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Cutaneous Adverse Reactions Due to Antineoplastic Agents.

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KEYWORDS

Cutaneous adverse reactions, antineoplastic agents, chemotherapy, anagen effluvium

ABSTRACT:

Background- Cancer is a leading cause of mortality and morbidity in the world. Traditional as well as the newer targeted antineoplastic agents are associated with a wide array of Cutaneous Adverse Reactions (CARs).

Objectives- The aim of our study is to find the prevalence of CARs and frequency of association with the antineoplastic agents at our centre.

Methods- An observational study was conducted on 100 patients in Dermatology and oncology department of our centre from April 2022 to April 2023. We excluded patients who were on concurrent radiotherapy, CARs due to internal malignancies, cutaneous symptoms before chemotherapy, receiving immunosuppressive agents for other causes and having other dermatological conditions. Detailed history, examination and consent were taken in all included patients and Skin biopsies for histopathology were done in relevant cases.

Results- Among 100 patients total 192 cutaneous adverse reactions were noted in our study affecting skin, hair and nail. In our study, skin was the most commonly affected site (53.13%) followed by hair (29.17%) and nail (17.71%) respectively. Anagen effluvium was the most common adverse effect finding reported in 50 patients (26.04%) followed by xerosis in 32 patients (16.66%). Most common nail changes were nail pigmentation in 20 patients (10.41%). Infusion site reaction was seen in only 10 patients (5.20%).

Conclusion-antineoplastic agents lead to various CARs pertaining to skin, hair and nail changes. Proper understanding of these CARs will help in early detection, timely management and proper counselling of cancer patients.

INTRODUCTION

Cancer is a leading cause of mortality and morbidity in both developed and developing parts of the world. Indian data reported 1.14 million new cases and 0.7 million cancer-related deaths in 2012.[1] New anticancer drugs developed over the last few decades have improved the survival rate in cancer patients. Traditional chemotherapy drugs as well as the newer targeted agents are associated with a wide array of cutaneous toxicities.[2] Toxic effects on skin, hair and nails can negatively affect the quality of life and also lead to interruption or discontinuation of these drugs.

The aim of our study is to find the spectrum of Cutaneous Adverse Reactions(CARs) and frequency of association with the chemotherapeutic agent(s).

MATERIAL AND METHODS

An observational study was conducted at our centre in between April 2022- April 2023, after obtaining ethical committee clearance. This study was conducted in IPD and OPD of Dermatology and oncology department of our centre. We excluded patients who were on concurrent radiotherapy, developed cutaneous adverse reactions due to internal malignancies, who already had

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cutaneous symptoms before the initiation of chemotherapy, patients who were receiving immunosuppressive agents for other causes and patients who developed dermatological condition due to other causes. We enrolled 100 consecutive cancer patients, who received chemotherapy in the oncology department in our study. Detailed history and examination were undertaken in all included patients and Skin biopsies for histopathology were done in relevant cases. Written informed consent was taken of all patients for data collection including photographs and publication.

Results

Demographic Data

Total 100 patients were included in the study. Among 100 patients 63 were females and 37 were males. Majority of patients (42 patients) belonged to 41-60 years age group in which 28 were females and 14 were males. This (41-60 years) was the most common age group for male as well as female category. **[Table 1]**

Prevalence of Carcinoma

Carcinoma breast was the most common indication for chemotherapy affecting 37 patients followed by carcinoma Lung (n=13), acute lymphoblastic leukaemia (n=10), carcinoma oral cavity (n=8) and carcinoma ovary (n=7). Most common carcinoma for female was carcinoma Breast while for males it was carcinoma Lung. Other cancerous condition were Sarcoma, renal cell carcinoma, squamous cell carcinoma of neck, oligoastrocytoma, carcinoma gall bladder, Non-Hodgkin's lymphoma, acute myeloid leukaemia, carcinoma cervix, carcinoma mandible, multiple myeloma, myelofibroma, carcinoma pancreas. **[Fig 1]**

Out of 100 patients 24 patients received single chemotherapy agent while 76 patients received multiple chemotherapy agents. Paclitaxel was the Most common chemotherapeutic agent used in 6 patients while paclitaxel, cyclophosphamide, epirubicin was the most common multi drug regimen used in 16 patients. 32 patients received 3 drug regimen while 35 patients received 2 drug regimen and 7 patients received 4 drug regimen and only 2 patients received 5 drug chemotherapy regimen.

Frequency of Cutaneous Adverse Reactions and association with various Drug regimens

Total 192 cutaneous adverse reactions were noted in our study affecting skin, hair and nail. In our study, skin was the most commonly affected site (53.13%) followed by hair (29.17%) and nail (17.71%) respectively.

Anagen effluvium was the most common adverse reaction finding reported in 50 patients (26.04%) followed by xerosis in 32 patients (16.66%). Most common nail changes were nail pigmentation in 20 patients (10.41%). Infusion site reaction was seen in only 10 patients (5.20%) **[Table 2]**

Most common multi drug regimen causing anagen effluvium in our study was pacitaxel, cyclophosphamide, epirubicin found to cause Anagen effluvium in 81.25% patients. Most common Single drug responsible for Anagen effluvium was paclitaxel found in 83.33% patients.

Xerosis was the most common skin related adverse reaction in our study found in 32 patients (16.66%). Most common drugs responsible for this were paclitaxel, carboplatin combination in multidrug regimen found in 53.33% patients. And in single drug regimen capecitabine was the most common drug responsible for 50% patients. **[Table 3a, 3b, 4]**

Discussion

Majority of patients (n=42) belonged to the 41- 60 years age group this was comparable to the findings of studies done by Kirthi c et al and Menon et al.[3,4]

In our study carcinoma breast was the most common indication for chemotherapy followed by carcinoma lung. In females carcinoma breast was the leading cause while in males carcinoma lung was the leading cause of cancer in our study. Menon et al found carcinoma oropharynx as the most common carcinoma while Rachel A et al found carcinoma breast as most common carcinoma followed by carcinoma ovary. [4,5]

In our study, skin was the most commonly affected site while study done by Menon et al found hair changes to be the most common presentation, followed by skin, nail, and mucosal changes.[4]

Anagen effluvium was the most common adverse reaction finding reported in 50 patients (26.04%) in our study. Most common multi drug regimen causing anagen effluvium in our study was pacitaxel, cyclophosphamide, epirubicin found to cause Anagen effluvium in 81.25% patients. Susser ws et al

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and Hinds G et al also found the same drug regimen to cause anagen effluvium most commonly.[2,6] **[Fig 2a & b]**

One of the rare hair finding we found in our study was greying of hairs caused by sunitinib. A study done by Routhouska S et al conclude that treatment with oral tyrosine kinase inhibitors like sunitinib resulted in reversible hair depigmentation and change in hair growth rate and texture, which were most likely due to an incomplete inhibition of SCF/c-kit signalling.[7]

Another rare finding is Plica Polonica (matting & uncombable hair) caused by paclitaxel and carboplatin. A case report by Gupta S et al found similar presentation by same drugs.[8]**[Fig 3]**

In our study Xerosis was seen in 32 patients (16.66%). Majority of patients (53.9%) noticed xerotic lesions by 3rd–6th week of therapy. Fabbrocini *et al*. reported an incidence of 41.7% of xerosis in his study.[9]

Skin Hyperpigmentation was the next most common adverse reaction observed in 26 (13.54%) patients in our study. Pavey *et al*. and Chiewchanvit *et al*. observed a frequency of 22.2% and 31.3% of hyperpigmentation in their respective studies.[5] The sites which were most commonly involved were dorsum of hands, feet, and face. The drugs found to cause hyperpigmentation in our study were paclitaxel, carboplatin, capecitabine, 5-fluorouracil, cyclophosphamide, cisplatin, doxorubicin and gemcitabine. The hyperpigmentation may be due to postinflammatory hyperpigmentation, stimulation of melanin synthesis by the increased action of adrenocorticotrophic hormone or it may be a result of hypersensitivity reactions.[10]**[Fig 4]**

Among Nail changes, nail pigmentation was the most frequently seen adverse event and occurred in 20 patients (10.41%) cases. Menon et al observed melanonychia in 15% cases.[4] Saraswat et al also reported diffuse hyperpigmentation of nails to be most common side effects among nails.[11] Drugs responsible for nail hyperpigmentation were paclitaxel, cyclophosphamide, epirubicin, carboplatin, gemcitabine and cisplatin. Melanonychia occurs due to melanocyte activation in matrix epithelium.[12,13] **[Fig 5a & b]** Other nail findings were brittle nails and nail dystrophy in 4.16% cases, hemorrhagic onycholysis in 3.12% cases.

Biswal SG et al observed Extravasation in 3.5% of patients treated with cisplatin + 5-FU and 5-FU + oxaliplatin therapy.[14] In our study Extravasation (Infusion Site Reaction) were noted in 5.2% of patients found due to various drugs like cyclophosphamide and paclitaxel + cisplatin + iphosphamide regimen and vincristine + donorubicin + methotraxate regimen.**[Fig 6]**

We found hand-foot syndrome in 2 patients. One of them was on triptorelin+ denosumab+rebociclib regimen while another patient was on Capecitabine. In literature, the most common chemotherapy drugs associated with HFS are docetaxel, capecitabine, cytarabine, liposomal doxorubicin, FU, and docetaxel.[15-20]**[Fig 7]**

Conclusion

Antineoplastic agents lead to various cutaneous adverse reactions pertaining to skin, hair and nail changes. Some of them are specific to certain drugs and drug regimens. Proper understanding of these adverse reactions will help clinicians and dermatologists in early detection, timely management and proper counselling of cancer patients regarding the same. This will help in improving the quality of life and reduce the psychological trauma of such patients. Limitation of our study was that we had limited number of sample size.

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Figure legends

Figure 1 Distribution of carcinoma according to their age and gender (N=100)

Figure 2 [a] Patient developed anagen effluvium after 2nd cycle of pacitaxel, cyclophosphamide, epirubicin drug regimen and **[b]** after 3rd cycle of cyclophospamide infusion

Figure 3 Matted mass of hair (Plica Polonica) in occipital area with non cicatricial hair loss in middle of the scalp after 2nd cycle of paclitaxel and carboplatin drug regimen

Figure 4 Gray-black diffuse Hyperpigmentation of face involving forehead, eyelids, nasal bridge, cheeks and perioral region

Figure 5 (a) showing Nail hyperpigmentation in all finger nails along with Acquired Icthyosis on both dorsum of hands **(b)** all Nails of hands and feet showing Hyperpigmentaion and brittleness

Figure 6 Infusion site reaction: development of erosion and hemorrhagic crust along with blackening and painful swelling of surrounding skin over right lower end of dorsal forearm after infusion of vincristine + donorubicin + methotraxate regimen

Figure 7 hand-foot syndrome: cutaneous desquamation with diffuse erythema over both soles after 3rd cycle of triptorelin+ denosumab+rebociclib regimen

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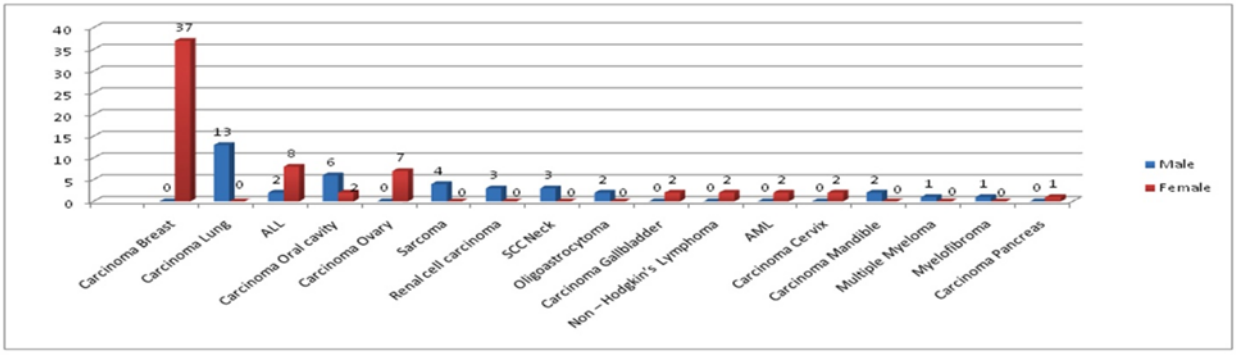
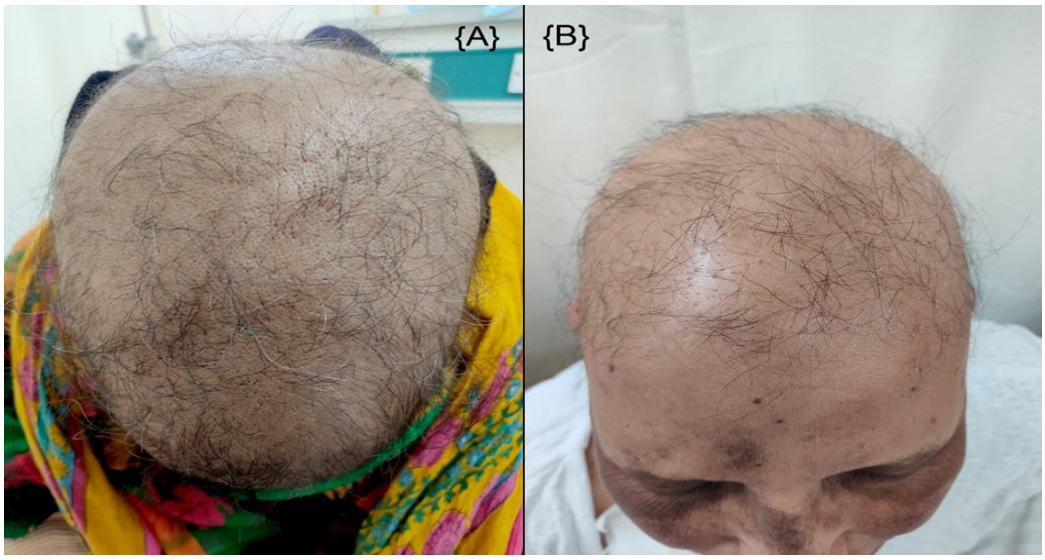


ALL : Acute lymphoblastic leukemia , SCC : Squamous Cell Carcinoma , AML: Acute Myeloid Leukemia



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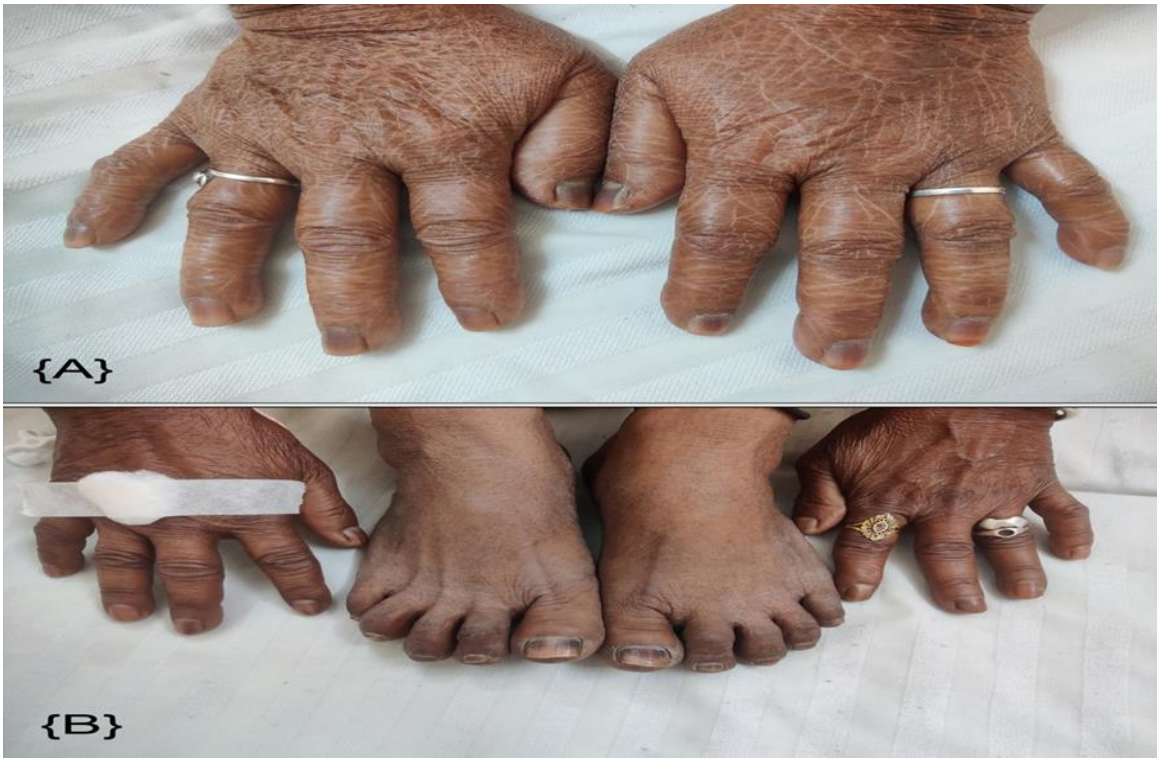

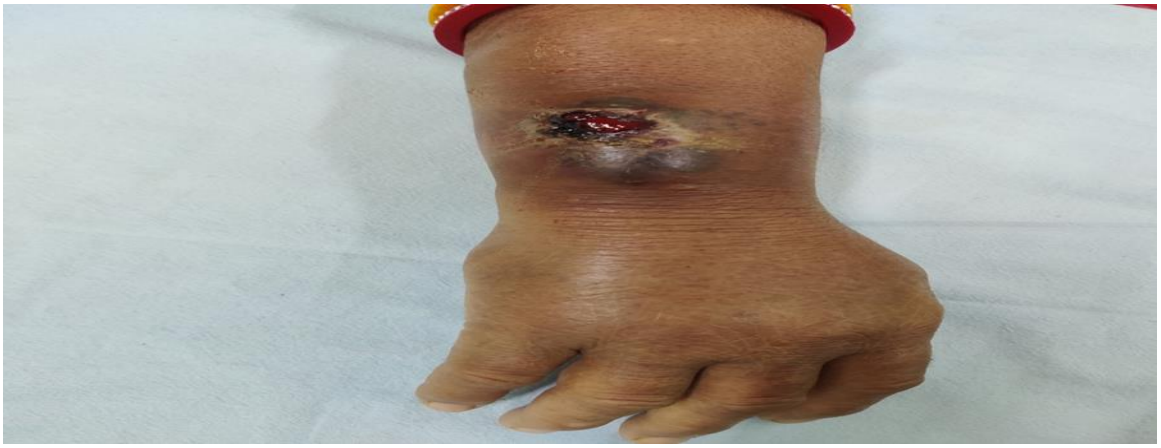

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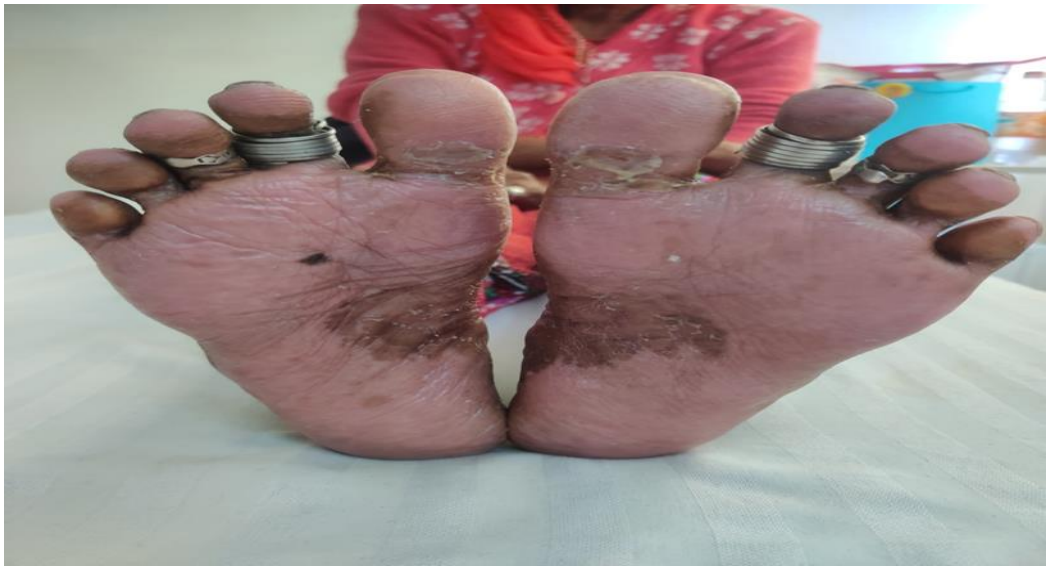

Table legends

Table 1 Distribution of cancer subjects according to their gender (N=100)
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Table 4 Cutaneous adverse reactions to single drug regimen

Table 1 Distribution of cancer subjects according to their gender (N=100)

Age group (years)	Male (n=37)		Female (n=63)		Total		χ^2	P – value
	Frequency	%	Frequency	%	Frequency	%		
0-20	2	5.40	4	6.34	6	6	0.0368	0.8478
21-40	11	29.72	10	15.87	21	21	2.6978	0.1004
41-60	14	37.83	28	44.44	42	42	0.4177	0.5181
> 60	10	27.02	21	33.33	31	31	0.4334	0.5103

Table 2 Frequency and prevalence of Cutaneous Adverse Reactions

S.No.	Type of adverse reactions	Total no. of Cases	Percentage
1	Anagen Effluvium	50	26.04
2	Xerosis	32	16.66
3	Skin Hyperpigmentation	26	13.54
4	Nail Pigmentation	20	10.41

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5	Skin Desquammation	16	8.33
6	Infusion Site Reaction	10	5.20
7	Brittle Nails & Nail Dystrophy	8	4.16
8	Acquired Icthyosis	6	3.12
9	Hemorrhagic Onycholysis	6	3.12
10	Skin Erythema	4	2.08
11	Madarosis	4	2.08
12	Maculopapular Rash	4	2.08
13	Acnefrom Eruption	2	1.04
14	Hand-Foot syndrome	2	1.04
15	Matting & Uncombable Hair (Plica Polonica)	1	0.52
16	Graying of Hair	1	0.52
	TOTAL Cases	192	100

Table 3a Skin related adverse reacctions due to multiple drug regimen

S.No.	Name of adverse reaction	Drug Regimen	Adverse reaction cases	Total no. of cases	Percentage
A	Xerosis	paclitaxel, cyclophosphamide, epirubicin	6	16	37.5
		paclitaxel, carboplatin	8	15	53.33
		docetaxel, cisplatin	4	4	100
		cisplatin, gemcitabine	2	2	100
		docetaxel, cisplatin, 5 florouracil	2	6	33.33
		vincristine, donorubicin, methotraxate	2	4	50
		paclitaxel, gemcitabine	1	1	100
		triptorelin, denosumab, rebociclib	2	2	100
		bortezumab, denosumab	1	1	100
B	Skin pigmentation	paclitaxel, carboplatin	8	15	53.33
		paclitaxel, trastazumab, cyclophosphamide,	3	4	75

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		epirubicin			
		paclitaxel, carboplatin,bevacizumab	2	2	100
		nevolumab, cabozantinib	2	2	100
		docetaxel, cisplatin, 5 florouracil	4	6	66.66
		triptorelin, denosumab, rebociclib	2	2	100
		bortezumab, denosumab	1	1	100
C	Infusion site reaction	paclitaxel, cisplatin, iphosphamide	2	2	100
		azacitidine, sorefenib	2	2	100
		vincristine, donorubicin, methotraxate	3	4	75
		bortezumab, denosumab	1	1	100
D	Acquired Icthyosis	carboplatin, bevacizumab	3	4	75
		docetaxel, cisplatin, 5 florouracil	2	6	33.33
		cyclophosphamide, 6 Mercaptopurine, cytarabine, methotraxaate	1	1	100
E	Skin Desquammation	paclitaxel, carboplatin	6	15	40
		docetaxel, gemcitabine	2	2	100
		cyclophosphamide, doxorubicin, rituximab, vincristine	2	2	100
		paclitaxel, gemcitabine	1	1	100
		bortezumab, denosumab	1	1	100
F	Skin Erythema	docetaxel, gemcitabine	2	2	100
		docetaxel, cisplatin, 5 florouracil	2	6	33.33
G	Acne Form Eruption	temozolamide and lopasamide	2	2	100
H	Hand-Foot syndrome	triptorelin, denosumab, rebociclib	1	2	50

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Table 3b Hair and Nail related adverse reactions due to multiple drug regimen

S.No.	Name of adverse reaction	Drug Regimen	Adverse reaction cases	Total no. of cases	Percentage
A	Anagen Effluvium	paclitaxel, cyclophosphamide, epirubicin	13	16	81.25
		paclitaxel, carboplatin	10	15	66.66
		docetaxel, cisplatin, 5 florouracil	6	6	100
		vincristine, donorubicin, methotraxate	2	4	50
		docetaxel, cisplatin	2	4	50
		cisplatin, gemcitabine	2	2	100
		paclitaxel, carboplatin,bevacizumab	2	2	100
		vincristine, adriamycin, cisplatin, iphosphamide, etoposide	2	2	100
		docetaxel, gemcitabine	2	2	100
B	Nail pigmentation	paclitaxel, cyclophosphamide, epirubicin	7	16	43.75
		paclitaxel, carboplatin	5	15	33.33
		paclitaxel, trastazumab, cyclophosphamide, epirubicin	2	4	50
		cisplatin, gemcitabine	2	2	100
C	Nail Dystrophy & Brittle Nails	paclitaxel, carboplatin	4	15	26.66
		paclitaxel, carboplatin,bevacizumab	2	2	100
D	Hemorrhagic Onycholysis	paclitaxel, carboplatin	4	15	26.66
		paclitaxel, trastazumab, cyclophosphamide, epirubicin	2	4	50
E	Matting & Uncombable Hair (plica polonica)	paclitaxel, carboplatin	1	15	6.66

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Table 4 Cutaneous adverse reactions to single drug regimen

S.No.	Name of Adverse reaction	Name of Drug	Adverse reaction Cases	Total no. of Cases	Percentage
A	Anagen Effluvium	Paclitaxel	5	6	83.33
		Cyclophosphamide	2	5	40
		Cisplatin	2	3	66.66
B	Nail Pigmentation	Paclitaxel	4	6	66.66
C	Nail Dystrophy & Brittle Nails	Cyclophosphamide	1	5	20
		Trastazumab	1	2	50
D	Graying of Hair	Sunitinib	1	1	100
E	Skin Desquammation	Paclitaxel	2	6	33.33
		Ruxolitinib	2	2	100
F	Skin Hyperpigmentation	Paclitaxel	4	6	66.66
		Capecitabine	2	4	50
G	Xerosis	Cyclophosphamide	2	5	40
		Capecitabine	2	4	50
H	MaculoPapular Rash	Capecitabine	1	4	25
		Methotrexate	1	1	100
I	Infusion Site Reaction	Cyclophosphamide	2	5	40
J	Hand-foot syndrome	Capecitabine	1	4	25