



## Pattern of Adverse Drug Reactions of Various Chemotherapeutic Agents in Cancer Patients in Kumaun Region

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### Abstract

**Aim/Objective:** To assess the ADRs due to cancer Chemotherapy in the tertiary care hospital in Kumoun region

**Materials and Methods:** It was a retrospective study conducted from ADR reporting form. The Study was conducted at the tertiary care centre at Dr. Sushila Tiwari Government Medical College Hospital & Swami Ram Cancer Institute Haldwani Nainital. The data was obtained from suspected ADRs reporting forms, between August 2015 to July 2016, from the Radiotherapy department to the ADRs monitoring centre attached to department of Pharmacology under the Pharmacovigilance programme of India (PvPi). The reported ADRs were assessed for causality using both WHO causality assessment scale and Naranjo's algorithm. The severity was assessed using Hartwig and Siegel scale

**Results:** 187 ADRs were reported from 65 ADR Forms. Most common age group in which the patients had ADRs was 50-59 yrs 36.92% followed by 50-59 yrs 23.07%. The most common cancer diagnosed were bronchogenic 21.53%, followed by carcinoma breast 18.46% and larynx 15.38% carcinoma cervix 7.69%, carcinoma nasopharynx and esophagus 6.15%. Most common occurring ADRs were nausea and vomiting 17.11%, headache 8.02%, Anxiety 6.95%, Dizziness 6.95%, Fever 5.88% and Elevated liver enzymes 3.20%. WHO causality scale indicated 59.89% of the reactions were "possible" and 40.10% "probable". 62.56% were "moderate" followed by "mild" 34.75% and "severe" 2.67%. Platinum compounds Cisplatin (40.00%) and Carboplatin (24.61%) followed by cyclophosphamide (7.69%) were the most frequent drugs causing ADRs

**Conclusion:** Cancer chemotherapeutic agents have a very high risk of ADR therefore there is a need for prompt detection of ADRs to decrease morbidity and mortality. Rational and judicious use of medicine and adapting preventive measures will reduce the burden of ADRs in the society and benefit mankind.

## Introduction

Adverse drug reaction (ADRs) are the leading cause of morbidity and mortality. It is defined by World Health Organization (WHO) as “Any responses to a drug which is noxious unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy.”<sup>[1]</sup> Thus considering the importance of monitoring ADRs, to improve health and minimize these adverse effects Pharmacovigilance programme of India (PvPI) was started in 2010 by Ministry of Health and Family Welfare, Government of India. Under this programme, ADR monitoring centers have been started in many medical colleges and hospitals all over the country. Pharmacovigilance (PV) is defined as the science and activities relating to the detection assessment understanding and prevention of adverse drug reactions or any drug related problems<sup>[2]</sup>

ADR may result in decreased quality of life, increased cost of treatment hospitalization, minor and major disabilities and even death. The occurrence of ADR is a price that our patients pay for the great benefits that the modern medicines produce, therefore early detection of these ADR is now mandatory by the regulatory authorities.

Use of polypharmacy, irrational prescribing, lack of knowledge and multiple chronic illness have increased the risk of ADRs making and prevention and detection more difficult. Therefore, the fundamental duty of Health Care professional (HCP) is actual detection, reporting and resolution of the drug related ADRs. With the marketing of thousands of drugs every year and enthusiastic prescription, it is important that we identify and prevent these, as far as possible, for the well being of the patients and society at large.

With rapid advances in the medical sciences, treatment of many cancer are no longer only palliative but rather curative. Chemotherapy is employed as multimodal approach to the treatment of many tumors. Chemotherapeutic drugs very often show ADRs. Nausea, Vomiting, bone marrow suppression, alopecia, neuropathy are very common ADRs<sup>[3]</sup>. Drugs like Cisplatin,

Cylophos phamide, 5-fluoro-uracil etc are some of the potent drugs with high toxicity rates. Many of the ADRs can be prevented or minimized by due diligence. So ADR monitoring becomes an important tool to detect uncommon and sometimes serious ADRs ensuring patients safety.<sup>[4,5]</sup>

Hence we conducted this study to assess the ADRs due to cancer Chemotherapy in the tertiary care hospital in Kumoun region

## Material and Methods

**Study Area:** The Study was conducted at the tertiary care centre at Dr. Sushila Tiwari Government Medical College Hospital & Swami Ram Cancer Institute Haldwani Nainital. Approval of the Institutional Ethical Committee was Obtained for the study.

**Study Period and Study Population:** The data was obtained from suspected ADRs reporting forms, between August 2015 to July 2016, from the Radiotherapy department to the ADRs monitoring centre attached to department of Pharmacology under the Pharmacovigilance programme of India (PvPi)

**Study Design:** It was a retrospective study conducted from ADR reporting form, reported from Radiotherapy department, who were treated with anti-neoplastic drugs during study period.

The demographic details of the patients were recorded. Details of medication given were also noted. Chief Complaint, past history, drug history were also recorded. Details about the occurrence and nature of ADRs, severity, de challenge and rechallenge were recorded. Concomitant medications administered were also obtained. Relevant laboratory investigations were also noted. Inclusion criteria- Patients of both sexes and all ages diagnosed with cancer and treated with chemotherapy for the same, developing at least one ADR during or after the treatment period were included in the study.

**Exclusion criteria:** Patients who developed ADRs due to fresh blood or blood products infusion or due to intentional or accidental

poisoning or history of drug abuse were excluded from the study [6].

**Study tool:** ADR reporting form designed by centre for Drug standard Control organization (CDSCO) was used to collect data. The reported ADRs were assessed for causality using both WHO causality assessment scale and Naranjo's algorithm [7]. The severity was assessed using Hartwig and Siegel scale [8]. The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and categorize into "Certain", "probable", "possible", "unlikely", "conditional", / "unclassified" and "unassessable" / "unclassifiable".

Naranjo's algorithm has 10 objective questions with three option for answer – yes, no and do not know. Scores are given accordingly and the causality is assessed as "definite", "probable", "possible", and "unlikely". The modified Hartwig and Siegel scale classifies severity as "mild", "moderate", and "severe". The data collected, analyzed using Microsoft excel and frequency and percentage were determined for each variable.

## Result

In the present study 187 ADRs were reported from 65 ADR Forms reporting to Swami Ram Cancer Institute. Out of these patients 70.76% were male and 32.30% were females. Most common age group in which the patients had ADRs was 50-59 yrs 36.92% followed by 40-49 yrs 23.07% and 60-69 yrs. 13.84%. Patients who smoked constituted around 27.69% whereas non-smokers 61.53% and ex. Smokers 10.76% constituted a larger proportion of the patients [Table-1].

**Table 1** Demographic Details of Patients

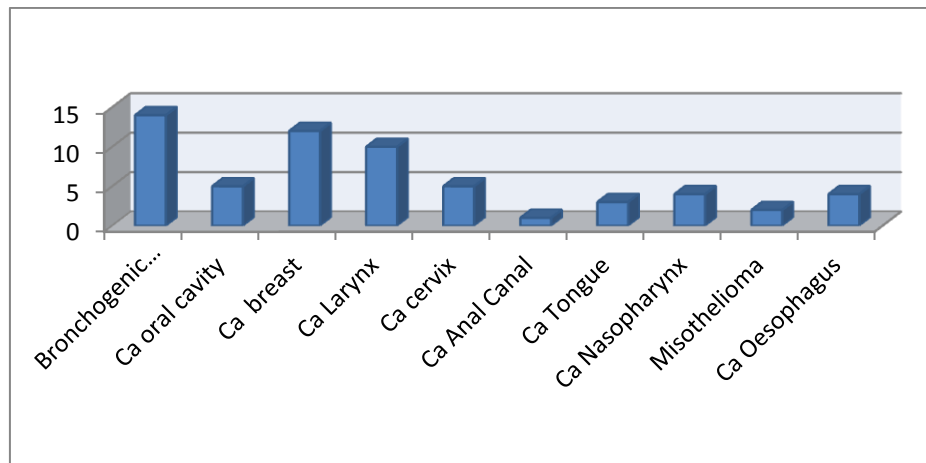
Variable	Number n=65	Percentage (%)
<b>Gender</b>		
Male	46	70.7
Female	21	32.3
<b>Age in Years</b>		
1-09	1	1.5
10-19	2	3.07
20-29	1	1.5
30-39	3	4.6
40-49	15	23.07
50-59	24	36.92
60-69	9	13.84
70 & above	10	15.38
<b>Smoking Status</b>		
Non-Smokers	40	61.53
Ex. Smoker	7	10.76
Current Smoker	18	27.69

The most common cancer diagnosed were bronchogenic 21.53%, followed by carcinoma breast 18.46% and larynx 15.38% carcinoma cervix 7.69%, carcinoma nasopharynx and esophagus 6.15% [Table-2 Fig. 1].

**Table 2** Distribution of Cancer (n=65)

Type of Cancer	Number (n=65)	Percentage (%)
Bronchogenic Carcinoma	14	21.53
Ca oral cavity	5	7.69
Ca breast	12	18.46
Ca Larynx	10	15.38
Ca cervix	5	7.69
Ca Anal Canal	1	1.53
Ca Tongue	3	4.61
Ca Nasopharynx	4	6.15
Misothelioma	2	3.07
Ca Oesophagus	4	6.15

Fig. 1 Distribution of Cancer



A total of 187 ADRs were identified and recorded. Most common occurring ADRs were nausea and vomiting 17.11%, headache 8.02%, Anxiety 6.95%, Dizziness 6.95%, Fever 5.88% and

Elevated liver enzymes 3.20%. Two patients reported anaphylaxis with breathing difficulties. [Table- 3].

Table 3. Pattern and causality assessment of Adverse Drug Reaction

Adverse Drug Reaction	Number of Drug Reaction					
	WHO causality			Naranjo Scale		
	Possible	Probable	Total	Possible	Probable	Total
Nausea / Vomiting	28	4	32	29	3	32
Diarrhea	5	0	5	1	4	5
Pain Abdomen	5	1	6	4	2	6
Gastritis	9	2	11	9	2	11
Constipation	0	7	7	3	4	7
Elevated Liver Enzymes	6	2	8	5	3	8
Leucocytopenia	10	6	16	10	6	16
Anemia	9	2	11	3	8	11
Thrombocytopenia	3	2	5	4	1	5
Rest lessness	0	8	8	2	6	8
Numbness of feet	2	3	5	0	5	5
Headache	11	4	15	11	4	15
Bodyache	0	9	9	1	8	9
Fever	10	1	11	9	2	11
Anxiety	0	13	13	12	1	13
Blurring of Vision	0	2	2	0	2	2
Restlessness	2	6	8	4	4	8
Dizziness	10	3	13	8	5	13
Anaphylaxis with difficulty in breathing	2	0	2	1	1	2
<b>Total</b>	<b>112</b>	<b>75</b>	<b>187</b>	<b>116</b>	<b>71</b>	<b>187</b>
<b>Percentage %</b>	<b>59.89</b>	<b>40.10</b>		<b>62.03</b>	<b>37.96</b>	

Assessment of the causality by WHO causality scale indicated 59.89% of the reactions were “possible” and 40.10% “probable”. There was no “certain” ADR as re-challenge was not attempted in any of the patient. According to Naranjo’s

algorithm 62.03% of the reactions were “possible” and 37.96% “probable”. [Table- 3].

The Severity of the reported ADRs were assessed by modified Hartwig and Siegel scale. 62.56% were “moderate ” followed by “mild ” 34.75% and “severe”2.67% [Table- 4].

**Table 4.**Severity of reported ADRs by Modified Hartvig and Siegel Scale (n=187)

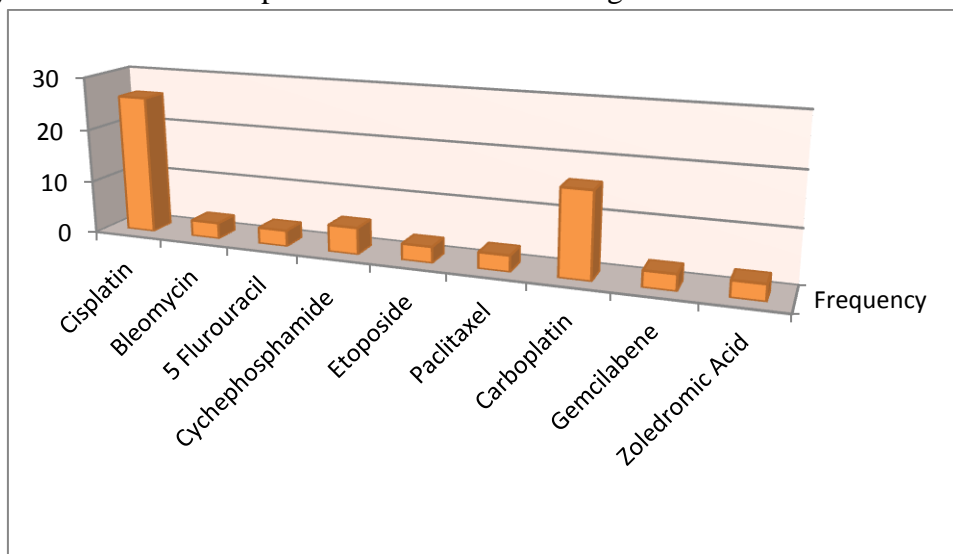
Severity of ADRs	No. of ADRs	% of ADRs
Mild	65	34.75
Moderate	117	62.56
Severe	5	2.67
Lethal	0	0

Platinum compounds Cisplatin (40.00%) and Carboplatin (24.61%) followed by cyclophosphamide (7.69%) were the most frequent drugs causing ADRs (Table-5 Fig. 2).

**Table 5.**Frequency Distribution of Suspected Medications Causing ADRs

Suspected Medication	Frequency	Percentage %
Cisplatin	26	40.0
Bleomycin	3	4.61
5 Flurouracil	3	4.61
Cycheosphamide	5	7.69
Etoposide	3	4.61
Paclitaxel	3	4.61
Carboplatin	16	24.61
Gemcilabene	3	4.61
Zoledromic Acid	3	4.61
Total	65	

**Fig. 2** Frequency Distribution of Suspected Medications Causing ADRs



The 187 ADRs were caused mostly by platinum compounds 54.01%, followed by cyclophosphamide 8.55% and 5 flurouracil 8.02% (Table-6).

**Table 6** Drugs responsible for ADR

Suspected Medicaiton	ADRs	Percentage %
Cisplatin	101	54.01
bleomycin	10	5.34
5-FU	15	8.02
Cyclophosphamide	16	8.55
Etoposide	7	3.74
Paclitaxel	4	2.13
Carboplatin	25	13.36
Gemcitabine	9	4.81
<b>Total</b>	<b>187</b>	

## Discussion

Our study evaluated the pattern of ADRs caused by cancer chemotherapy in a tertiary care teaching hospital of Kumoun region. The ADRs significantly affect the quality of life, increases hospitalization, prolongs hospital stay and increases mortality. Cancer chemotherapy have a significant number and type of adverse effect whose accurate documentation and reporting is very valuable<sup>[9]</sup>. This helps in safe, efficacious and rational use of medicine.

In our study 65 ADRs reporting forms were evaluated which contained 187 ADRs during the study period. We found that male and female ratio. This is consistent with some of the studies<sup>[10,11]</sup>

The increased incidences of the ADRs can be attributed to the fact that males are exposed more often to environmental toxins, Smoking, substance of abuse and occupational hazards. Most of the ADRs were seen in the patients in the age group of 50-59 yrs (36.92%) which was in agreement with the study done by Poddar et al and Prasad et al<sup>[12, 13]</sup>. This could be due to the sub optimal functioning of the vital organs like liver and kidney as the patient ages, cancer cachexia as well as decreased immunological profile among others, leading to increase risk of ADRs.

Majority of the patients 61.53% were nonsmokers. Similar results were reported by other studies<sup>[12, 14]</sup> Most common cancer diagnosed was Bronchogenic carcinoma 21.53%, Carcinoma breast 18.46%, followed by carcinoma larynx 15.38% and carcinoma cervix 7.69%. This was similar to other studies<sup>[12, 13]</sup> Malik et al and Poddar et al have reported lung and breast cancer as the most common<sup>[11,15]</sup> whereas Sunil Bellare et al reported oropharyngeal cancer as the commonest cancer reported<sup>[19]</sup>. Surindiran et al reported cervical cancer as the commonest cancer<sup>[16]</sup> The differences found in our study may be due to variation in geographic regions, food habits and life styles, occupational and environmental conditions

Commonest ADR reported in our study were nausea & vomiting 17.11% followed by Headache 8.02%, Anxiety and Dizziness 6.95%. Few other studies reported nausea & vomiting as the commonest ADR<sup>[17,18]</sup>. Cancer chemotherapy causes damage to rapidly dividing cells of the bone marrow and gastrointestinal epithelium. It also stimulates the chemoreceptor trigger zone causing increased incidences of nausea and vomiting. The causality assessment by both the scales, WHO-UMC system and Naranjo's ADR probability scale demonstrated that most of the reactions were "possible 59.89%; 62.03% followed by probable 40.10%; 37.96% respectively. There was no certain reaction as rechallenge was not done in any of the patient. Good correlation between the two scales of assessment was in agreement with Mittal et al and Sunil Bellary et al.<sup>[19,20]</sup> However few other studies reported poor correlation between the scales<sup>[20, 21]</sup> Causality assessment is to some extent subjective, so a definitive inferences may differ between two observer which was commented by other researchers as well<sup>[22, 23]</sup> Hartwig and Siegel scale assessed most of the reactions as "moderate" 62.56% followed by "mild" 34.75% and "severe" 2.67% and did not warrant withdrawal of the concerned drugs except in two patients who experienced features of anaphylaxis and were treated accordingly. This was in agreement to a study conducted by Sharma et al<sup>[6]</sup> None of the drugs caused lethal ADR. Cisplatin 40.00% and carboplatin 24.61% were the common suspecting medications causing bone marrow suppression leading to neutropenia, thrombocytopena and anaemia conforming the findings of several other studies<sup>[12,13,17]</sup> Cisplatin was responsible for 54.01% of the ADRs which were nausea, vomiting, leucocytopenia, palpitation, alopecia, GIT upset, headache and two incidences of anaphylaxis. This finding was consistent with the prevalent literature of the drug. This study therefore provides basic information regarding safety profile of different chemotherapeutic drugs.

A major limitation of the study is that only 65 ADR forms were received and analyzed due to underreporting of ADRs as a result of cancer chemotherapeutic agents during the study period.

### Conclusion

Cancer chemotherapeutic agents have a very high risk of ADR therefore there is a need for prompt detection of ADRs to decrease morbidity and mortality. Pharmacovigilance should be encouraged and a holistic approach should be adopted by health care professional, drug manufactures, drug regulators, policy makers and the government . Rational and judicious use of medicine and adapting preventive measures will reduce the burden of ADRs in the society and benefit mankind.

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