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STUDY OF ADVERSE DRUG REACTIONS OF ANTI-NEOPLASTIC AGENTS IN DIFFERENT STAGE OF CANCER

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ABSTRACT

To evaluate the clinical adverse drug reactions (ADRs) reported in cancer patients taking anticancer drugs in different stage of cancer. Adverse drug reactions (ADRs) are a global problem in different stages of cancer. Anti-cancer drugs are prone to cause ADRs and there is lack of Pharmacovigilance data on such drugs. Therefore the present prospective observational study was undertaken to monitor possible ADRs in the chemotherapy of different stage of cancer. Adverse drug interactions may enhance or diminish the antitumor effects and result in improvement or treatment failure; drug interactions may also increase or decrease the side-effect profile of the anti-neoplastic drug. Precaution must be taken when prescribing other therapeutic agents to patients undergoing active anticancer therapy. The study is the clinical assessment of adverse drug reaction in cancer patients by Naranjo's ADR probability scale after the clinical pharmacist intervention of a government hospital. We have conducted the prospective study to analyze the ADRs in the oncology department for the period of six months from December 2015 to May 2016 in Government Headquarters, Krishnagiri by the Doctor of Pharmacy (Pharm D) students. The study population consists of 150 patients in total. Among them 54.6 % (n=82) of the patients were females. On classifying the patients on age 32 % (n=48) of the patients were of age group 50-59. From the total prescription 34.66% (n=52) patients were diagnosed as stage II cancer. From this clinical study it may be concluded that chemotherapeutic agents have a narrow therapeutic index and dosage needed to achieve a therapeutic response usually proves toxic to the bodies rapidly proliferative cells. However, early detection of drug toxicity helps to modify the doses or the drug regimen to minimize toxic effects.

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INTRODUCTION

Chemotherapy is employed as part of a multimodal approach to the treatment of many tumors [1]. Chemotherapy regimens are immensely complex, and cancer patients are a susceptible population with little tolerance. The WHO defines an adverse drug reaction as any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function [2]. Thus this definition excludes overdose (either accidental or intentional), drug abuse, and treatment failure and drug administration errors. The term adverse drug reaction and adverse drug event is not synonymous. Adverse drug reactions (ADRs) are types of adverse drug events (ADEs). ADEs include ADRs, medication errors and other drug-related problems. The WHO definition of adverse drug event is an untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a casual relationship with the treatment. Hospital-based ADR monitoring and reporting programmes aim to identify and quantify the risks associated with the use of drugs. The information may be useful in identifying and minimizing preventable ADRs while generally enhancing the knowledge of the prescribers to deal with ADRs more efficiently. The participation of pharmacists in national Pharmacovigilance programmes is not a common feature. The pharmacist's involvement in such programmes is seen only in some countries. In India, clinical pharmacy is still evolving and hence, pharmacist's involvement in such activities has been low [3]. The aim of the present study was to undertake ADR monitoring in a government hospital where a clinical pharmacy programme is well established. The primary objectives included monitoring and documenting ADRs and evaluating them according to set criteria. The secondary objective was to analyze the cost burden involved in managing ADRs [4]. The frequency of ADRs in the general population is unknown. However, the reported rates of new occurrences for ADRs are noted for selected patient populations. A Meta analysis of 39 prospective studies reported an overall incidence of serious ADRs in hospitalized patients of 6.7% and of fatal ADRs of 0.32%.The fatality rate makes ADRs the fourth to sixth leading cause of death in the United States. Another meta-analysis of 36

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studies indicated that approximately 5% of hospital admissions are due to ADRs. The costs of ADRs are estimated to be $1.56-$4 billion in direct hospital costs per year in the United States [5]. The epidemiology of ADRs in Indian population is not known only few studies is carried out. A recent study from All India institute of medical sciences (AIIMS) New Delhi in which both inpatients and outpatient where included, indicate that 22.3% of patients experienced adverse drug reactions. A vast majority of these were dose dependent and potentially preventable. Hospital-based ADR monitoring and reporting programs can help in identifying and assessing the risks associated with the use of drugs [6-9].This data may help the prescribers to identify ADRs and deal with them more efficiently and also help in preventing the occurrences of these ADRs in future [9-12]. ADR monitoring and reporting activity is still in the early stages in India. Lack of an organized and efficient ADR monitoring and reporting program is posing a great challenge to drug safety screening in the Indian subcontinent. Lack of awareness and fear of litigations on the part of the prescriber are main causes for under-reporting of ADRs [13-17]. Scarcity of studies relating to drug safety monitoring in India led us to undertake this study where we tried to evaluate the pattern of ADRs occurring in patients of different stage of cancer treated with chemotherapy in a tertiary care hospital in South India.

THE ROLE OF CLINICAL PHARMACISTS IN MANAGEMENT OF ADR

a) Monitoring the patients who are at the greater risk of developing ADRs.
b) Monitoring the patients who are prescribed with drugs highly susceptible to ADRs.
c) Assessing and documenting the patient's previous allergic status.
d) Assessing the patient's drug therapy for its appropriateness.
e) Assessing the possible drug interaction in case of multiple therapies.
f) Assessing the health care professionals in detection and assessment of ADRs.
g) Encouraging the health care professionals in reporting an ADR.
h) Documentation of suspected reported reaction for further references.
i) Follow-up of the patients to assess the outcome of the reaction and the management.
j) Obtaining feedback about the reported reaction.

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k) Educating the health care professionals about the importance of reporting an ADR.
l) Educating patients.
m) Creating awareness about ADRs amongst health care professional, patients and public.
n) Preparation and utilization of promotional material.
o) Communication with other healthcare professionals such as community pharmacists and nurses.
p) Presentation of reports in meeting and conferences.
q) Conducting workshop or seminars on ADRs to other healthcare professionals.
r) Disseminating of signals generated through publication of reports in bulletins or journals (G Parthasarathi).

NARANJO ALGORITHMS

The Naranjo algorithm, Naranjo scale, or Naranjo nano gram is a questionnaire designed by Naranjo *et al*. for detecting the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, Probable, Possible or Doubtful. Values obtained from this algorithm are sometimes used in Peer Reviews to verify the validity of author's conclusions regarding adverse drug reactions. It is also called the Naranjo Scale or Naranjo Score. The ADR probability scale consist of ten questions that are answered as either yes, No or don't know. Different point values (-1, 0, +1 or +2) are assigned to each answer. Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, Probable if 5 to 8, Possible if 1to 4, and Doubtful if 0 or less, which are mentioned in Table.3.

A simplified version of the 10 questions is provided below:

1) Are there previous conclusive reports of this reaction?
2) Did the adverse event appear after the drug was given?
3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
4) Did the adverse reaction reappear upon re administering the drug?
5) Were there other possible causes for the reaction?
6) Did the adverse reaction reappear upon administration of placebo?
7) Was the drug detected in the blood or other fluids in toxic concentrations?
8) Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?
9) Did the patient have a similar reaction to the drug or a related agent in the past?

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10) Was the adverse event confirmed by any other objective evidence?

The actual ADR Probability Scale form and instructions on how it is completed are provided below. Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less. While this scale includes all of the usual features that are important in assessing causality, the scale is not weighted for the most critical elements in judging the likelihood of drug induced toxicities, such as specific time to onset, criteria for time of recovery, and list of critical diagnoses to exclude, making the scale of limited use in assessing antineoplastic drug toxicity. The Naranjo scale also relies upon testing for drug levels, which is rarely helpful in idiosyncratic drug induced liver disease. Finally, the scale was designed for use in clinical trials, and points are subtracted if the reaction reappears with administration of placebo, which does not apply to the usual case of drug induced liver disease. Direct comparisons to the RUCAM system have shown that the ADR Probability Scale is easier to apply, but has less sensitivity and specificity in assigning causality to cases of drug induced adverse effects of antineoplastic drugs (Naranjo CA).

INSTRUCTIONS FOR USING THE ADR PROBABILITY SCALE

The response "Do not know" should be used sparingly and only when the quality of the data does not permit a "Yes" or "No" answer. "Do not know" can be applicable if the information is not available and also if the question is inapplicable to the case. When more than one drug is involved or suspected, the ADR Probability Scale is usually applied separately to each of the possible etiologic agents, and the drug with the highest score should be considered the causative agent. In addition, the potential of interaction should be evaluated

MATERIAL AND METHOD

This clinical study was conducted at Government Head Quarters Hospital, Krishnagiri. It is a 200 bedded teaching hospital located in a socioeconomically backward region in Northeastern Krishnagiri, providing health care services in different specialties with highly qualified health professionals. The oncology department was selected for the study after the intervention of clinical pharmacist. This study is a prospective observational, single centered study conducted over a period of 6 months from December 2015 to May 2016. A prospective observational, single centered study was carried out in the oncology

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department for 6 months data collection from December 2015 - May 2016. The study was approved by the Institutional Ethical Committee of Government Head Quarters Hospital, Krishnagiri. Cancer patients who visited the Oncology department at Government Head Quarters Hospital, Krishnagiri and satisfying the inclusion/exclusion criteria were enrolled in the study. The hospital caters to both urban and rural population. Most of the patients belong to poor, lower-middle and upper-middle strata of the society. Habits of smoking, tobacco chewing and alcohol drinking were common to the study population. Educational status of the population was of mostly illiterate, with basic education (can able to read/ write), and graduate while Occupation was of unemployed, technical, house wife, farmer and professional are observed in our study population. This study data was analyzed by using Microsoft Excel and SPSS. The P value and Chi square was analyzed for assessing the findings.

RESULT AND DISCUSSION

Table No.1 shows that more patients were observed in definite category with 65 patients followed by probable with 50 patients, possible with 35 patients, and no patients in doubtful category. Figure 1 represents that more patients are in definite category with 43.33% and less in doubtful category with no patients. From the table no.2 and graph no.2 it is observed that ADR increases with stage. The study is the assessment of adverse drug reaction in cancer patients of a government hospital. We have conducted the prospective study to analyze the ADRs in the oncology department for the period of six months from December 2015 to May 2016 in Government Headquarters, Krishnagiri. The study population consists of 150 patients in total. Among them 54.6 % (n=82) of the patients were females. On classifying the patients on age 32 % (n=48) of the patients were of age group 50-59. From the total prescription 34.66% (n=52) patients were diagnosed as stage II cancer. From the study it may be concluded that chemotherapeutic agents have a narrow therapeutic index and dosage needed to achieve a therapeutic response usually proves toxic to the bodies rapidly proliferative cells. Early modifications in dosage regimen of chemotherapeutic agents may minimize the hazardous ARDs. According to the ADR probability assessment scale, stage wise distribution is highly correlated with the adverse drug reactions. From this

clinical study done by clinical pharmacist, it may be concluded that chemotherapeutic index and dosage needed to achieve a therapeutic response usually proves toxic to the bodies rapidly proliferating cells. Early modifications in dosage regimen of chemotherapeutic agents may minimize hazardous ADRs.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Committee of Government Head Quarters Hospital, Krishnagiri.

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EXPERIMENTAL FIGURE AND TABLE

Table No. 1: ADR Assessment scale in oncology patients in our Hospital

S. No	**ADR Score**	**No. of Patients**	**Percentage**
1	Doubtful	0	0
2	Possible	35	23.33
3	Probable	50	33.33
4	Definite	65	43.33

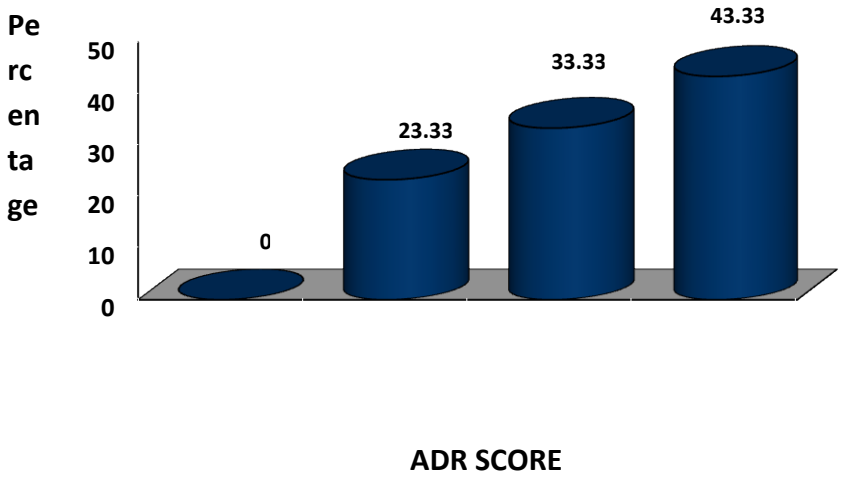

Fig No.1: ADR Assessment scale of oncology patients in our hospital

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Table.2: Associations between ADR score and stages of cancer

ADR -Score	Stage-I	Stage-II	Stage-III	Stage-IV	Association between ADR score and stage	
					Chi-square	p-value
Doubtful	-	-	-	-	18.04	0.006*
Possible	2	18	10	5		
Probable	8	22	12	8		
Definite	15	12	17	21		
Total	25	52	39	34		

***P<0.001 -highly significant**

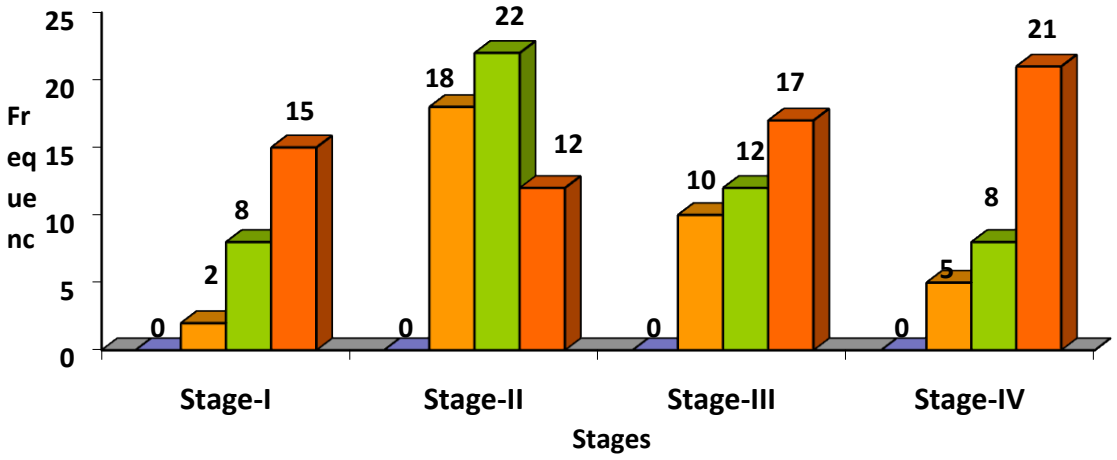

Fig no.2: Associations between ADR score and stages of Cancer

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Table.3: Naranjo algorithm-ADR probability scale

SCORE	INTERPRETATION OF ALGORITHN ADR PROBABILITY SCORE
Total Score >_9	**DEFINITE:** The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re exposure.
Total Score 5 to 8	**PROBABLE:** The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total score 1 to 4	**POSSIBLE**: The reaction (1) follower a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score <_0	**DOUBTFUL:** The reaction was likely related to factors other than a drug.