Original Article

A Prospective Observational Study on Evaluation of Chemotherapy Induced Adverse Drug Reactions in Cancer Patients in a Tertiary Care Hospital

Priya Saji Koliyakodu[1,*], Rona Sudhakar[1], Manesh Mathews Kurian[1], Jishnu R. K[2], Raj Kumar[2], V. Lalitha[3], Haja Sherief[4], T. Sivakumar[1]

[1]Department of Pharmacy Practice, Nandha College of Pharmacy, Erode, Tamil Nadu, INDIA.
[2]Department of Oncology, GKNM Hospital, Coimbatore, Tamil Nadu, INDIA.
[3]Department of Pharmacology, Nandha College of Pharmacy, Erode, Tamil Nadu, INDIA.
[4]Department of Pharmacy Practice, Nandha College of Pharmacy, Erode, Tamil Nadu, INDIA.

ABSTRACT

Aim: To analyze the incidence of adverse drug reactions due to chemotherapy by studying the prescribing patterns and thereby evaluating their causality and severity. **Materials and Methods:** It was a prospective observational study conducted for a period of 6 months, from February 2018-July 2018 in a tertiary care hospital. The specifics were collected based on the inclusion and exclusion criteria from the Oncology department. The reported ADRs were assessed for causality using both WHO and Naranjo's algorithm and severity were assessed using Modified Hartwig and Siegel scale. **Results:** It was observed that 852 ADRs were reported from 250 patients. Most common age group in which patient had ADRs were 46-60 years (39.2%) followed by age group above 60 years (35.2%). Cervix cancer was the most commonly distributed (23.2%) followed by breast cancer (13.6%). The prescribing pattern of combination therapy (83.6%) was more compared to monotherapy (16.4%). Cisplatin and cisplatin–paclitaxel regimen induced more ADRs in monotherapy and combination therapy respectively. WHO causality scale indicated 68.4% of the reactions were "probable" and 25.6% were "possible". Modified Hartwig and Siegel scale indicated that 71.2% were moderate followed by mild 24.8% and 4% were severe. **Conclusion:** Treatments like chemotherapy makes the disease real. Benefits of treatment should outweigh the risk. We assessed the incidence of ADRs, analyzed the prescribing patterns categorized the causality and severity and notified the suspected ADRs in order to promote the judicious use of suspected drugs with regular and sustained monitoring. This knowledge helps in preventing the occurrence of similar reactions in future.

Key words: Cancer, Adverse Drug Reactions, Chemotherapy, Monotherapy, Combination therapy.

INTRODUCTION

WHO defines ADR as 'Any response to a drug which is noxious and unintended and which occurs of doses used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.[1] Adverse drug reactions (ADRs) are a global problem and constitute a major clinical problem in terms of human suffering.[2] The high toxicity and narrow therapeutic index of chemotherapeutic agents makes oncology pharmacovigilance essential.[3]

Adverse effects of anti-neoplastic are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells. Most common ADRs due to cancer chemotherapy are nausea and vomiting, alopecia, myelosuppression etc.

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.[4] Many studies have been done all over the world in patients having chemotherapy with individual drugs especially, Cisplatin and combination drug regimens with cisplatin which include FAC, CHOP and PC which should be strictly and continuously monitored for the symptoms of ADRs.[5] The results of those studies

DOI: 10.5530/ijopp.14.1.2

Address for correspondence:
Dr. Priya Saji Koliyakodu
Pharm.D Graduate,
Department of Pharmacy Practice
Nandha College of Pharmacy,
Perundurai, Erode-638052, Tamil Nadu, INDIA.
Phone no: +91 8943608178
Email Id: dr.priyasaji@gmail.com

www.ijopp.org

highlighted the importance of monitoring the patients on cancer chemotherapy for any signs of ADRs. In addition to increasing the length of hospital stay, ADRs also significantly increase the health cost. Most of these ADRs are unreported due to unawareness of health care professionals and lack of time to report. The early detection and prompt management of these ADRs can reduce its health-related and economic effects on the patients. Hence it is necessary to recognize the pattern of ADR occurring with anticancer drugs so as to enhance the quality of life and to reduce the cost of ADR related issues in cancer patients. Thus, the objective of the present study was to evaluate the pattern of ADRs occurring in cancer patients treated with chemotherapy in a tertiary care hospital in Southern India.[6]

MATERIALS AND METHODS

Study area: The study was conducted at G. Kuppuswamy Naidu Memorial Hospital, Coimbatore. Approval of Institutional Ethical Committee was obtained for the study. Confidentiality of patient identity was maintained.

Study period and study population: The data was obtained from 330 prescriptions, between February 2018-July 2018 from the IP and OP of Oncology Department.

Study design: It was a prospective observational study conducted by evaluating 330 prescriptions containing anti-neoplastic drugs from Oncology Department. The demographic details of the patients, details of medications, chief complaints, past history, drug history, concomitant medications administered and relevant laboratory investigations were noted. Details about the occurrence and nature of ADRs, severity, de-challenge and re-challenge were recorded.

Inclusion criteria: We selected patients of both sexes and age above 18 diagnosed with cancer, treated with chemotherapy for the same. Only those who are willing to participate in the study were included.

Exclusion criteria: Patients who are unwilling to participate and patients who are in need of a surgery or radiotherapy were excluded from the study.

Study tool

Here 330 patients were recruited for the study and data regarding demographic, clinical and treatment details were collected in a specially designed data collection form. The ADR reporting form designed by Central drugs standard control organization (CDSCO) was used for reporting of ADRs. The reported ADRs were assessed for causality using both WHO causality assessment scale and Naranjo's algorithm. The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADRs and categorized them into "certain", "probable", "possible", "unlikely", "conditional/unclassified" and "unassessable/unclassifiable". Naranjo's algorithm determines the causality of ADRs classified into definite, probable, possible and doubtful. It consists of set of 10 questions with each questions score given from -1 to 2. Based on the score ADRs were classified as ≥9= definite ADR; 5-8= probable ADR; 1-4 = possible ADR. The Modified Hartwig and Siegel scale classifies severity as "mild", "moderate" and "severe".

RESULTS

In our study we enrolled 330 patients out of which 250 patients developed ADRs. Out of these patients, most common age group that experienced maximum ADRs were 46-60 years (39.2%) followed by age group above 60 years (35.2%) and 18-45 years (25.2%) (Figure 1). Out of 250 patients, 154 (61.6%) were females and 96 (38.4%) were males (Figure 2). The most common cancer spotted during the study period was carcinoma of cervix (23.2%) followed by carcinoma of breast (13.6%), esophagus (9.2%) and stomach (8.8%) (Figure 3). The prescribing pattern of combination therapy (83.6%) was more compared to monotherapy (16.4%) as described in Figure 4. Platinum compound which includes Cisplatin was found to be the most common cause of ADRs followed by Taxanes (Figure 5). The most commonly prescribed combination regimens were PC, FOLFOX, TC, ECF and DC (Figure 6). WHO causality assessment scale indicated that 68.4% of the reactions were 'probable', 24.6% of the reactions were 'possible' and

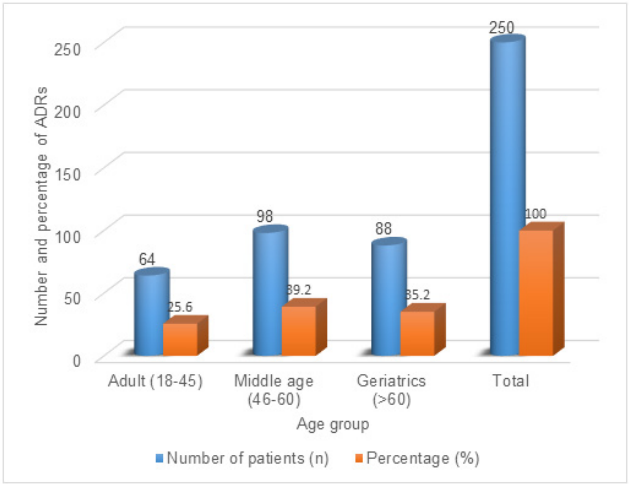

Figure 1: Age distribution of patients who developed ADRs while undergoing chemotherapy.

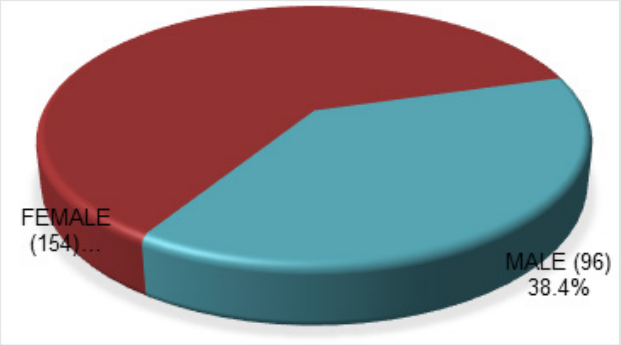

Figure 2: Gender wise distribution of patients who developed ADRs while undergoing chemotherapy.

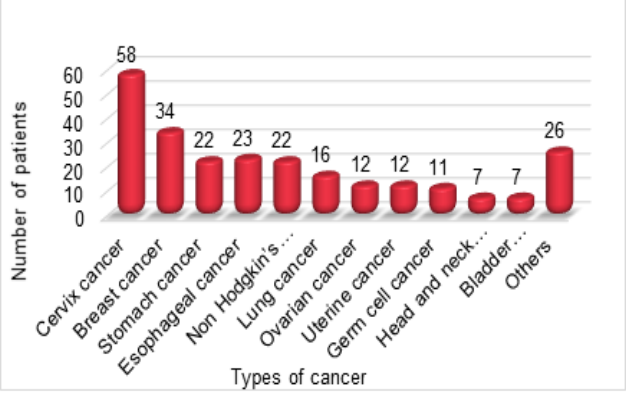

Figure 3: Distribution of different type of cancer in the study population.

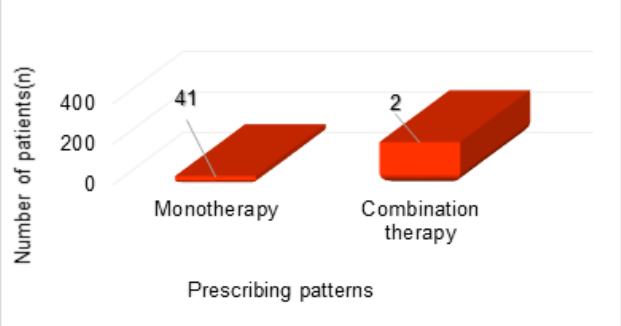

Figure 4: Prescribing patterns of chemotherapeutic agents.

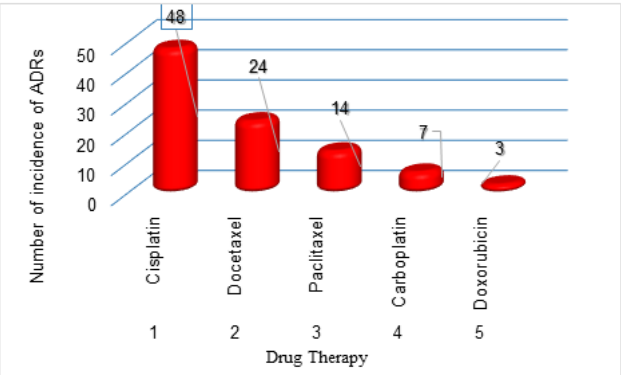

Figure 5: Occurrence of ADRs due to monotherapy.

'certain' were less (6%) (Figure 7). According to Naranjo's algorithm, 68.4% of the reactions were 'probable' and 24.6% of the reactions were 'possible' (Figure 8). The severity of the reported reactions were observed using Modified Hartwig and Siegel Scale and most of the ADRs were categorized as 'mild' (24.8%), 'moderate' (71%) and 'severe' (4%) (Figure 9). The reversible

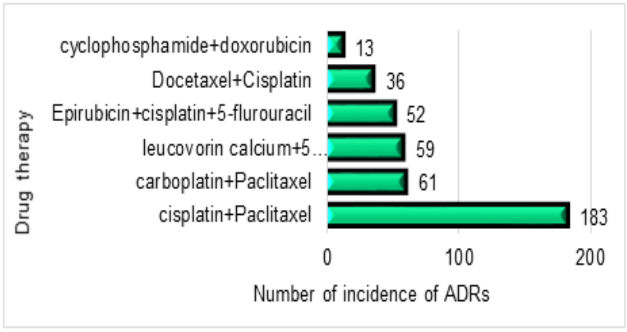

Figure 6: Occurrence of ADRs due to combination drug therapy.

PC = Cisplatin+ Paclitaxel; TC = Carboplatin+ Paclitaxel; FOLFOX = 5-Fluorouracil+Leucovorin+ Oxaliplatin; ECF= Epirubicin+Cisplatin+5-Fluorouracil; DC=Docetaxel+Cisplatin; AC=Doxorubicin + Cyclophosphamide

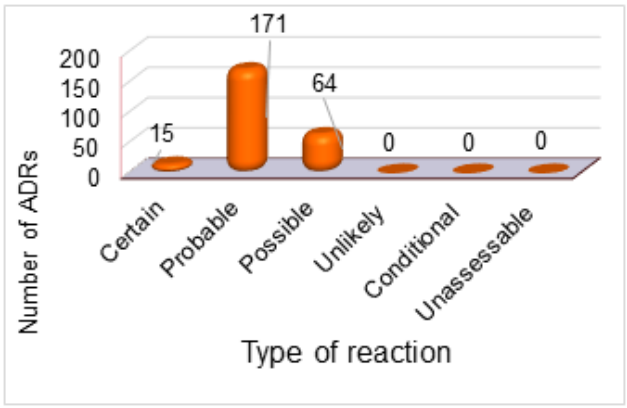

Figure 7: WHO causality assessment of ADRs.

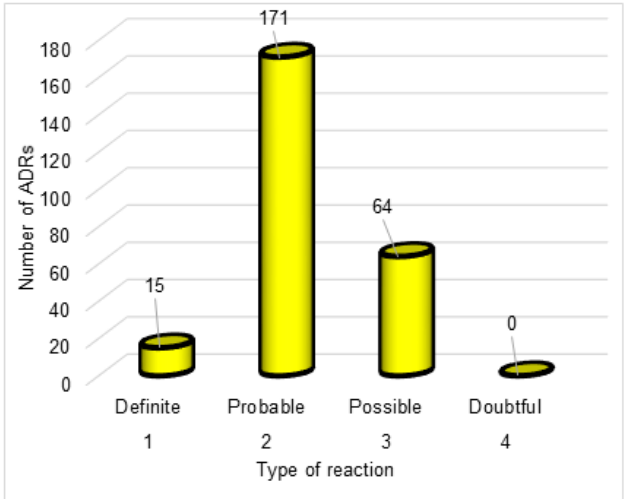

Figure 8: NARANJO causality assessment of ADRs.

ADRs observed were vomiting, nausea, diarrhea, anemia, peripheral neuropathy and neutropenia (Figure 11). Few of the patients experienced some significant life-threatening adverse events like cardiotoxicity and nephrotoxicity. Six cases of ototoxicity (35.29%), five cases of toxic epidermal necrolysis (29.41%) and two cases of nephrotoxicity (11.76%) were seen in patients who received cisplatin. Four cases of hepatotoxicity (23.5%) (Figure 10 and 12). Gastrointestinal system was more affected by ADRs followed by hematological, dermatological, neurological and other systems (Figure 11). Common ADRs observed due to cisplatin were nausea and vomiting (combination therapy=64.2%, monotherapy=78.2%) followed by diarrhea (combination therapy=12.8%, monotherapy=52.1%), peripheral neuropathy (combination therapy=22.01%, monotherapy=26.08%) and anemia (combination therapy=27.52%, monotherapy=30.43%) (Figure 13). Among the population, 160 patients were continued with the suspected drug of which 58 were continued by dose reduction. About 25 patients were either discontinued with the suspected drug or an alternative drug was given and 7 patients were shifted to ICU (Figure 14).

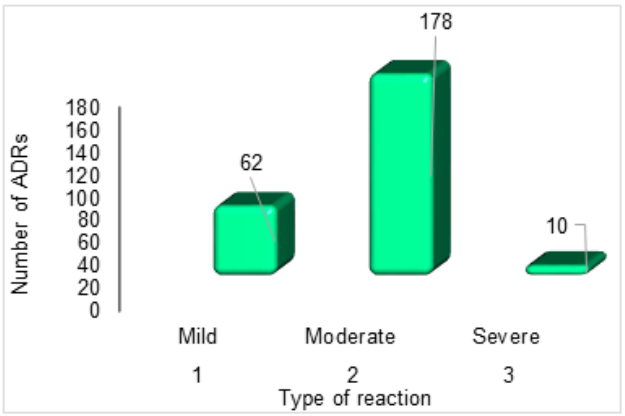

Figure 9: Severity of ADRs by Modified Hartwig and Seigel Scale.

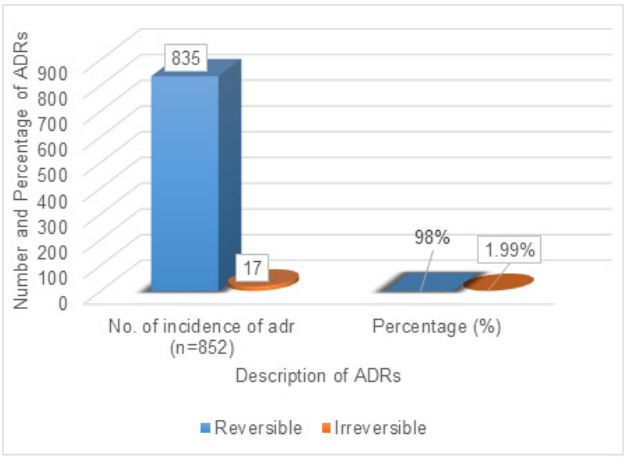

Figure 10: Description of incidence of ADRs in patients receiving chemotherapy.

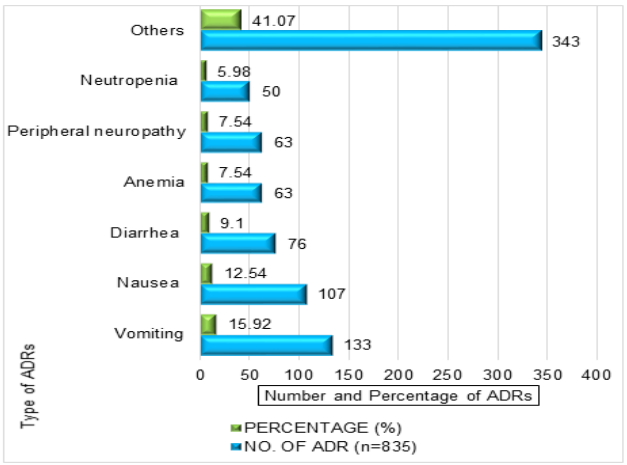

Figure 11: Reversible ADRs.

DISCUSSION

In this prospective observational study, we enrolled 330 patients undergoing chemotherapy among which 250

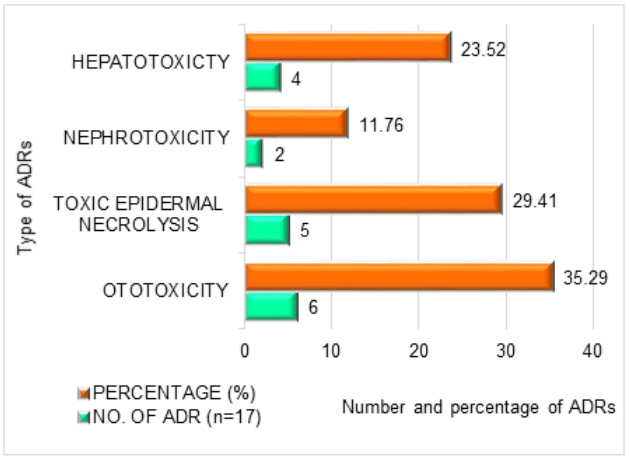

Figure 12: Irreversible ADRs.

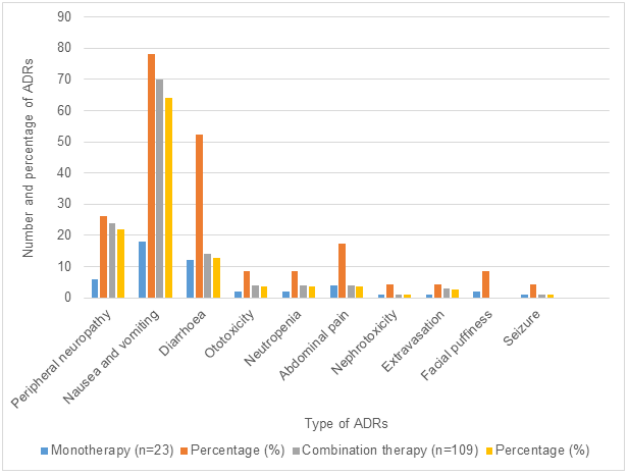

Figure 13: Cisplatin induced ADRs in chemotherapy.

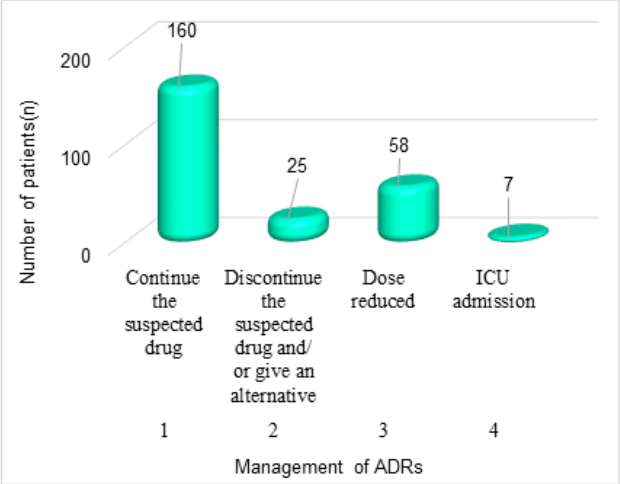

Figure 14: Management of adverse drug reactions.

patients developed ADRs. We evaluated the incidence of ADRs occurring in cancer patients treated with chemotherapy in a tertiary care hospital. We also studied the causality and severity by using respective assessment scales.

In this study 852 adverse events (ADRs) were observed in patients with nausea and vomiting (78% in monotherapy and 67% in combination therapy) being the most common. Anticancer drugs are more prone to cause ADRs as they are cytotoxic and can damage the normally dividing cells along with the cancer cells. Another reason is that the patient remain on multi drug treatments making them more vulnerable to ADRs.[7]

Frequency of adverse drug events in the age group 46-60 (39.2%) years were observed to be 98 when compared to other age groups. This may be because of the decreased metabolizing capacity and excretory functions leading to the accumulation of drugs[8,9] in the body and other comorbidities.[4] Here 64 (25.6%) patients under 46 years and 88 (35.2%) patients above 60 years developed chemotherapy induced ADRs respectively. This was in agreement with the findings of Poddar *et al.* were maximum number of adverse events were in the age group of 41-60 years.[10]

Study correlates to the fact that risk of cancer increases as age progresses.[11] This is similar to the study done by Karthigeyan *et al.* which says that, the incidence rises in 30-35 years of age and peaks at 55-65 years, with a median age of 38 years (age 21-67 years).[12]

In our study it was observed that, the most common cancer presented during the study period was carcinoma of cervix (23.2%) followed by carcinoma of breast (13.6%), esophagus (9.2%) and stomach (8.8%). These may be due to variations in the food habits and lifestyles in different geographical location. This was in accordance with the study done by Sharma A *et al.*[13]

We found that majority of patients were females (61.6%) when compared to males (38.4%). It is consistent with the study done by Rademaker M *et al.*[14] The reason for this increased risk includes gender related differences in pharmacokinetics, immunological and hormonal factors.[15,16] Women generally have lower body mass, reduced hepatic clearance and metabolize drugs at different rates compared to men.[17] This variation can also be due to difference in medications and treatment guidelines followed in different setups.[7]

The prescribing pattern of combination therapy (83.6%) is more compared to monotherapy (16.4%). The most commonly prescribed drugs in monotherapy were cisplatin followed by docetaxel, paclitaxel, carboplatin and doxorubicin. Cisplatin was commonly used because of its reasonable cost and prevalence of cancer for which cisplatin is a treatment option in our centre. This was in contrast to the study done by Behera SK *et al.* which reported imatinib was the most commonly prescribed drug.[6]

The cytotoxic effects of platinum compounds is due to the inhibition of replication by cisplatin- DNA adducts and induction of apoptosis.[18] They are often selected due to their strong anti-tumor activity despite its severe adverse effects.[19] Even though platinum responsiveness is high, patients undergoing monotherapy will ultimately relapse with cisplatin-resistant disease which leads to cisplatin resistance. The mechanism of cisplatin resistance includes changes in cellular uptake and efflux of cisplatin, increased biotransformation and detoxification in the liver and increase in DNA repair and apoptotic mechanism. In order to overcome the resistance, cisplatin is used in combination with other drugs.[20] The most commonly prescribed combination regimens were PC, FOLFOX, TC, ECF and DC.

In our present study, monotherapy developed more ADRs when compared to combination therapy. Cisplatin was the drug causing more adverse drug reactions in monotherapy and the regimen PC (cisplatin+ paclitaxel) in combined therapy. The study is contrast with the study done by Vijay M Motghare *et al.* in which incidence of ADRs observed with combination therapy were more compared to monotherapy.[21]

Assessment of causality by WHO causality assessment scale indicated that 68.4% of the reactions were 'probable', 24.6% of the reactions were 'possible' and

'certain' were less (6%) as re-challenge was not attempted in many of the patients.

According to Naranjo's algorithm, 68.4% of the reactions were 'probable' with a score ranging from 5-8 and 24.6% of the reactions were 'possible' with a score ranging from 1-4.

The severity of the reported reactions were assessed using Modified Hartwig and Siegel Scale and accordingly,[9] most of the ADRs were categorized as 'mild' (24.8%), 'moderate' (71. %) and 'severe' (4%).

Out of 852 ADRs developed, we observed 835 (98%) reversible ADRs and 17 (1.99%) irreversible ADRs.

The reversible ADRs observed were vomiting, nausea, diarrhea, anemia, peripheral neuropathy and neutropenia.

Few of the patients experienced some significant life-threatening adverse events like cardio toxicity and nephrotoxicity. This is similar to the study done by Prathyusha *K et al*.[22]

Six cases of ototoxicity (35.29%), five cases of toxic epidermal necrolysis (29.41%) and two cases of nephrotoxicity (11.76%) were seen in patients who received cisplatin. Four cases of hepatotoxicity (23.5%). More common ADRs observed due to cisplatin were nausea and vomiting (combination therapy=64.2%, monotherapy=78.2%) followed by diarrhea (combination therapy=12.8%, monotherapy=52.1%), peripheral neuropathy (combination therapy=22.01%, monotherapy=26.08%) and anemia (combination therapy=27.52%, monotherapy=30.43%). This is in accordance with study by Surendiran *et al*.[23] The mechanism of chemotherapy induced nausea and vomiting is through activation of chemoreceptor trigger zone.[24,25]

In relation to the organ system, our results are consistent with the previous studies,[16] where the reactions affecting gastrointestinal tract were found to be among the most frequently affected ADRs.

Despite experiencing life threatening ADRs, it was analysed that 160 patients were continued with the suspected drug of which 58 where continued by dose reduction. 25 patients were either discontinued with the suspected drug or an alternative drug was given and 7 patients were shifted to ICU.

CONCLUSION

Cancer chemotherapeutic agents have a high propensity to cause ADRs owing to their action on rapidly dividing cells. Hence early detection of these ADRs may help in minimizing the harm either by modifying the dose or by changing the concerned drug with a suitable alternative.

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.

Prescribing patterns of anticancer drug in combination therapy was more compared to monotherapy. Cisplatin-based chemotherapy caused various adverse effects in cancer patients.

The causality assessment revealed that most of the ADRs occurred were of 'possible' and 'probable' category.

There were no fatal reactions that claimed the life of a patient during study period. By implementing Pharmacovigilance one can promote drug safety, better patient care and early detection of ADRs.

In our study, we assessed the incidence of Adverse Drug Reactions, analyzed the prescribing patterns, categorized the causality and severity of ADRs, notified the suspected ADRs in order to promote the judicious use of suspected drugs with regular and sustained monitoring. This knowledge may help in preventing the occurrence of similar reactions in future.

This study suggests that the hospital-based monitoring of ADRs by clinical pharmacists is an essential role in prevention of ADRs.

ACKNOWLEGEMENT

We would like to express our heartfelt gratitude and regards to our guides Dr. Jishnu R.K, Mrs. V. Lalitha and Dr. Rajkumar for their guidance, monitoring and constant encouragement throughout the course of this research project. Support and guidance given by Dr. Haja Sherief were remarkable. Co-operation of patients and healthcare professionals led to the successful completion of this Project. Last but not least, we thank almighty for his blessings and express our gratitude towards parents for their support and encouragement.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADR: Adverse Drug Reactions; **PC:** Cisplatin+

Paclitaxel; **TC:** Carboplatin+ Paclitaxel; **FOLFOX:** 5-Fluorouracil+Leucovorin+ Oxaliplatin; **ECF:** Epirubicin+Cisplatin+5-Fluorouracil; **DC:** Docetaxel+Cisplatin; **AC:** Doxorubicin + Cyclophosphamide.

SUMMARY

A prospective observational study was performed in cancer patients receiving chemotherapy to analyze the incidence of adverse drug reactions by studying the prescribing patterns and thereby evaluating their causality and severity. We enrolled 330 patients undergoing chemotherapy among which 250 patients developed ADRs. 852 ADRs were observed in patients with nausea and vomiting (78% in monotherapy and 67% in combination therapy) being the most common. The prescribing pattern of combination therapy (83.6%) was more compared to monotherapy (16.4%). The causality assessment revealed that most of the ADRs occurred were of possible and probable category.

REFERENCES

1. Dipiro J, Talbert RL, Yee GC, Matzke GR, Wells BG, *et al*. Pharmacotherapy: A pathophysiologic approach; (6th edn) MC Graw-Hill companies, Inc, USA. 2005.
2. Lamy PP. Adverse drug effects. Clinics in Geriatric Medicine. 1990;6(2):293-307.
3. Fyhr A, Akselsson R. Characteristics of medication errors with parenteral cytotoxic drugs. European Journal of Cancer Care. 2012;21(5):606-13.
4. Gunaseelan V, Mandal SK, Prasad VN, Khumukcham R, Devi PP, Singh TT. Adverse drug reactions to cancer chemotherapy in a regional cancer center in Northeast India. Int J Pharm Sci Res. 2014;5(8):3358-63.
5. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: Risks, consequence and new directions for its management. Cancer. 2004;100(2):228-37.
6. Behera SK, Kishtapati CR, Gunaseelan V, Dubashi B, Chandrasekaran A, Selvarajan S. Chemotherapy Induced Adverse Drug Reactions in Cancer Patients in a Tertiary Care Hospital in South India. Journal of Young Pharmacists. 2017;9(4):593.
7. Hanlon JT, Ruby CM, Artz M. Geriatrics: Pharmacotherapy A Pathophysiologic Approach. 5th Ed. New York: McGraw Hill Inc. 2002;79-89.
8. Kaur K, Sood M, Bhagat S, Singh T, Jain M, Arora D, *et al*. Spontaneous adverse drug reaction monitoring in oncology: Our experience. Indian Journal of Cancer. 2015; 52(3):467.
9. Sharma A, Kumari KM, Manohar HD, Bairy KL, Thomas J. Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care teaching hospital in Bangladesh. Dhaka Univ J Pharm Sci. 2009;8(1):11-6.
10. Rademaker M. Do women have more adverse drug reactions?. American Journal of Clinical Dermatology. 2001;2(6):349-51.
11. Pearce A, Haas M, Viney R, Pearson SA, Haywood P, Brown C, *et al*. Incidence and severity of self-reported chemotherapy side effects in routine care: A prospective cohort study. PLoS One. 2017;12(10):e0184360.
12. Kaarthigeyan K. Cervical cancer in India and HPV vaccination. Indian Journal of Medical and Pediatric Oncology. Official Journal of Indian Society of Medical and Pediatric Oncology. 2012;33(1):7.
13. Prasad A, Datta PP, Bhattacharya J, Pattanayak C, Chauhan AS, Panda P. Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care teching hospital in Gujarat. Int J Basic Clin Pharmacol. 2015;4:284-9.
14. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. Pharmacological Research. 2007;55(2):81-95.
15. Poddar S, Sultana R, Sultana R, Akbor MM, Azad MA, Hasnat A. Pattern of adverse drug reactions due to cancer chemotherapy in tertiary care teaching hospital in Bangladesh. Dhaka University Journal of Pharmaceutical Sciences. 2009;8(1):11-6.
16. Rout A, Panda RK, Mishra V, Parida P, Mohanty S. Pharmacovigilance in cancer chemotherapy in regional cancer center of Eastern India: Prospective observational study. International Journal of Basic and Clinical Pharmacology. 2017;6(8):1910-6.
17. Bressler R, Bahl JJ. Principles of drug therapy for the elderly patient: In Mayo clinic proceedings. Elsevier. 2003;78(12):1564-77.
18. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: Molecular mechanisms of action. European Journal of Pharmacology. 2014;740:364-78.
19. Gottesman MM, Fojo TSE. Multidrug resistance in cancer: Role of ATP dependent transporters. Nat Rev Cancer. 2002;2(1):48-58.
20. Motghare VM, Dhargawe NH, Bajait CS, Mahobia V, Diwan AK. Study of prescription patterns and adverse drug reaction monitoring in patients of oral cavity malignancies attending radiotherapy department in a tertiary care teaching institute. Indian Journal of Pharmacy and Pharmacology. 2017;4(1):38-41.
21. Surendiran A, Balamurugan N, Gunaseelan K, Akhtar S, Reddy KS, Adithan C. Adverse drug reaction profile of cisplatin-based chemotherapy regimen in a tertiary care hospital in India: An evaluative study. Indian Journal of Pharmacology. 2010;42(1):40.
22. Prathyusha K, Rao AY, Praneeth G, Kishore P. Pattern of Adverse Drug Reactions in Cancer Patients at a Tertiary Care Hospital in Telangana Region of South India. Breast. 2017;71(15.38):53-23.
23. Stewart DJ, Kucharczyk J, Miller AD. Nausea and vomiting: Recent research and clinical advances. CRC Press, Boca Raton, USA. 1991.