THE PROSPECTIVE OBSERVATIONAL STUDY ON CUTANEOUS ADVERSE DRUG REACTIONS TO CHEMOTHERAPY

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ABSTRACT

INTRODUCTION

There are a wide spectrum of adverse cutaneous drug reactions (ACDRs) varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN). With the advent of newer and targeted therapy in the field of dermatology, the pattern of cutaneous adverse drug eruptions and the drugs responsible for them keep changing every year. Hence, this study was undertaken to ascertain the clinical spectrum of ACDRs and the causative drugs, in a tertiary care centre in South India.

MATERIALS AND METHODS

This study was a prospective, observational study conducted in Department of Medical Oncology, Government Rajaji Hospital, Madurai Medical College, Madurai during the period of March 2015 - August 2015 (6 months). Severity of the reaction was assessed using CTCAE (Common Terminology Criteria for Adverse Events) scale version 4.1. Causality of the drug was assessed using Naranjo Causality Assessment Scale. The scale was calculated first for the regimen and then for individual drugs separately. The adverse events with score of 6 or more (probable and definite adverse events) were taken for the study.

RESULTS AND CONCLUSION

The overall incidence of ACDRs found in this study was 85%. Alopecia was the commonest ACDR occurring in 51.6% of patients. Nail pigmentation and supravenous pigmentation were the next common ACDRs, recorded in 35% and 16% of patients respectively. Imatinib caused generalised hypopigmentation in 40% of patients. Bleomycin induced, flagellate erythema and pigmentation in 17% of patients and stomatitis was seen in 11% of patients. Acneiform eruptions were recorded with erlotinib and gefitinib therapy. Supravenous pigmentation was common with 5-fluorouracil and docetaxel, occurring in 53% & 48% respectively. Newer targeted therapies like EGFR (Epidermal growth factor receptor) inhibitors recorded low incidence of ACDRs like alopecia as against conventional antineoplastic agents. The cancer chemotherapeutic drugs are associated with varied adverse effects. Knowledge of these drug eruptions, the causative drugs and the prognostic indicators are essential for the treating clinician.

KEYWORDS

Chemotherapy, Adverse Cutaneous Drug Reaction.

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INTRODUCTION: An adverse drug reaction (ADR) is defined by World Health Organization (WHO) as "Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy."[(1)] Antineoplastic agents are defined as substances that inhibit or prevent the proliferation of neoplasms. Many of the adverse effects of antineoplastic are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells.

The skin, mucous membranes, adnexa, hair and nails are tissues with rapid cellular proliferation, and thus susceptible to adverse reactions (Toxic or hypersensitive) resulting from systemic chemotherapeutic treatment.

Some dermatologic reactions to new antineoplastic agents, such as epidermal growth factor receptor inhibitors, are considered to be surrogate markers of antitumoural efficacy.

A recent study from a South Indian tertiary care teaching hospital on pattern of adverse drug reactions has reported Dermatological system (23.5%) as the most commonly affected organ system with Antineoplastic agents (21.8%) as the drug class most commonly involved.[(2)]

There is a wide spectrum of cutaneous adverse drug reactions varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN).[(3)] With the advent of newer drugs for chemotherapy, the pattern of cutaneous adverse drug eruptions and the drugs responsible for them keep changing every year. Hence, this study was undertaken to ascertain the clinical spectrum of ACDRs and

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the causative drugs, in a tertiary care centre in South India.

MATERIALS AND METHODS: This study was a prospective, observational study conducted in Department of Medical Oncology, Government Rajaji Hospital, Madurai Medical College, Madurai during the period of March 2015 - August 2015 (6 months). Approval from institutional ethical committee was obtained before starting the study. Informed consent was obtained from all patients before enrolling them for the study.

Inclusion Criteria: All patients admitted in Medical Oncology Department, Government Rajaji Hospital during the study period were included in the study.

Exclusion Criteria: Patients who have undergone radiotherapy during the past 3 months and who are currently on radiotherapy were excluded from the study.

Patients satisfying the inclusion criteria were enrolled in the study and demographic details were recorded. Diagnosis and regimen of chemotherapy given were noted. A detailed clinical history and examination was done and all the Adverse Cutaneous Drug Reactions (ACDRs) which occurred were noted according to predesigned proforma. Severity of the reaction was assessed using CTCAE (Common Terminology Criteria for Adverse Events) scale version 4.1. Causality of the drug was assessed using Naranjo Causality Assessment Scale. The scale was calculated first for the regimen and then for individual drugs separately. The adverse events with score of 6 or more (probable and definite adverse events) were taken for the study.

OBSERVATIONS AND RESULTS:

1. **Total incidence of ACDRs:** Out of total 281 patients, who received chemotherapy during the study period of 6 months, 243 patients had at least one ACDR. The overall incidence of ACDRs in this study was found to be 86%

Sl.No.	Total Patients in Study	No. of Patients Having At least one ACDR	No. of Patients Having no ACDR
1	281	243(86.48%)	38(13.53%)
Table I			

2. **Occurrence of various clinical types of ACDRs:**

Sl. No.	Adverse event	No.	Percentage
1	Alopecia	145	51.60%
2	Nail pigmentation	98	34.87%
3	Supravenous pigmentation	45	16.01%
4	Melasma	32	11.38%
5	Mucositis	22	15.17%
6	Mucosal pigmentation	15	5.33%
7	Peripheral neuropathy	12	4.27%

3. **ACDRs Occurring in Various Regimens:**

A. Doxorubicin/cyclophosphamide regimen:

Sl. No.	ACDR	No. of patients	Percentage
1	Alopecia	68	93.1
2	Nail pigmentation	55	75.34
3	Mucositis	5	6.84
4	Mucosal pigmentation	10	13.69
5	Palmoplantar pigmentation	18	24.65
Table II: Total Patients who received Doxorubicin/Cyclophosphamide Regimen - 73			

B. ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) regimen:

Sl. No.	ACDR	No. of patients	Percentage
1	Alopecia	7	70
2	Nail pigmentation	6	60
3	Peripheral Neuropathy	3	30
4	Supravenous pigmentation	3	30
5	Mucosal pigmentation	2	20
6	Melasma	1	10
7	Acanthosis Nigricans	1	10
8	Lichenoid Drug Reaction	1	10
9	Streaky Hyper pigmentation	1	10
10	Palmoplantar Pigmentation	1	10
Table III: ABVD Regimen (Total Patients 10)			

C. R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, prednisolone) regimen:

Sl. No.	ACDR	No. of Patients	Percentage
1	Alopecia	3	60
2	Nail pigmentation	2	40
3	Mucositis/stomatitis	1	20
4	Peripheral neuropathy	1	20
5	Palmoplantar pigmentation	1	20
Table IV: Total patients 5			

4. **Adverse cutaneous reactions to specific drugs:**

Sl.No.	ACDR	No. of Patients	Percentage
1	Alopecia	4	23.52
2	Flagellate erythema	3	17.64
3	Mucositis	2	11.76
4	Lichenoid drug reaction	1	5.88
Table V: Bleomycin Total Patients 17			

D. Carboplatin: Twenty four patients received chemotherapy with carboplatin and 1 patient developed a maculopapular rash with carboplatin. No other adverse cutaneous drug reaction was noted with carboplatin.

E. Cyclophosphamide:

Sl.No.	ACDR	No. of patients	Percentage
1	Alopecia	78	83.87
2	Nail pigmentation	61	65.59
3	Palmoplantar pigmentation	23	24.73
4	Mucosal pigmentation	12	12.9
5	Mucositis	12	12.9

Table VI: Total Patients who received Cyclophosphamide: 93

F. Docetaxel:

Sl.No.	ACDR	No. of patients	Percentage
1	Supravenous discoloration of skin	16	48.48
2	Eczema at site of extravasation	9	27.27
3	Horizontal banding of nails	2	6.06
4	Thrombophlebitis	1	3.03

Table VII: Total Patients who received Docetaxel – 33

G. Doxorubicin:

Sl.No.	ACDR	No. of patients	Percentage
1	Alopecia	78	80.41
2	Nail pigmentation	69	71.13
3	Palmoplantar pigmentation	28	28.86
4	Mucosal pigmentation	11	11.34
5	Mucositis	9	9.27

Table VIII: Total Patients who received Doxorubicin – 97

H. Etoposide: Nineteen patients received etoposide of whom 12 patients developed alopecia (63.15%). No other cutaneous adverse effects were noted with etoposide.

I. Gefitinib:

Sl.No	ACDR	Total no. of patients	Percentage
1	Ichthyosis/xerosis	2	50
2	Facial melanosis	2	50
3	Mucositis/stomatitis	2	50
4	Peripheral neuropathy	1	25
5	Acneiform eruptions	1	25

Table IX: Total Patients who received Gefitinib– 4

J. Gemcitabine: Nine patients received chemotherapy with gemcitabine of whom alopecia was seen in 2 (22.22%) patients. No other cutaneous adverse effect was noted with gemcitabine use.

K. 5-Fluorouracil:

Sl. No.	ACDR	Total no. of patients	Percentage
1	Supravenous pigmentation	33	53.22
2	Mucositis/stomatitis	6	9.67
3	Nail pigmentation	5	8.06
4	Hand foot syndrome	2	3.22
5	Plica polonica	2	3.22
6	Nail pitting & banding	1	1.61
7	Alopecia	1	1.76
8	Palmoplantar pigmentation	1	1.67

Table X: Total Patients who received 5-fluorouracil – 62

L. Imatinib:

Sl.No.	ACDR	Total no. of patients	Percentage
1	Melasma	26	56.52
2	Generalised hypopigmentation	17	39.95
3	Lichenoid eruption	3	6.52
4	Prurigo nodularis	1	2.17
5	Pyoderma	1	2.17
6	Peripheral neuropathy	1	2.17
7	Horizontal banding of nails	1	2.17
8	Angular cheilitis	1	2.17
9	Pompholyx	1	2.17

Table XI: Total Patients who received Imatinib – 46

M. Paclitaxel:

Sl.No.	ACDR	Total no. of patients	Percentage
1	Alopecia	31	67
2	Peripheral neuropathy	5	10.86
3	Plica polonica	1	2.17

Table XII: Total Patients who received Paclitaxel- 46

N. Sorafenib:

Sl.No.	ACDR	Total no. of patients	Percentage
1	Ichthyosis	1	25
2	Acneiform eruptions	1	25
3	Hidradenitis suppurativa	1	25
4	Mucositis/stomatitis	1	25
5	Hand foot syndrome	1	25
6	Superficial folliculitis	1	25
7	Melasma	1	25

Table XIII: Total Patients who received Sorafenib – 4

DISCUSSION:

1. **Total incidence of ACDRs:** Out of total 281 patients who received chemotherapy during the study period of 6 months, 243 patients had at least 1 ACDR. The overall incidence of ACDRs in this study was found to be 86.48%. The incidence of ACDRs has been found to be 86.53% by a study done by Prasad et al which matches with that of our study.[4]

2. **Occurrence of various clinical types of ACDRs:** The commonest ACDR in our study is alopecia seen in 145 patients (51.60%) which is lower than that reported by Treub et al (65%).[5] The next common ACDR encountered was nail pigmentation seen in 98 patients (34.87%). It was seen as a dark pigmentation of nails observed as diffuse, transverse, or longitudinal band patterns similar to Dasanu et al study.[6] These nail changes were asymptomatic and resolved with completion of therapy; further, they did not require treatment as observed in another study by Dasanu et al.[7] Supravenous pigmentation was seen in 45 patients (16.1%). It was observed frequently with 5-fluorouracil and docetaxel. The pigmentation persisted for a few months after discontinuation of therapy. It was asymptomatic. The incidence observed in our study is higher than that reported by Hrushesky et al where it was 5%.[8] Mucositis was seen in 22 patients (16.7%) which is lower than that encountered (20%) in the study done by McGowan et al.[9] The mucositis was more severe on the second day of infusion and got better by 1 week. Peripheral neuropathy was seen in 12 patients (4.27%) It is comparable to the study done by Picollo et al were it was 5.2%.[10] The patients experienced severe burning sensation and pain over their feet. Two patients needed intervention, and in 1 patient paclitaxel was stopped and was shifted to alternate regimens due to the severity of the reaction.

3. **ACDRs occurring in various regimens:**
   - **A. Doxorubicin/Cyclophosphamide regimen:** Out of 73 patients, 68 patients (93.1%) developed generalised alopecia involving the scalp. Both the drugs doxorubicin and cyclophosphamide are known to cause alopecia and when given in combination the incidence of alopecia increases.[11] The alopecia is usually reversible after discontinuation of therapy. 18 patients (24.65%) developed palmoplantar pigmentation which was diffuse, Addisonian like pigmentation. This is greater than that found in the study done by Harrison et al which showed 18% of palmoplantar pigmentation.[12] Mucositis was seen in 5 patients (6.845) which was comparable to the study done by Pavey et al.[13]
   - **B. ABVD Regimen:** Out of total 10 patients who received these regimen, 3 patients (30%) developed peripheral neuropathy. Peripheral neuropathy in ABVD regimen is most commonly due to vinblastine. Patients experienced burning sensation over both feet accompanied by tingling and numbness sensation. This is less than the incidence found in the study done by Hausheer et al.[14] The symptoms were mild in all 3 patients and the regimen was continued without interruption. All 3 patients were managed symptomatically. Alopecia was noticed in 70% of patients in our study which is comparable to the study done by Treube et al where it was 65%.[5]
   - **C. R-CHOP Regimen:** Out of 5 patients who received R-CHOP regimen, 3 patients developed alopecia (60%). This correlates with the study done by Ahmed et al.[15]

4. **Adverse cutaneous reactions to specific drugs:**
   - **A. Bleomycin:** A total of 17 patients received bleomycin of whom 3 patients had flagellate erythema involving the trunk. The pigmentation was streaky in nature. Similar pigmentation has been recorded with bleomycin by Polla et al.[16] One patient developed lichenoid skin lesions. Similar pattern of drug reaction has been recorded in the study done by Cohen et al.[17]
   - **B. Carboplatin:** With carboplatin one patient developed maculopapular exanthema accounting for 4.17%. This is less when compared with the study done by Zorzou et al which showed an incidence of 10%.[18]
   - **C. Cyclophosphamide:** A total of 93 patients received chemotherapy with cyclophosphamide. Alopecia was seen in 78 patients (83.87%). This is higher when compared with the study done by Ahmed et al.[15] Nail pigmentation is seen in 61 patients (65%), which is comparable to the study done by Harrisson et al, where it was 61%.[12] Mucositis was observed in 12 patients with cyclophosphamide and it is similar to the study done by McGowan et al.[9] Palmoplantar pigmentation was seen in 24% of patients in our

study which is a little higher when compared to the study done by Harrison et al.[12]

D. Docetaxel: A total of 33 patients received docetaxel of whom 16 patients (48%) developed supravenous pigmentation. This is comparable to the study done by Schrijvers et al where it was 46%.[19] Horizontal banding of nails was seen in 2 patients (6%) which is less when compared with the study done by Pavithran et al where it was 10%.[20] At the extravasation site, 9 patients developed an eczematous reaction which subsided over a period of 3-6 days. Similar reaction was recorded in the study done by Zimmermann et al.[21]

E. Doxorubicin: A total of 97 patients received doxorubicin of whom 78 patients (80%) developed alopecia. This is similar to the study by Trebe et al where it occurred in 82% of patients.[5] Nail pigmentation was seen in 69% and mucosal pigmentation in 11%. This is comparable to the study done by Curran et al where it was 67% and 12% respectively. [22]

F. Etoposide: Nineteen patients received etoposide of whom 12 patients developed alopecia (63.15%). No hypersensitivity reactions were noted with etoposide as seen in other studies.[23]

G. Gefitinib: Four patients were treated with gefitinib of whom 1 patient developed severe peripheral neuropathy. Two patients had oral ulcers, 2 patients developed acneiform eruptions over trunk and upper limbs and ichthyosis was noticed in 2 patients. Acneiform eruptions occurring with targeted therapy was well documented in various studies as seen by the study by Boone et al.[24]

H. Gemcitabine: A total of 9 patients were treated with gemcitabine of whom 2 patients had alopecia. This is high when compared to the study done by Tonato et al where it was only 0.5%.[25]. But that study included only WHO stage 3 alopecia where as we included all stages of alopecia and that could probably have caused the difference.

I. 5-Fluorouracil: A total of 62 patients received chemotherapy with 5-fluorouracil. Supravenous pigmentation was noticed in 33 patients (53.2%). This is high when compared to the study done by Hrushesky et al where it was seen only in 38% of patients.[26]Stomatitis was seen in 9% patients in our study whereas it was recorded in 12% of patients in the study done by McGowan et al.[9] Hand-foot syndrome developed in 2 patients (3.22%) which is similar to the study done by Feldman et al.[27]

J. Imatinib: A total of 46 patients received chemotherapy with imatinib. A generalised hypopigmentation was noticed by 39% of patients at some point of treatment. It improved with continuation of therapy. When compared with the study done by Sharma et al our study has registered only a lower percentage.[28] In their study, generalised hypopigmentation was seen in more than 50% of patients. Melasma was noticed in 56% of people in our study and it was comparable to the study done by Scheinfeld et al, where it was seen in 53% of patients.[29] Lichenoid eruption was noticed in only 6.5% of patients in our study whereas it was noticed in 10% of patients in the study done by Ena et al.[30]

K. Paclitaxel: A total of 46 patients received chemotherapy with paclitaxel. Alopecia and peripheral neuropathy were the major cutaneous adverse events encountered with paclitaxel therapy. Alopecia was seen in 67% of patients who received paclitaxel therapy. This is higher when compared with the study done by Gelmon et al where it was seen in 58% of patients only.[31] Peripheral neuropathy occurred in 10% of patients and it was comparable to the study done by Onetto et al where it was seen in 11% of patients.[32] Paclitaxel was discontinued in 1 patient because of peripheral neuropathy.

L. Sorafenib: A total of 4 patients were treated with sorafenib. Hand-foot syndrome developed in 1 patient and another patient developed acneiform eruptions and hidradenitis suppurativa. The incidence was higher when compared with other studies probably due to less number of patients treated.[33]

CONCLUSION: The overall incidence ACDRs found in this study was 85%.

Alopecia was the commonest ACDR occurring in 51.6% of patients. Nail pigmentation and supravenous pigmentation were the next common ACDRs recorded in 35% and 16% of patients respectively. Mucositis occurred in 15% of patients. Peripheral neuropathy occurred in 4% of patients.

Among various regimens, doxorubicin & cyclophosphamide regimen recorded highest incidence of alopecia occurring in 93% of patients. Palmoplantar pigmentation was also highest in this regimen occurring in 25% of patients. But supravenous pigmentation was higher in 5-fluorouracil containing regimens. Peripheral neuropathy was common among paclitaxel containing regimen and ABVD regimen.

Imatinib caused generalised hypopigmentation in 40% of patients. Paradoxically, melasma was noticed in 56% of patients on imatinib therapy. In contrast to generalised hypopigmentation which resolved spontaneously on continuation of therapy, melasma was stable. Lichenoid eruption was also commonly noted in imatinib in 6.5% of patients. Peripheral neuropathy occurred commonly in paclitaxel therapy (10%).

Bleomycin induced flagellate erythema was seen in 17% of patients and stomatitis in 11% of patients. Acneiform eruptions were recorded with erlotinib and gefitinib therapy.

Supravenous pigmentation was common with 5-fluorouracil and docetaxel occurring in 53% & 48% respectively. In addition, 5-fluorouracil caused stomatitis in 9% of patients and docetaxel induced an extravasation reaction in 27% of patients.

Appendix: Naranjo Causality Scale (adapted).

1. Are there previous conclusive reports on this reaction?
   Yes (+1), No (0), Do not know or not done (0).

2. Did the adverse event appear after the suspected drug was given?
   Yes (+2), No (-1) Do not know or not done (0).

3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
   Yes (+1), No (0), Do not know or not done (0).

4. Did the adverse reaction appear when the drug was readministered?
   Yes (+2), No (-1), Do not know or not done (0).

5. Are there alternative causes that could have caused the reaction?
   Yes (-1), No (+2), Do not know or not done (0).

6. Did the reaction reappear when a placebo was given?
   Yes (-1), No (+1), Do not know or not done (0).

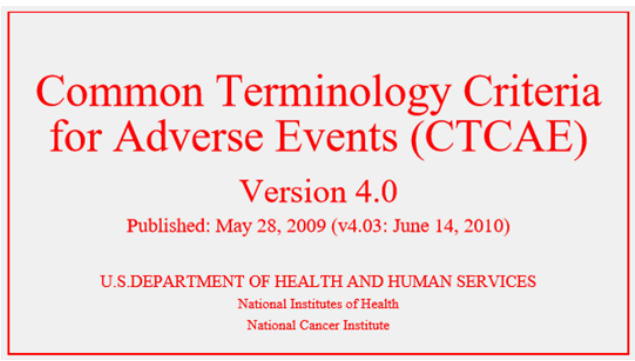
7. Was the drug detected in any body fluid in toxic concentrations?
   Yes (+1), No (0), Do not know or not done (0).

8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?
   Yes (+1), No (0), Do not know or not done (0).

9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
   Yes (+1), No (0), Do not know or not done (0).

Scoring:

> 9 = definite ADR.
5-8 = probable ADR.
1-4 = possible ADR.
0 = doubtful ADR.
Naranjo et.al. ClinPharmacol Ther. 1981 Aug;30(2):239-45.



Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					

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