A Retrospective Evaluation of Adverse Drug Reactions Due to Cancer Chemotherapy in a Tertiary Care Hospital in South India

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ABSTRACT

Introduction: To evaluate the adverse drug reactions (ADRs) due to cancer chemotherapy in a tertiary care hospital in South India. **Materials and Methods:** This was a retrospective descriptive study. The data was obtained from patients who developed, at least, one ADR due to cancer chemotherapy during the period June 2014 to May 2015. The causality of the ADRs were evaluated by WHO-UMC causality assessment system and Naranjo's ADR probability scale, the severity of ADRs were assessed by Hartwig and Siegel ADR severity assessment scale, and preventability of ADRs were determined by the Schumock and Thornton ADR preventability assessment scale. **Results:** One hundred fourteen ADRs due to cancer chemotherapy were reported in 73 patients. Hyponatremia (20.2%), neutropenia (11.4%), infections of the lung (11.4%), leucopenia (9.6%) were the commonly suspected ADRs. Cisplatin (62.3%), carboplatin (18.4%), cetuximab (3.5%), gefitinib (2.6%) were the commonly suspected medications. As per the WHO-UMC causality assessment system 66(57.8%) ADRs were possible and 48(42.1%) were probable. Naranjo's ADR probability scale showed that 74(64.9%) ADRs were possible and 40 (35.1%) were probable. There was a very good agreement between the two scales (kappa=0.853). All ADRs

were classified as level 4 severity barring one. None of the ADRs reported were preventable. **Conclusion:** Since 80% of the ADRs were suspected to be due to platinum containing anticancer drugs this provides a focus for further research on devising methods for prevention or early detection of ADRs. Prompt detection of ADRs is important to decrease morbidity and mortality.

Key words: Adverse Drug Reaction, Cancer Chemotherapy, Naranjo's ADR probability scale, Causality assessment, Pharmacovigilance, WHO-UMC causality assessment system.

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INTRODUCTION

A number of studies have reported the incidence of adverse drug reactions (ADR) among hospitalized patients to be between 1.5% to 6.7%.[1-3] It is one of the leading cause of morbidity and mortality with an estimated economic burden of about 30 billion to 130 billion US dollars annually.[4] ADRs are an inevitable, albeit unwanted aspect of cancer chemotherapy.

The US Food and drug administration has approved more than 150 new anticancer drugs in past 20 years. Cancers which were previously fatal like testicular cancer, lymphomas, and leukemia, now have a treatment. Patients with cancer following surgery, can now prevent tumor relapse and prolong their life with adjuvant chemotherapy. Multimodal approach with chemoradiation of locally advanced cancers has now allowed for a more limited surgery.[5] However, the newer drugs are also associated with a significant risk of ADRs.[6] This is despite the various preventive concomitant medications administered to tackle the ADRs.

The data regarding ADRs collected during the different phases of clinical trials before regulatory approval is invariably incomplete. Moreover, there are differences in the occurrence of ADRs between countries, with locally derived data having greater relevance. Many of the ADRs are preventable and due diligence is necessary to avoid drugs which are problematic and monitor drugs with predictable toxicity. So ADR monitoring becomes an important tool to detect uncommon and sometimes serious ADRs, ensuring patient safety.[4,7] Hence we conducted this study to assess the adverse drug reactions due to cancer chemotherapy in a tertiary care hospital in South India.

MATERIALS AND METHODS

This was a retrospective descriptive study. The data was obtained from patients who developed, at least, one ADR due to cancer chemotherapy

during the period June 2014 to May 2015 in a tertiary care hospital in South India. It was conducted after receiving approval from the Institutional Ethics Committee. All the ADRs which were reported by the Oncology department between June 2014 to May 2015 were assessed. The data was obtained from the suspected adverse drug reaction reporting form used in the hospital for reporting ADRs to the ADR monitoring center as a part of the Pharmacovigilance program of India. The causality of the ADRs were evaluated by using the WHO-UMC causality assessment system and Naranjo's ADR probability scale. The causality was assessed by two study investigators independently and any discrepancy in the causality assessed was resolved by consensus. The severity of ADRs were assessed by Hartwig and Siegel ADR severity assessment scale, and preventability of ADRs were determined by the Schumock and Thornton ADR preventability assessment scale.

The WHO-UMC causality assessment system evaluates the causality of the ADRs and categorizes them as Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified and Un-assessable/Unclassifiable.[8] The Naranjo's ADR probability scale also evaluates the causality of the ADRs but categorizes them as Definite, Probable, Possible and Doubtful.[9] The Hartwig and Siegel ADR severity assessment scale assesses the severity of the ADR and classifies them from Level 1 to Level 7.[10] The Schumock and Thornton ADR preventability assessment scale determines the preventability of the ADRs and labels them as Preventable and Not preventable.[11]

The data was analyzed using SPSS (Statistical Package for the Social Sciences), IBM Corporation, version 20 and summarized using frequencies and percentages. The measure of agreement between the WHO-UMC causality assessment system and Naranjo's ADR probability scale was done using kappa (K) test.

Table 1: Gender wise distribution of various malignancies in the study sample

Males			Females		
Malignancy	Frequency (N)	Percentage (%)	Malignancy	Frequency (N)	Percentage (%)
Esophagus	17	27.0	Cervix uteri	17	33.3
Oropharynx	11	17.5	Breast	08	15.7
Nasopharynx	09	14.3	Submandibular gland	05	11.8
Base of the tongue	06	9.5	Hypopharynx	04	7.8
Larynx	04	6.3	Thyroid gland	04	7.8
Penis	04	6.3	Base of the tongue	04	7.8
Hypopharynx	03	4.8	Cheek mucosa	02	3.9
Others	09	14.3	Others	06	11.9
Total	63	100	Total	51	100

Tables 2: Distribution of suspected adverse drug reactions due cancer chemotherapy

Suspected Adverse Drug Reaction	Frequency (N)	Percentage (%)
Hyponatremia	23	20.2
Neutropenia	13	11.4
Infection - Lung	13	11.4
Leucopenia	11	9.6
Anemia	11	9.6
Thrombocytopenia	10	8.8
Hypokalemia	07	6.1
Diarrhea	06	5.3
Fever	05	4.4
Renal Failure	05	4.4
Others	10	9

Table 3: Distribution of suspected medication causing adverse drug reaction

Suspected Medication	Frequency (N)	Percentage (%)
Cisplatin	71	62.3
Carboplatin	21	18.4
Cetuximab	4	3.5
Gefitinib	3	2.6
Sunitinib	3	2.6
Paclitaxel	3	2.6
Temozolamide	2	1.8
Cytarabine	2	1.8
Others	5	4.5

RESULTS

One hundred fourteen ADRs due to cancer chemotherapy were reported in 73 patients during the study period. Among the ADRs reported, 63(55.3%) were in males and 51(44.7%) in females. The mean age of the patients was 55.98 ± 6.53 years in males and 52.96 ± 10.09 years in females. Oropharyngeal malignancy (24.6%) was the most common groups of cancers followed by malignancy affecting the digestive organs (16.7%), female genital organs (15.8%) and breast (7%). Among these, malignancy of cervix uteri (14.9%) and esophagus (14.9%) were the most common cancers. The gender-wise distribution of different malignancies is shown in Table 1.

ADRs affecting blood (38.5%) were the most common suspected category of ADR, followed by metabolic abnormalities (29.8%) and infections (15%). Table 2 shows the various ADRs reported in the study population. Hyponatremia (12%), respiratory tract infection (9%) and neutropenia (7%) accounted for 44.4% of the ADRs in males. Hyponatremia (21.6%); neutropenia, diarrhea, anemia (11.8%); leucopenia, thrombocytopenia (9.8%) accounted for 76.6% of the ADRs in females. Seventy-four (64.9%) ADRs were considered to be recovering at the time of reporting,

Table 4: Causality assessment using WHO-UMC causality assessment system and Naranjo's adverse drug reaction probability scale

Causality assessment		Naranjo's adverse drug reaction probability scale		Total
		Probable	Possible	
WHO-UMC causality assessment system	Probable	40	08	48
	Possible	0	66	66
Total		40	74	114

28(24.6%) were considered to have recovered 11(9.6%) were continuing and 1(0.9%) was fatal.

The most common suspected class of medicateons were platinum compounds (81.6%) followed by tyrosine kinase inhibitors (5.6%). Cisplatin (62.3%) was the most common suspected medication followed by carboplatin (18.4%) (Table 3).

As per the WHO-UMC causality assessment system 66 (57.8%) ADRs were possible and 48 (42.1%) were probable. Naranjo's ADR probability scale showed that 74 (64.9%) ADRs were possible and 40 (35.1%) were probable (Table 4). There was avery good agreement between the two scales of assessment (kappa=0.853). The Hartwig and Siegel ADR severity assessment scale classified all the ADRs as level 4 severity barring one, which was level 7. None of the ADRs reported were preventable as per the Schumock and Thornton ADR preventability assessment scale.

DISCUSSION

In our study, we evaluated the ADRs due to cancer chemotherapy in a tertiary care hospital in South India. The mean age of the patients was 54.63 ± 8.40 years. There is a link between increasing age and incidence of ADRs. This may be due to change in the pharmacokinetics and pharmacodynamics of the drug with increasing age. In addition to this, chronic illness, treatment with multiple medications also add to the burden of ADRs.[12-14] Among the ADRs reported, 55.3% were in males and 44.7% in females. A review of 48 cohort studies in the UK showed that females are more commonly affected than males, which was attributed to increased consulting rates for women compared to men in these studies.[14] As a group, oropharyngeal cancers were the commonest cancer reported in our study, although individually malignancy of the cervix was the commonest cancer followed by malignancy of the esophagus. Surendiran *et al.* reported cervical cancer as the commonest cancer.[15] While, Mallik *et al* and Poddar *et al* have reported lung and breast cancer as common cancers.[16,17] The incidence and type of cancer affecting individuals show a geographical variation, which may have been responsible for this difference noted between the studies.[18]

In general, ADRs affecting the bloodwere the most common suspected category of ADR, Individually, hyponatremia was the commonest suspectted ADR followed by neutropenia and lung infections. All ADRs reported in our study were of level 4 severity, barring one which was fatal. Mallik *et al.* reported neutropenia as the commonest suspected ADR followed by emesis and alopecia.[16] While, Poddar *et al.* reported elevated ESR, alopecia, vomiting and neutropenia as the common suspected ADRs.[17] And Surendiran *et al.* reported nausea, alopecia, anorexia and vomiting as the suspected common ADRs.[15] Except neutropenia, other ADRs were not reported in our study. A possible reason could be that the oncologists reported only those ADRs which they deemed significant and/or severe.

Proximal convoluted tubules, an important site of sodium and water reabsorption in the kidney is damaged by chemotherapeutic agents leading to hyponatremia.[19] These agents also suppress the hematopoietic system, impairing host protective mechanisms leading to cytopenia's like neutropenia, anemia, and thrombocytopenia. Neutrophils are an important component of innate immunity and form the first line of defense against exogenous infections. Neutropenia caused by these agents blunts the immune response predisposing patients to infections.[20] Platinum compounds like cisplatin and carboplatin were the commonlysuspected medication. These findings are similar to a previous study reported by Mallik *et al*.[16]

None of the ADRs reported in our study were assessed to be preventable. Surendiran *et al.* reported that ADRs like nausea and vomiting were definitely preventable. This difference may have been due to ADRs like nausea and vomiting not being reported in our study.

The causality assessent by both the WHO-UMC causality assessment system and Naranjo's ADR probability scale showed that most of the ADRs were possible. Previous studies have all shown that most common causality was 'possible'.[15-17] There was a very good agreement between the two scales of assessment. While, Mittal *et al.* had reported good agreement between the scales, Machedo *et al.* reported moderate agreement between the scales and Behelkar *et al.* reported poor agreement between the scales.[21-23] Studies have shown that causality assessment of ADR is subjective, imprecise and low level of agreement exists between two observers.[24,25] This may be responsible for the difference noted between the studies. We tried to ensure objective evaluation of causality by two investigators independently assessing the ADRs.

The main limitations of the study are that it was a retrospective study and included only ADRs which were spontaneously reported by the oncologist. Incomplete documentation of ADRs, particularly the description of the adverse reaction might have led to the incorrect assessment of causality and preventability by Schumock and Thornton ADR preventability assessment scale. Wherever lab investigations were supposed to be performed to prevent an ADR but was not documented, it was assumed to have been performed. Non-reporting of ADRs may have also affected the observed pattern of results. There is a need for along-term prospective study to evaluate the ADRs due to cancer chemotherapy in India.

CONCLUSION

Electrolyte disturbance, blood dyscrasias and lung infection were the most commonly reported ADRs in our study. Since 80% of the ADRs were suspected to be due to platinum containing anticancer drugs this provides a focus for further research on devising methods for prevention or early detection of ADRs. Prompt detection of ADRs is important to decrease morbidity and mortality since those reported in our study were considered non-preventable. Our study also emphasizes the need to encourage the treating physicians to report ADRs which may be considered common and not significant. Considering the increasing number of chemotherapeutic drugs available and their increasing use in the diverse patient population, it is important to track the potential adverse effects of these drugs. There is a need for holistic approach to pharmacovigilance with patients, healthcare professionals, drug manufacturers, drug regulators and policy makers, all having complementary roles to achieve what is envisaged.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

ABBREVIATIONS USED

ADR: Adverse Drug Reaction; **WHO-UMC:** World Health Organization-Uppsala Monitoring Centre; **SPSS:** Statistical Package for the Social Sciences; **ESR:** Erythrocyte Sedimentation Rate.

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