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## ADVERSE DRUG REACTIONS TO CANCER CHEMOTHERAPY IN A REGIONAL CANCER CENTER IN NORTHEAST INDIA

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### ABSTRACT:

**Background:** With the dramatic advances in the medical science, treatment of many cancers is not just palliative, but rather curative in today's world. The dosage regimen and the method of administration can greatly affect their efficacy and toxicity.

**Aims and Objects:** To study the patterns of adverse drug reaction to cancer chemotherapy and to assess the causality, severity and predictability of those adverse reactions.

**Materials and Methods:** The study was conducted in the department of Radiotherapy for a period of 6 months. It is a prospective study and included all in-patients & outpatients with adverse effects during the study period. The data was collected using ADR (adverse drug reaction) form designed by CDSCO (Centre for Drug Standard Control Organization) and statistical analysis was done using SPSS 20.


**Results:** A total of 224 adverse reactions were noted in 178 patients with M:F ratio of 1:1.5. 54.5 % of the reactions were observed in age group of 40-60 years. The most common single drug causing reaction is cisplatin and regimen is CHOP regimen. Anemia is the most commonly seen side effect. Most of the reactions were probable in causality, moderate in severity and unpredictable in nature.

**Conclusion:** Chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells. Hence by early detection of the reaction and by prophylactic management, treatment can be made effective.

**INTRODUCTION:** Adverse Drug Reactions (ADRs) are the fourth to sixth leading cause of death in USA. Therefore detection, prevention and management of ADRs have become an important issue in the health system<sup>1</sup>.

According to the Centre for Health Policy Research, more than 50% of the approved drugs in the United States were associated with some types of adverse effect not detected prior to approval. After the "thalidomide tragedy" many countries have established drug monitoring systems for early detection and prevention of possible drug related morbidity and mortality<sup>2</sup>.

World Health Organization (WHO) defines a ADRs as "any response to a drug which is noxious, unintended and occurs at doses used in man for

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prophylaxis, diagnosis or therapy”<sup>3</sup>. ADRs are one of the major complications of drug therapy leading to morbidity and mortality as well as increasing cost of therapy. Many of the adverse effects of anti-neoplastics are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells<sup>4</sup>.

Common adverse drug reactions (ADRs) due to cancer chemotherapy are nausea and vomiting, alopecia, myelosuppression, haemorrhagic cystitis, mucositis, increased toxicity with impaired renal function, cardiac toxicity, hot flushes, electrolyte imbalance, deep vein thrombosis etc.<sup>5</sup>. The definition of ADR, study population, genetic variation, sampling size, dosage and medications, race and other study factors affect the pattern of adverse effects seen with different studies.

The practice of cancer chemotherapy has changed dramatically as curative treatments for many previously fatal malignancies is employed as part of a multimodal approach to the treatment of many tumours<sup>6</sup>. Adverse drug reactions induced by chemotherapy agents have become one of the major complications of cancer therapy that affect the patient's survival, treatment outcomes and morbidity and mortality rates<sup>2</sup>.

The safety profile of cancer chemotherapy is not available in Manipur. So the present study was carried out to evaluate the pattern of adverse drug reactions (ADRs) in cancer patients treated with chemotherapy in tertiary care hospitals in Manipur.

**MATERIALS AND METHODS:** The study was conducted in the department of Radiotherapy, RIMS, Imphal for over a period of 6 months (may-october 2013). It was a prospective, observational study. The ADR reporting forms prescribed by central drugs standard control organization (CDSCO) were used for collection of ADRs. All the cancer patients who presented with ADRs in the Radiotherapy department were included except patients on concurrent Radiotherapy and patients with altered hepatic or renal parameters prior to chemotherapy.

An approval from the Institutional Ethics Committee for research involving human subjects was obtained before the study was conducted. Confidentiality of the patient's identity was maintained.

**Evaluation of data:** Reported ADRs were analyzed with respect to the nature, type, time of onset and duration of the reactions, characteristics of the drugs involved, and their causality, severity and predictability.

**Causality assessment** was done by using Naranjo's algorithm (**Table 1**) whereby the ADRs were classified into definite, probable & possible.<sup>7</sup> It consists of a set of 10 questions with each question being given score from -1 to 2. Based on the score the ADRs were classified as  $\geq 9$  = definite ADR; 5-8 = probable ADR; 1-4 = possible ADR.

**TABLE 1: NARANJO ALGORITHM OR ADVERSE DRUG REACTION PROBABILITY SCALE**

S. No.	QUESTIONS	YES	NO
1.	Are there previous conclusive reports on this reaction?	1	0
2.	Did adverse drug reaction (ADR) appear after the suspected drug was administered?	2	-1
3.	Did ADR improve when the drug was discontinued or a specific antagonist was administered?	1	0
4.	Did the adverse reaction appear when the drug was re-administered?	2	-1
5.	Are there any alternative causes (other than the drug) that could have caused the reaction?	-1	2
6.	Did the reaction reappear when placebo was given?	-1	1
7.	Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	1	0
8.	Was the ADR more severe when dose was increased or less severe when dose was decreased?	1	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0
10.	Was the adverse event confirmed by any objective evidence?	1	0

**Severity assessment** - ADRs were classified into mild, moderate and severe reactions using the criteria developed by Hartwig *et al*<sup>8</sup>.

**Mild ADRs** were self-limiting and able to resolve over time without treatment and do not contribute to prolongation of length of stay.

**Moderate ADRs** required therapeutic intervention and hospitalization prolonged by 1 day but resolved in 24 hrs or change in drug therapy or specific treatment to prevent a further outcome.

**Severe ADRs** were life threatening, producing disability and those that prolonged hospital stay or lead to hospitalization, required intensive medical care, or lead to the death of the patient.

**Predictability assessment:** The Council for International Organizations of Medical Sciences guidelines for preparing core clinical-safety information on drugs was adapted for assessment of predictability<sup>9</sup>. Patients who have had the drug on previous occasion(s): If the drug was previously well-tolerated at the same dose and route of administration, the ADR is *not predictable*; if there was a history of allergy or previous reactions to the drug, the ADR is *predictable*. Patients who have never had the drug previously: Incidence of the ADR reported in product information or other literature determines its predictability.

Statistical analysis was done by using SPSS 20 & represented in simple frequency & percentage.

**RESULTS:** Our study comprised of 178 patients, in whom a total of 224 adverse reactions were noted. About 54.5% of the ADRs were seen in 40-60 years age group followed by 60 & above (Refer **table 2**). More commonly females (60.7%) were affected than males (39.3%) as mentioned in Table-3. The average number of ADR per person was 1.25. Most common malignancy which was associated with ADR was blood & lymphoid malignancy (27%) followed by head & neck (23.5%) and GIT (gastrointestinal tract) cancer (18.5%) (Refer **figure 1**). Most common individual drug that was associated with ADR was cisplatin (5.6%) followed by 5-FU (4.2%) (Refer **figure 2**).

And the regimen most commonly associated with ADR was CHOP regimen (12.2%).

Anaemia (27%) was the most commonly encountered ADR followed by neutropenia (23%) as shown in **figure 3**.

According to the Naranjo's algorithm, nearly 37.5% of the reactions were probable in causality, 33.9% definite and 28.6 % possible as shown in **figure 4**.

The severity of reactions was assessed by Hartwig's scale and we observed 74.1% of the ADRs were moderate in severity followed by 17.9 % of reactions which are mild in severity. Only 8% of the ADRs were severe in nature (**figure 5**).

The Council for International Organizations of Medical Sciences guidelines (CIOMS) for preparing core clinical-safety information on drugs was adapted for the assessment of predictability.

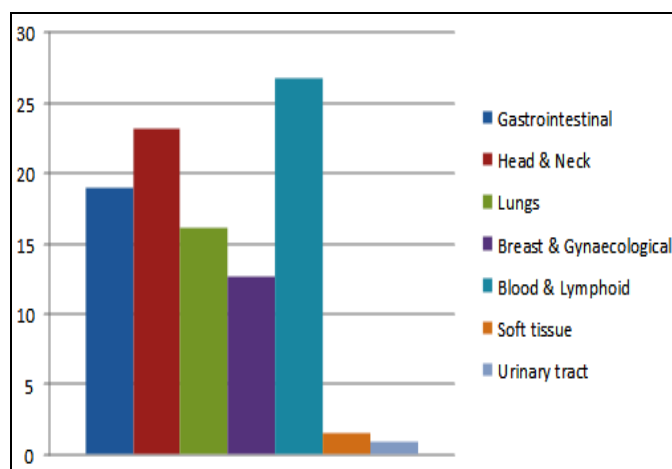
According to the guidelines, about 55.4 % of the ADRs were unpredictable and 44.6% of the ADRs were predictable as mentioned in **figure 6**.

**TABLE-2: AGE DISTRIBUTION OF THE PATIENTS**

AGE CATEGORY	PERCENTAGE % (NUMBER)
0-20	1.8 (3)
21-40	11.6 (21)
41-60	54.5 (97)
61 & ABOVE	32.1 (57)

**TABLE 3: SEX DISTRIBUTION OF THE PATIENTS**

SEX	PERCENTAGE % (NUMBER)
MALE	39.3 (70)
FEMALE	60.7 (108)



**FIGURE 1: DISTRIBUTION OF VARIOUS CANCERS**

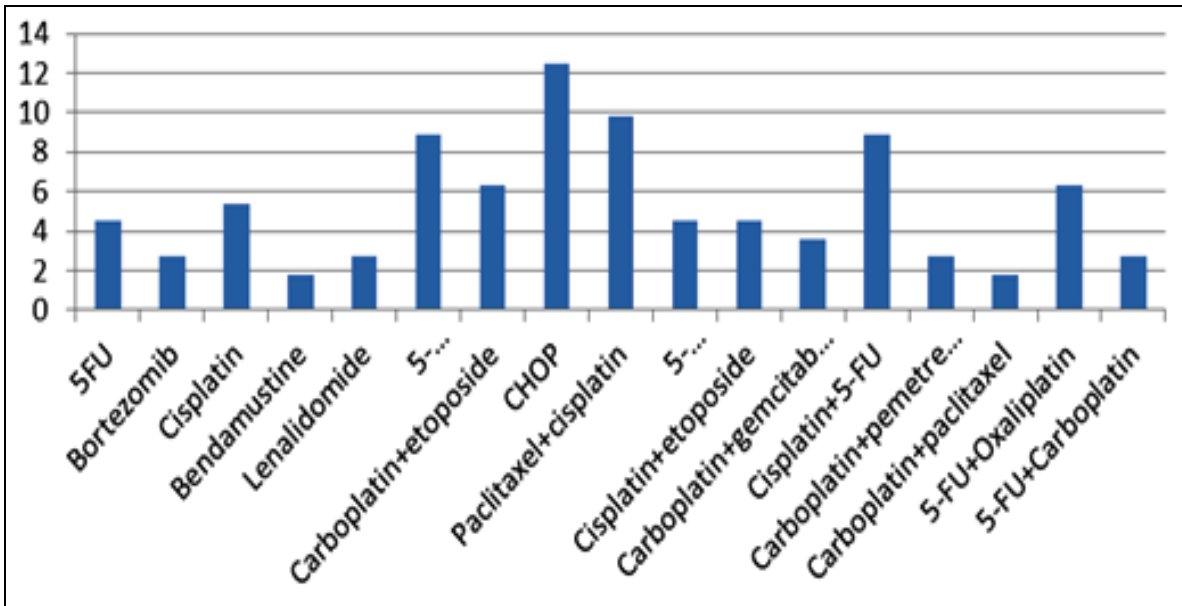


FIGURE 2: DRUG REGIMES ASSOCIATED WITH ADVERSE REACTIONS

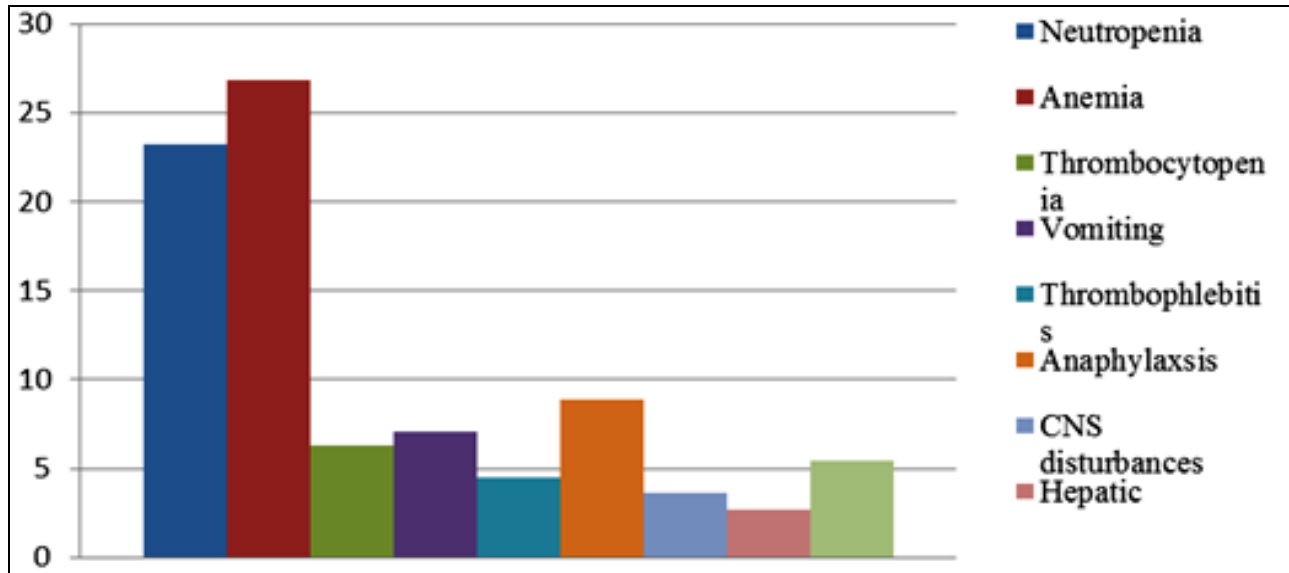


FIGURE 3: DISTRIBUTION OF VARIOUS ADVERSE DRUG REACTIONS

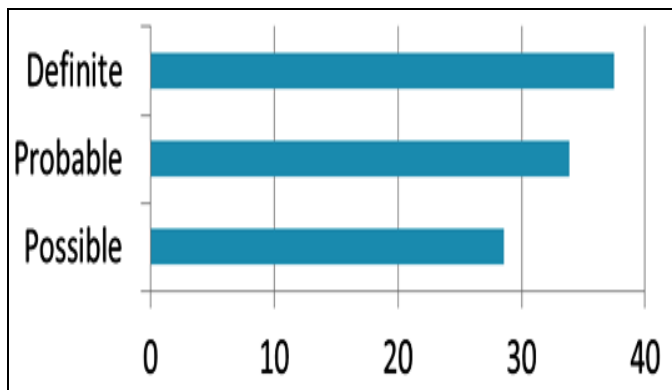


FIGURE 4: ASSESSMENT OF CAUSALITY OF ADVERSE DRUG REACTIONS

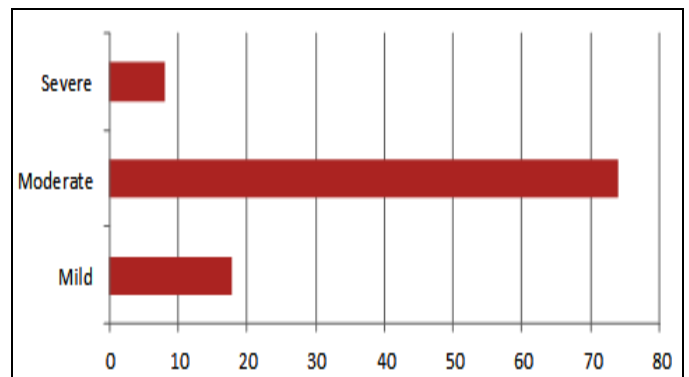
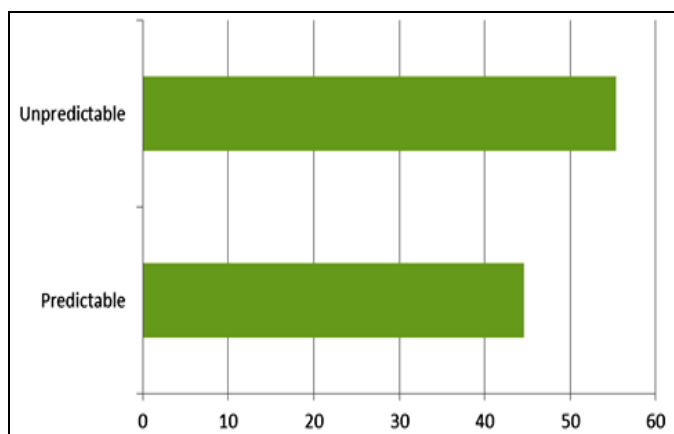


FIGURE 5: ASSESSMENT OF SEVERITY OF ADVERSE DRUG REACTIONS



**FIGURE 6: PREDICTABILITY OF THE ADVERSE DRUG REACTIONS**

**DISCUSSION:** A total of 224 adverse reactions were noted in 178 patients. On an average number of ADRs per person was 1.25. ADRs were more common in females (60.7%) than in males (39.3%). This is probably because of their smaller body size and mental make-up<sup>10</sup>. ADRs were common in the adult & elderly age group 54.5% (40-60 age gr) and 32.1% (60 & above). This may be because of increased incidence of cancer in the elderly, decreased metabolism of drugs and associated comorbidities like diabetes mellitus & hypertension. Our finding also correlates with the study conducted by Podar *et al*<sup>11</sup>.

Most common malignancy associated with ADRs is blood and lymphoid malignancy followed by head & neck and GIT tumours. Similar study conducted by Mrugank BP *et al*<sup>12</sup> showed that GIT and breast cancer were more frequently associated with ADRs. Study conducted by Prasad A *et al*<sup>13</sup> showed that bronchogenic carcinoma followed by breast cancer were more frequently associated with ADRs. This difference may be attributed to difference in the geographic distribution & genetic makeup of the population.

Cisplatin was the most common individual drug associated with ADR followed by 5FU. The drug regimen most frequently associated with ADRs was CHOP regimen. Among the ADRs anemia (26.8%) was most common followed by neutropenia (23.2%). This is due to the fact that bone marrow cells are rapidly dividing cells and anticancer drugs act mainly on the rapidly dividing cells. Also anemia may be associated with the disease process itself.

Surprisingly, the incidence of GI symptoms like nausea & vomiting were less common. This may be due to increased & regular use of pre-medications like proton pump inhibitors and anti-emetics like ondansetron prior to chemotherapy. Advances in the development of supportive care in oncology, for example, 5HT3 antagonists for the control of chemotherapy-induced nausea, have led to reductions in drug-related toxicity. There is evidence to show that medical perspectives do not necessarily coincide with those of patients who are being treated<sup>14, 15</sup>. Blood related ADRs were seen mostly during second or third week following chemotherapy. There was no change in regimen because of ADR but dose was reduced to tolerable dose in few cases.

Most of the ADRs were mild (17.9 %), moderate (74.1%) in severity with only 8% of ADRs in severe category. 5% of patients required hospitalisation because of ADR. This shows that ADRs are due to cancer chemotherapy are rarely life threatening with appropriate pre-medications and early detection. According to Naranjo's scale, 33% of the ADRs were definite. This is because of un-certainty of whether the reaction was due to chemotherapy or disease process. According to CIOMS guidelines 44.6% of ADRs were predictable either based on earlier response or from clinical practice. However, only few of the predictable ADRs can be prevented. ADRs like fatigue though predictable can be prevented whereas ADRs like vomiting, neutropenia can be prevented to some extent with adequate pre-medications. The duration of the study was only for six months, a major limitation of the study. The number of patients developing the ADRs was also less.

**CONCLUSION:** Chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells. The reactions seen are not just because of the drugs but a combined effect of the disease, patient condition and drug. Most of the reactions are either mild or moderate in severity but unpredictable.

Cisplatin-based chemotherapy has a high potential to cause various adverse effects in cancer patients.

Most of the ADRs were not preventable due to the poor predictability of the ADRs and poorly understood mechanisms to explain their cause. However, with adequate pre-medication, common ADRs like nausea and vomiting can be prevented. This brings out the possible toxicity that the treating physician should anticipate and counsel the patient adequately prior to starting of therapy. Similar studies covering more patients from different regions are needed to validate the findings of this study.

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