines	8	Fluorouracil,epirubicin,cyclophosphamide, epirubicin,oxaliplatin
3	Mee's lines	4	Cyclophosphamide,doxorubicin,vincristine,prednisolone (CHOP)
4	Beau's lines	2	Fluorouracil,doxorubicin,cyclophosphamide

Table 3: Mucosal and hair toxicity of anticancer drugs

S.No	Mucosal and hair toxicity	Number of cases	Causative Drugs
1	Tongue pigmentation	2	Hydroxyurea,Doxorubicin,Cyclophosphamide
2	Stomatitis	2	Capecitabine
3	Anagen effluvium	40	Paclitaxel,carboplatin, vincristine,daunorubicin, Daunorubicin,cyclophosphamide, paclitaxel,daunorubicin

Discussion

Anti-cancer drugs usually affect rapidly growing cellsand hence, the skin, hair follicles and nail matrixare the frequent targets of their toxicities.

Various anti-cancer drugs such as epidermal growth factor receptor (EGFR) inhibitors including cetuxima bandgeftinib, multikinase inhibitors (imatinib, sorafenib),taxanes (paclitaxel), vinca alkaloids(vincristine,vinblastine),antimetabolites(6-mercaptopurine,5-fluorouracil,cytarabine,capecitabine, gemcitabine), genotoxic agents(cisplatin,carboplatin, oxaliplatin, etoposide, cyclophosphamide,and anthracyclines like doxorubicin, daunorubicin,epirubicin),hydroxyurea,cyclophosphamide,doxorubicin,vincristine,prednisolone(CHOP)and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimens areassociated with prominent and sometimes doselimiting dermatologic complications.

Hand-foot syndrome represents the clinically significant and occasionally dose-limiting skin toxicity of cytarabine, doxorubicin, 5-fluorouracil, sorafenib,and sunitinib. Dual inhibition of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) disrupts the normal repair process involving capillaries and fibroblasts.

This blockade, in combination with repeated subclinical trauma and friction to areas such as palmsand soles, leads to inflammation. It usually presentsas painful symmetric erythema over the then arorhypothenar eminences and pad of distal phalanges and less often on the soles.In severe cases, blistering develops over the swollen erythematous areas.In our study, a single case of hand-foot syndrome wasseen in a patient on sorafenib which occurred during the first cycle of treatment. The patient wastreated with cold compresses, emollients and topicalsteroids, and the drug was temporarily stopped. Thedrug was restarted at slightly lower dose once the skin lesions improved.One case of extravasation was seen in a patient onpaclitaxel and carboplatin. Both drugs are documented to be irritant agents and cause burning, warmth,erythema and tenderness in

the extravasated area with occasional necrosis. In our case, both drugs were stopped temporarily and cold compresses and limb elevation were undertaken. A single case of toxic epidermal necrolysis due to capecitabine was seen in our study, which was also reported by Matos-Fernandez *et al.*In our case, the drug was completely stopped[7-10].

Conclusion

Dermatological side effects related to chemotherapeutic agents is common but timely recognized, being a visible occurrence most of the times. Although this creates an alarming apprehension among the treating physician as well as the patients and their attendants, yet most of the times, the features are not of such serious nature as to warrant withdrawal or changeover of the therapy. But a thorough knowledge is essential to alleviate such an apprehension and avoid a wrong decision.

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