



A retrospective analysis of adverse drug reactions induced by cancer chemotherapeutic agents at a tertiary care hospital in South India

M Malathi¹, K Raadhika², T Thirumalai Nambi³

¹ Coordinator, ADR Monitoring center, Institute of Pharmacology Madurai Medical College, Madurai, Tamil Nadu

² Associate Professor, Institute of Pharmacology, Madurai Medical College, Madurai, Tamil Nadu

³ Senior Pharmacovigilance Associate, ADR Monitoring center, Madurai Medical College, Madurai, Tamil Nadu

Abstract

Aim: To Retrospectively analyze the Adverse Drug Reactions (ADR) induced by Cancer Chemotherapeutic agents at a Tertiary Care Hospital using WHO-UMC Causality assessment scale (WCAS).

Background: Advancement in modern era of Chemotherapy has brought significant survival benefits to patients. However, ADR are very common, with considerable economic and clinical implication leading to disability and even death. Documentations of ADRs associated with cancer chemotherapy and analysis of their severity and preventability would create awareness among health care providers and prevent recurrence in subsequent chemotherapeutic cycles. 1680-1700 newly diagnosed cancer patients are registered every year for Chemotherapy in this tertiary care hospital. Breast, Ovarian, lung, hematological cancers are the commonest. Most of the adverse events were non-serious like vomiting, headache, abdominal pain, itching, dyspepsia, anemia, vertigo and oral mucositis. Also, serious events like raised urea, serum creatinine, elevated liver enzymes, hyperbilirubinaemia, hematemesis, hemoptysis, thrombocytopenia and pancytopenia were also reported. This study will help to monitor the adverse events caused by the anti-cancer drugs and subsequent management and prevention of adverse events by symptomatic treatment without disturbing the cycle of chemotherapy.

Materials and Methods: All in-patients newly registered for cancer chemotherapy for whom ADR were reported by Individual Case Safety Reports (ICSR) were retrospectively analyzed from January 2018 to December 2018. The causality Assessment was carried out by Causality Assessment Committee (CAC) using WHO Causality Assessment Scale and reported as "certain", "probable" and "possible. The outcomes of reactions were reported as Recovered, Recovering, Not recovered, Fatal, Recovered with sequelae, and Unknown as per guidance document for spontaneous reporting, Indian Pharmacopoeia Commission-2014.

Results: Out of 72 reported ADRS 35 were male patients and 37 Female patients. Non serious reactions of 60 ICSR's and 12 were serious reactions. Outcome of reactions was recovering/ recovered from the ADR. Most of the ICSR's were reported as Probable as per WHO-UMC Causality assessment scale. The drugs like Cisplatin, Paclitaxel, Doxorubicin, Docetaxel, Imatinib, Oxaliplatin, Vincristine and Zoledronic acid were reported for both serious and non-serious adverse events.

Conclusion: Among 72 reported ICSR's majority are non-serious reactions and treated symptomatically without breaking the cycle of chemotherapy. Serious ADR's like nephrotoxicity (or) liver toxicity were monitored periodically and the dose adjusted or the cycle was stopped to prevent further catastrophe. ADR reports will help in monitoring drug safety in oncology and prevent the sufferings of patient.

Keywords: individual case safety reports, suspected adverse drug reaction reporting form, WHO-UMC causality assessment scale

1. Introduction

Background

According to the National Cancer Registry Programme of the India Council of Medical Research (ICMR), more than 1300 Indians die every day due to cancer. Between 2012 and 2014, the mortality rate due to cancer increased by approximately 6%. Side effects of cancer therapy are one of the most important issues faced by cancer patients during their illness. Pharmacovigilance, namely the science and activities aimed at monitoring the safety of drugs, is particularly important in oncology due to the intrinsic biologic toxicity of antineoplastic agents, their narrow therapeutic windows, and the high doses and rigid timing of treatment regimens. In oncology, clinical research is regularly producing new drugs to use in chemotherapy protocols. The introduction of new drugs that act on specific molecular targets has led to the expectation of low systemic

toxicity. Indeed, the safety profiles of new drugs differ from the typical toxicity patterns of conventional chemotherapy, so patients taking these new drugs must be monitored closely to identify new adverse effects.

2. Materials and Methods

This retrospective, descriptive, case record study was conducted on patients admitted to the Medical Oncology ward of the tertiary care hospital. The data regarding ADRs, necessary demographic details of patient, were directly collected from patients case sheets as recorded by the doctors and residents of Medical Oncology Department. 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.

The Suspected Adverse Drug Reaction Reporting Form

(SADRRF) given by Pharmacovigilance program of India (PvPI) was used. The study involved analysis of Adverse Drug Reactions of 72 different patients reported by Individual Case Safety Reports (ICSR) from January 2018 to December 2018. The causality Assessment was carried out by Causality Assessment Committee (CAC) using WHO Causality Assessment Scale and reported as “certain”, “probable” and “possible”. The seriousness of reactions were categorized as Fatal, Life threatening, Hospitalization, Congenital anomaly, Disability and Other Medically important. The outcomes of reactions were reported as Recovered, Recovering, Not recovered, Fatal, Recovered with sequelae, and Unknown as per guidance document for spontaneous reporting, Indian Pharmacopoeia Commission-2014.

3. Results

Clinical Diagnosis

Most of the patients were affected by Breast cancer (17.0%) followed by hematological cancer (11.8 %). lung cancer (10.9%), head and neck cancer (10%), stomach cancer (9%), rectal, colonic cancer 4.1%, cervical cancer (6.7%) and ovarian cancer (8.9%).

Gender wise distribution

As per Gender distribution, 35 Male patients and 37 Female patients were reported with adverse drug reaction. (Table 1).

Table 1: Gender wise distribution of ADRs

S. NO	Gender	Number OF ICSR's (N=72)
1	Male	35
2	Female	37

Age wise distribution

The age of the subjects ranges from 0-3 years-nil; 3-16 years-1; 16-40 years-19; 40-60 years-40; above 60 years-12. (Table 2) and (Figure 2). Lung cancer, stomach cancer and colonic cancer were the most prevalent cancer types in males whereas in females, breast cancer, ovarian cancer, cervical cancer and lung cancer were found to be more common

Table 2: Age wise distribution of ADRs

S. No	Age Wise Distribution	Number of ICSR's (N=72)
1	0-3	Nil
2	3-16	1
3	16-40	19
4	40-60	40
5	>60	12

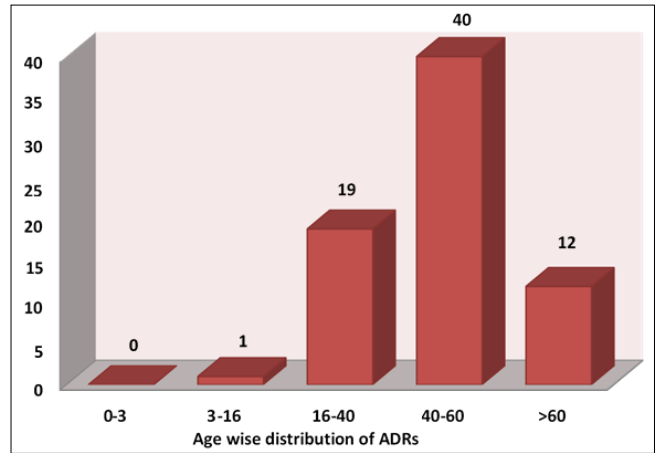


Fig 2: Age wise distribution of ADRs

ADRs Severity and outcome

Out of the 72 adverse drug reactions, 12 patients were reported as serious cases and 60 patients were reported as Non-serious cases. (Table 3) and (Figure 3).

Outcomes of 72 ICSR's reported were analyzed, it was noted that patients belonged to the category of Recovered cases-14; Recovering cases-51; Not recovered cases-2; Fatal case-1; Unknown cases-4. (Table 4) and (Figure 4).

Table 3: Severity of ADR

S. No	Severity Level	Number of ICSR's (N=72)
1	Serious case	12
2	Non serious case	60

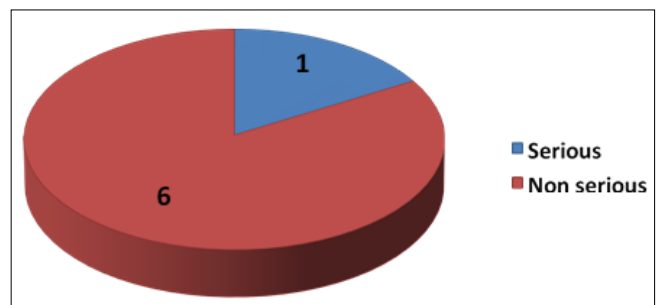


Fig 3: Severity of ADRs

Table 4: Outcomes of Reactions

S.NO	Outcomes of reaction	Number of ICSR'S (n=72)
1	Recovering	51
2	Recovered	14
3	Unknown	4
4	Not recovered	2
5	Fatal	1

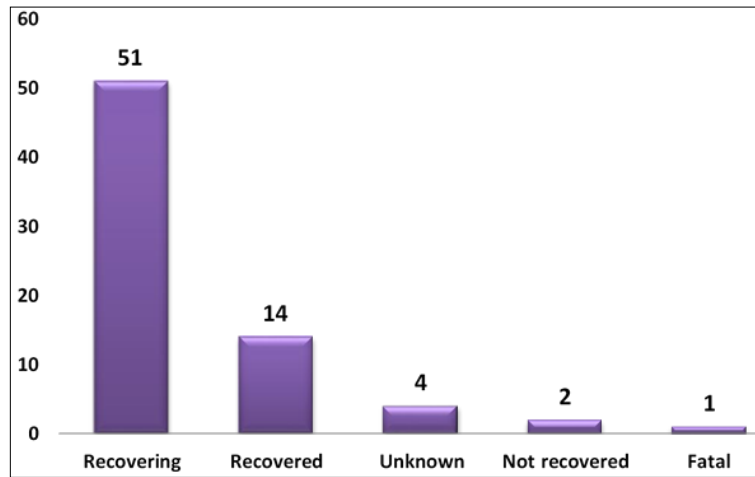


Fig 4: Outcomes of Reactions

Causality assessment

As far as causality assessment concerned, the cases were reported as Certain-2; Probable-42; Possible-28 cases and

no unclassifiable and unassessable case was reported as per WHO-UMC Causality assessment scale. (Table 5) and (Figure 5).

Table 5: Causality Assessment (As per WHO-UMC Causality Assessment Scale)

S.NO	Causality Assessment	Number of ICSR's (N=72)
1	Certain	2
2	Probable	42
3	Possible	28
4	Unlikely	0
5	Unassessable	0
6	Unclassifiable	0

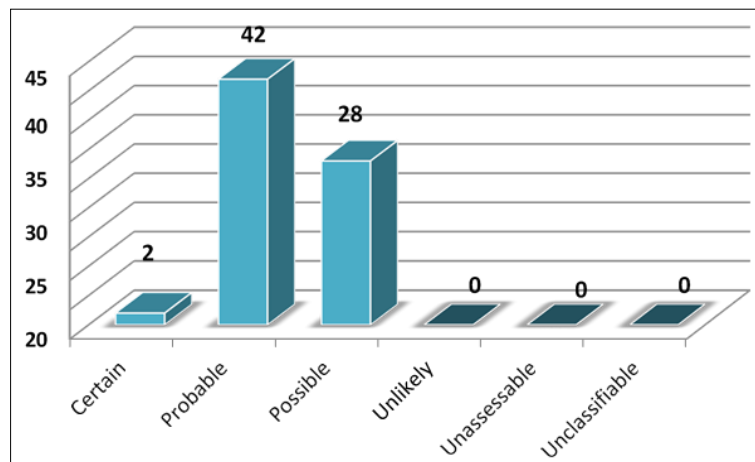


Fig 5: Causality Assessment

Chemotherapeutic agents

According to the list of drugs, Cisplatin caused most of the adverse events including serious reactions like increased urea and creatinine, hyperbilirubinaemia, elevated liver

enzymes and anaemia and followed by Paclitaxel, Doxorubicin, Docetaxel, Oxaliplatin, sorafenib, Vincristine and Methotrexate with various other events (Table 7)

Table 7: Drugs causing the adverse event

S. No	Adverse event	Drugs
1	Abdominal Pain	Oxaliplatin
2	Anemia	Cisplatin and Imatinib
3	Deep vein thrombosis	Paclitaxel and Doxorubicin
4	Dyspepsia	Doxorubicin and Imatinib
5	Erythematous rash	Paclitaxel
6	Haemoptysis	Methotrexate
7	Haemetemesis	Paclitaxel
8	Headache	Paclitaxel and Doxorubicin
9	Hearing loss	Imatinib

10	Hyperbilirubinaemia	Cisplatin, Docetaxel, Doxorubicin, Oxaliplatin, Paclitaxel and Vincristine.
11	Hyperpigmentation skin	Imatinib
12	Itching	Cisplatin and Imatinib
13	Liver enzymes elevated	Cisplatin, Docetaxel, Doxorubicin, Oxaliplatin, Paclitaxel and Imatinib.
14	Oral Mucositis	Doxorubicin and Vincristine.
15	Pancytopenia	Imatinib
16	Palmar-Plantar erythrodyesthesia	Sorafenib
17	Peripheral oedema	Oxaliplatin
18	Peripheral neuropathy	Paclitaxel and Zoledronic acid
19	Thrombocytopenia	Imatinib
20	Urea/creatinine increased	Cisplatin, Docetaxel, Doxorubicin, Paclitaxel and Zoledronic acid
21	Vertigo	Imatinib
22	Vomiting Severe	Paclitaxel and Doxorubicin

Table 8

S. No	Adverse event	Number of events
1	Abdominal Pain	1
2	Anemia	2
3	Deep vein thrombosis	2
4	Dyspepsia	3
5	Erythematous rash	1
6	Haemoptysis	1
7	Haemetemesis	1
8	Headache	2
9	Hearing loss	1
10	Hyperbilirubinaemia	10
11	Hyperpigmentation skin	1
12	Itching	3
13	Liver enzymes elevated	9
14	Oral Mucositis	2
15	Pancytopenia	1
16	Palmar-Plantar erythrodyesthesia	3
17	Peripheral oedema	1
18	Peripheral neuropathy	4
19	Thrombocytopenia	5
20	Urea/creatinine increased	16
21	Vertigo	1
22	Vomiting Severe	2
	Total	72

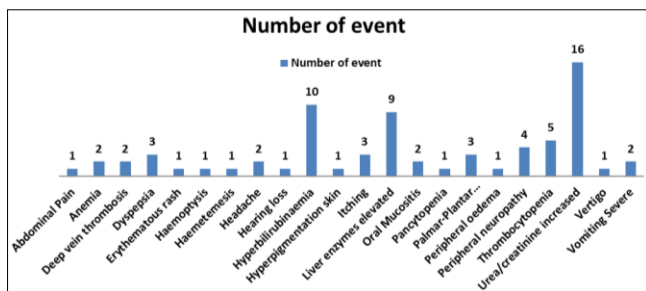


Fig 6: Number of adverse events

Prophylaxis during chemotherapy

Nausea and vomiting are preventable side effects of cancer chemotherapy. Ondansetron alone and Ondansetron in combination with Domperidone were given in 17.2% and 67.2% patients respectively for the prevention of cancer chemotherapy induced nausea and vomiting. For prevention of medications induced gastrointestinal irritation, Ranitidine 150BD mg, Omeprazole: 20 mgOD were used. The medication given for the prevention of chemotherapy induced mucositis and stomatitis were B Complex and multivitamin tablets Besides medications other prophylactic lifestyle modifications such as maintaining good oral hygiene, adequate hydration, healthy diet were encouraged.

Length of hospital stay

Patients developing ADRs stayed in the hospital for extra 1-4 days depending upon the severity of ADR and response to treatment.

4. Discussion

In total number of 72 adverse drug reactions cases, the distribution among male and female was almost same. Among the age group, the age group of 40-60 years reported for more adverse drug reactions than any other group, and followed by 16-40 years patients were affected. As far as seriousness of adverse events concerned, only 17% of the cases were reported as serious cases and remaining 83% of the cases were reported as non-serious cases. As per guidance document of Indian Pharmacopoeia Commission the majority of reaction Outcome was recovering with 51 cases, 14 cases were reported for recovered category, 2 cases were reported for not recovered, 1 fatal case and 4 unknown cases were reported. As per “WHO-Uppsala Monitoring Center” Causality Assessment, 3% of the cases were reported as “Certain”, 58% was “Probable”, 39% was reported as “Possible”, and no case was reported as “Unlikely”, “Unpredictable”, and “Unassessable”. As far as the adverse events were concerned 22 % was reported for elevated serum urea and creatinine; 14 % reported for Hyperbilirubinaemia; 13% reported for elevated liver

enzymes; 7% reported for thrombocytopenia; 6 % reported for Peripheral neuropathy and followed by other events like anaemia, Vomiting, headache, abdominal pain, hematemesis, Haemoptysis, hearing loss, itching, Palmar-Plantar erythrodyesthesia and Vertigo. It was observed that the chemotherapy with Cisplatin, Docetaxel, Doxorubicin, Paclitaxel and Oxaliplatin should be monitored for renal parameter, liver enzymes and bilirubin level to prevent the damage of the organ. The patients on Imatinib should have a periodic monthly monitoring of complete blood count to prevent bone marrow suppression. The non-serious events like headache, vomiting, itching, oral mucositis and dyspepsia can be managed symptomatically without disturbing the cyclic chemotherapy as the benefit of the drug was more than these non-serious adverse events.

5. Conclusion

The anti-cancer drugs induced adverse drug reactions are very common in patients undergoing cyclic chemotherapy for various carcinoma. Among 72 reported ICSR's most of them are non-serious reactions. The non-serious ADR's can be treated symptomatically without breaking the cycle of chemotherapy. But the serious ADR's like nephrotoxicity and liver toxicity can be monitored periodically and the dose can be adjusted or the cycle can be stopped to prevent further damage of the particular organ. Hence measures can be taken to monitor and report ADR's to understand the impact of ADR's. Pharmacovigilance is a part of healthcare systems worldwide. The WHO leads pharmacovigilance operations and provides technical support in reporting ADRs. Many countries have well-built pharmacovigilance systems, but actual incidence of ADRs is much higher than what is reported. Finally, the phenomenon of under-reporting requires great attention in oncology, especially because oncologists often consider adverse drug reactions caused by cytotoxic drugs as a "normal" phenomenon. Moreover, the underlying clinical conditions of cancer patients often make it difficult to distinguish ADRs from symptoms of cancer. Efficient management of spontaneous ADR reports is essential to monitor drug safety in oncology, where pharmacotherapy is de facto affected by a high prevalence of drug-related complications and a narrow therapeutic window.

The importance of pharmacovigilance in oncology must be highlighted with every effort, to improve safety and offer cancer patients every possible help to improve their quality of life during such a critical period of their lives.

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