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HAEMATOLOGICAL AND BIOCHEMICAL ADVERSE DRUG REACTIONS DUE TO ANTICANCER DRUGS IN A TERTIARY CARE HOSPITAL

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Abstract : Objectives of the study were to evaluate the pattern of hematological and biochemical Adverse Drug Reactions due to anticancer Drugs and to assess the causality, severity and preventability of ADR using suitable scale.The retrospective study was carried out in the Dept of Oncology during Jan- June, 2018. **Method**: Data of twenty five patients who had received chemotherapeutic agents were recorded for hematological and biochemical adverse effects. **Results**: Out of the twenty five patients received chemotherapy, there were thirty five episodes (35) of hematological adverse effects and twenty two episodes of (22) biochemical adverse effects were recorded. Anemia was the most common hematological ADR (18) seen followed by leucopenia (9). Cisplatin was the most common drug responsible for anemia followed by paclitaxel and carboplatin combination . Hyponatremia being the most common adverse reaction followed by reduced serum creatinine and hypochlorimia. Cisplatin being the common drug responsible followed by paclitaxel and carboplatin. As per our study, 54.81% of ADRs were probable category and 45.85% were of possible nature.

Probable category of causal association was established in 56% ADRs while 44% cases possible category was established. Mild ADRs constituted for 63% and moderate severity accounted for the rest(37%). More than half (56%) ADRs fell into definitely preventable category while nearly one third of ADR belonged to probably preventable category.

Keywords: *Adverse Drug Reactions, Anaemia, Hyponatremia, Cisplatin,*

Introduction

Cancer is one of the leading cause of death in both the worlds.[1] An estimated 14.1 million new cases and 8.2 million cancer related deaths occurred in 2012 as per the International agency for the Research on Cancer. The incidence of new cases may go up to 19.3 million by the year 2025. [2] Chemotherapy along with radiotherapy, surgery, immunotherapy and hormonal therapy are the treatment option available for cancer.[3]

WHO defined Adverse Drug Reactions (ADRs) as any response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of the disease or for the modification of physiological function. [4] Adverse drug reactions among hospitalized patients are found to be between 1.5-6.7 % . [5-7] It also accounts for significant morbidity and mortality.[8] Anticancer drugs have low therapeutic index. Despite the availability of ameliorating medications, the adverse drug reactions to anticancer drugs and combination regimens are common problem seen in cancer patients.

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.[9] Epidemiological studies done at Australia revealed that antineoplastic and immunosuppressive drugs are associated with 11% of adverse drug reactions.

Unawareness of healthcare professionals about ADRs, lack of time to report and lack of sufficient staff in the hospital were reported to be reasons for underreporting of ADRs from the hospital. Hematological adverse effects induced by the chemotherapy may range from anemia, leucopenia and thrombocytopenia individually or in combination as pancytopenia.[12]

Biochemical alteration was one of the major adverse reactions reported by Pai et al [10] Available reports suggest that ADRs will cost 1.7% of the total hospital budget. [13] Hence it becomes essential to recognize the pattern of ADRs occurring due to various anticancer drugs specifically concentrating on the hematological and biochemical adverse effects. . There are a very few studies done in this area of hematological and biochemical adverse effects due to anticancer drugs. The rational of the study was to evaluate the pattern of ADRs due to anticancer drugs so that we can estimate causality, severity and the preventable ADRs among patients receiving anticancer agents.

Pai SB et al reported that hyponatremia followed by neutropenia, infections, and leucopenia were the common ADR encountered with cancer chemotherapy. Cisplatin, carboplatin, cituximab, geftinib were the common culprits.[10] Shahrasbi A et al documented that anemia, neutropenia and thrombocytopenia are the three common adverse drug reactions seen in patients receiving anticancer drugs.[12] Ajitha Sharma et al reported that infections, nausea and vomiting, febrile neutropenia were the common ADRs reported due to cancer chemotherapy. Platinum related compounds, nitrogen mustards, taxanes, antibiotics were the offending agents.[14] Behera SK et al reported that anemia, neuropathy and neutropenia were the three commonest ADRs reported due to imatinib, docetaxel and gemcitabine and paclitaxel.[15] As per Danno Kastuki et al, neutropenia, peripheral sensory neuropathy diarrhea and thrombocytopenia were common adverse effects due to Oxaliplatin + Capecitabine combination.[16]

Objectives

1. To evaluate the pattern of hematological and biochemical Adverse Drug Reactions due to anticancer Drugs.
2. To find out the common chemotherapeutic agents responsible for adverse drug reactions.
3. To assess the causality ,severity and preventability of ADR using suitable scale.

Methods:

Study design : Retrospective study

Study period: Patients received chemotherapy during July- October 2017

Sample size: 25 cases

Inclusion Criteria: All patients who have received chemotherapeutic agents during the above

mentioned period at K S Hegde Charitable Hospital, Deralakatte, Mangalore with hematological and biochemical adverse effects..

Exclusion Criteria: ADRs due to drugs other than anticancer Drugs

Ethical Issue: Ethical approval was taken from Institutional Ethics Committee, KSHEMA and permission MS and HOD, Medical Oncology will be obtained.

In this retrospective study, the details of chemotherapy cycles(drug, dose, route of administration, hematological(anemia, leucopenia, thrombocytopenia), electrolyte imbalance, LFT Abnormality and renal abnormality) were recorded in the data collection proforma. Also the type of cancer, staging of cancer were noted.

Statistical Analysis: The collected information was summarized by using frequency, percentage for qualitative data and mean ± SD for quantitative data.Probability, Severity and Preventability assessment was done by using Naranjo algorithm [17], Hartwig's severity [18] assessment scale and Schumock and Thornton scale respectively [19]

Results

Twenty five cases of various cancer who had received chemotherapy were analysed. Out of this 25 patients, 18 were males and 7 were female patients. The mean age of male patients was 56.28±11.73 and 52.33±9.18 in females. The percentage of patients of different age group is given in fig 1. There were thirteen different types of cancer for which six different chemotherapy regimens were employed (Table 1) .

Hematological and Biochemical Adverse Drug Reactions: Our study focused on identifying the hematological and biochemical adverse effects reported in the case record forms. Out of these twenty five patients received chemotherapy, there were thirty five episodes (35) of hematological adverse effects and twenty two episodes of (22) biochemical adverse effects were recorded. The details were given in Table 2 and table 3 respectively.

Hematological ADR: Anemia was the most common hematological ADR (18) seen followed by leucopenia (9). Cisplatin was the most common drug responsible for anemia followed by paclitaxel and carboplatin combination (Table 2, fig 2&3). Electrolyte disturbances were the most common adverse reactions seen among biochemical ADRs. Hyponatremia being the most common followed by reduced serum creatinine and hypochlorimia (Table 3).

Drug responsible for ADR: Cisplatin being the common drug responsible followed by paclitaxel and carboplatin.(fig 4) We have estimated the causality of association of ADR with suspected drug by applying the Naranjo scale. [17] As per our study, 54.81% of ADRs were probable category and 45.85% were of possible nature (Table 4).

The majority of ADRs (61.4%) and (1.75%) were level-1 and level-2, which falls into mild severity of ADRs as per Hartwig's scale. In our study 36.84% ADRs were level-3 severity (Table 5)

The Schumock and Thornton scale was used to estimate the preventable ADRs. As per this criteria, 56.14%,28.07% and 15.78% ADRs were of definitely preventable, probably preventable and non preventable nature respectively (Table 6).

Discussions

In this retrospective study, the ADR of anticancer drugs mentioned in the case record forms were collected for a period of 4 months (June-Sept 2018) in the department of Medical Oncology. A total of 57 ADRs were found from the case record form out of which 35 related to hematological system (61.4 %) and 22 biochemical ADRs (38.6%). As per the Behera SK et al, 24% of ADRs belonged to hematological system and 1% representing the biochemical alteration in parameters.[15]. The percentage in their study was totally different due to inclusion of ADRs belonged to all systems. The higher percentage of these parameters in our study could be due to the focus only on alteration in hematological and biochemical parameters.

Common age group at which the ADRs seen was between 50-59 yrs (36%) followed by 60-69yrs (20%) and 40-49 yrs and >70 yrs (15%) each in our study . Our study findings were similar to Sharma A et al and Behera SK et al.[14,15] Male patients were affected more commonly in our study (72%) as against female patients (28%)/ This was in contrast to previous study Behera SK et al. [15]

Anemia contributed for 51.42%, Leucopenia for 25.71% and thrombocytopenia for 5.71 % of hematological ADRs in our study in contrast to anemia (24%), neutropenia (8.40%) and

thrombocytopenia (8.3%) as per Shahrasbi et al.[12] The higher percentage in our study could be due to fewer number of ADRs. Cisplatin was the commonest drug responsible for hematological

ADRs (67.64%) followed by paclitaxel and carboplatin combination (17.64%) chemotherapy regimens which constituted 80% of ADRs in our study. As per Behera SK et al imatinib and docetaxel were the two commonest drug responsible for ADRs. (14% and 9.55% respectively) [15]

In our study, 31.81% of biochemical ADRs were due to hyponatremia. Cisplatin was the common suspected drug to cause this ADR followed by paclitaxel and carboplatin. (Table 2). Pai SB et al had also reported similar trend of hyponatremia with Cisplatin. [10]

Conclusions

Anemia, leucopenia were the two common ADRs of the hematological system. Cisplatin , Paclitaxel in combination with carboplatin were the suspected drugs responsible for the above ADRs. Hyponatremia being the common biochemical ADR seen and Cisplatin, Paclitaxel with carboplatin again was the suspected drug to cause this ADR.

Probable category of causal association was established in 56% ADRs while 44% cases possible category was established. Mild ADRs constituted for 63% and moderate severity accounted for the rest(37%). More than half (56%) ADRs fell into definitely preventable category while nearly one third of ADR belonged to probably preventable category.

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Table 1: Pattem of cancers and chemotherapy regimen

Type of cancer	Cisplatin	Pacli+ Carboplatin	Pammetrexade+ Carboplatin	Oxaliplatin+ CapIcitabine	Rituximab+ Adriamycin+ Cyclophos+ Vincristine	Mtx	Total	ıge
Esophagus	2	2	Nil	Nil	-	-	4	16
Cervix	3	Nil	Nil	Nil	-	-	3	12
Lung	-	1	2	2	-	-	3	12
Buccal mucosa	3	-	-	-	-	-	3	12
Tongue	3	-	-	-	-	-	3	12
Pyriform fossa	2	-	-	-	-	-	2	8
Hypopharynx	1	-	-	-	-	-	1	4
Soft palate	1	-	-	-	-	-	1	4
GE Junction	1	-	-	-	-	-	1	4
Supraglottis	1	-	-	-	-	-	1	4
NHL	-	-	-	-	1	-	1	4
Rectum	-	-	-	-	-	-	1	4
Vallecula	Nil	-	-	-	-	1	1	4
Total	17	3	2	2	1	1	25	100
Percentage	68	12	8	8	4	4	100	

Table 2: Hematological Adverse effects due to cancer chemotherapy regimens

ADRs	Cisplatin	Pacli+ Carbo	Pammetrexade+ Carbo	Oxaliplatin+ Capicitabine	Ritux+Adria+ Cyclophos+Vincrist	Methotrexate	Total(N)	%
Anemia	10	4	1	1	1	1	18	51.42
Leucopenia	8	1	0	0	0	0	9	25.71
Thrombocytopenia	2	0	0	0	0	0	2	5.71
Leucocytosis	2	1	0	0	0	0	3	8.57
Thrombocytosis	1	0	1	1	0	0	3	8.57
Total	23	6	2	2	1	1	35	100
ADRs	67.64	17.64	5.88	5.88	2.94	2.94	100	

Table 3: Pattern of biochemical ADRs due to cancer chemotherapy regimens

ADRs	Cisplatin	Paclitaxel+ Carboplatin	Pammetrexade+ Carboplatin	Oxaliplatin +Capecitabine	Total	Percent
Hyponatremia	4	2	1	-	7	31.81
Decreased Creatinine	1	2	1	-	4	18.18
Hypochlorimia	3	-	-	-	3	13.63
Decreased Blood urea	-	-	1	1	2	9.1
Hypoalbuminemia	1	1	-	L	2	9.1
Hyperkalemia	-	-	-l	1	1	4.54
Hypokalemia	1	-	-	-	1	4.54
Hypouricemia	1	-	-	-	1	4.54
Hypocalcemia	-	1	-	-	1	4.54
Total	11	6	3	2	22	100
Percent	50	27.27	13.63	9.1	100	

Table 4:Causality Assessment by Naranjo Scale

Type of Association	**No of ADR**	**Percentage of ADR**
Definite(≥9)	0	0
Probable (5-8)	32	56.14
Possible (0-4)	26	43.85
Doubtful (≤ 0)	0	0
Total	57	100

Table 5: Severity Assessment of ADR as per Hartwig's Scale [19]

Level	Explanation	Number and percentage of ADRs (n=57)
Level 1 Mild	The ADR requires no change in treatment with the suspected drug	35 (61.4%)
Level 2 Mild	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or treatment is required or no increase in length of stay.	1(1.75%)
Level 3 Moderate	The ADR requires the suspected drug to be withheld, discontinued or otherwise changed and or an antidote or treatment is required with no increase in length of stay.	21 (36.84%)
Level 4 Moderate	Any level 3ADR that requires the length of hospital stay by atleast 1 day or the ADR is the reason for admission	Nil
Level 5 Severe	Any level 4 ADR that requires intensive medical care	Nil
Level 6 Severe	ADR that causes permanent harm to the patient	Nil
Level 7 Severe	ADR either directly or indirectly leading to death of the patient	Nil
		57(100%)

Table 6:ADR Preventability Scale: (Schumoch and Thornton) [18]

Type of preventability	No of ADR	Percentage of ADR
Definite preventable	32	56.14%
Probable preventable	16	28.07%
Not preventable	09	15.78%

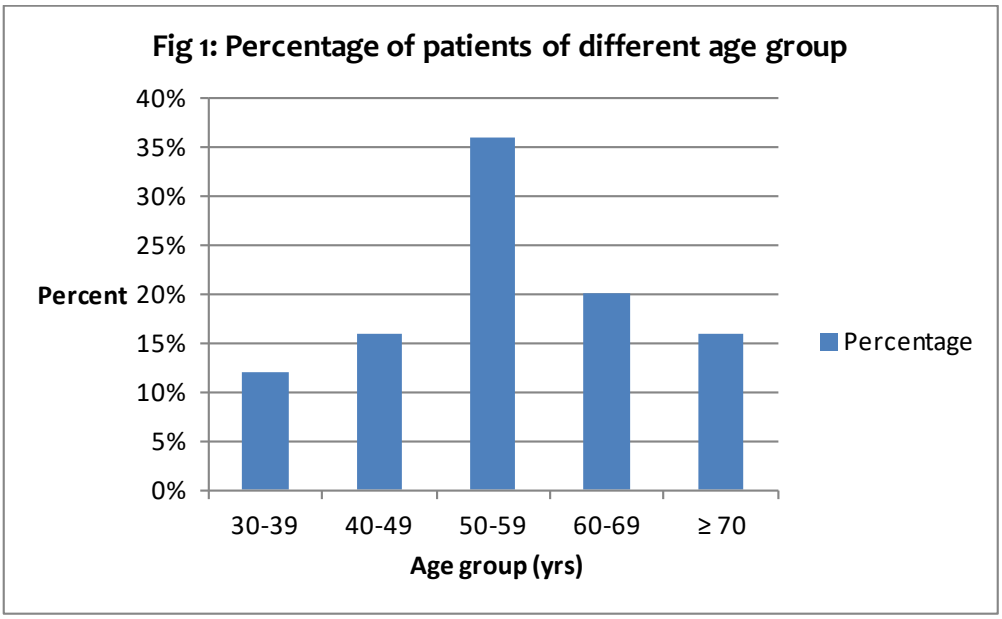
Fig 1: Percentage of patients of different age group
40%
35%
30%
25%
Percent 20%
15%
10%
5%
0%
30-39
40-49
50-59
60-69
≥ 70
Age group (yrs)
Percentage

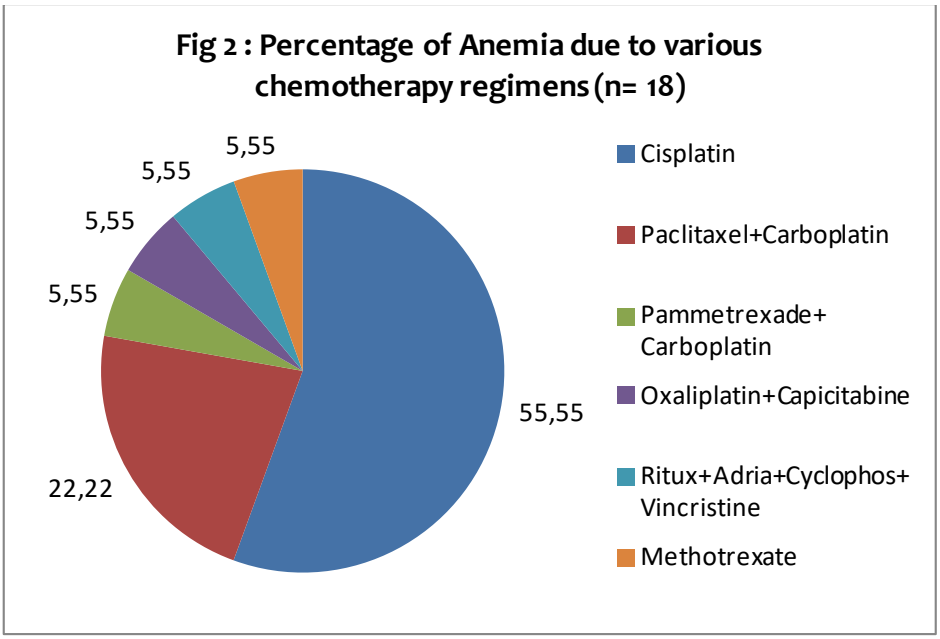
Fig 2 : Percentage of Anemia due to various chemotherapy regimens (n= 18)
5,55
5,55
5,55
5,55
55,55
22,22
Cisplatin
Paclitaxel+Carboplatin
Pammetrexade+ Carboplatin
Oxaliplatin+Capicitabine
Ritux+Adria+Cyclophos+ Vincristine
Methotrexate

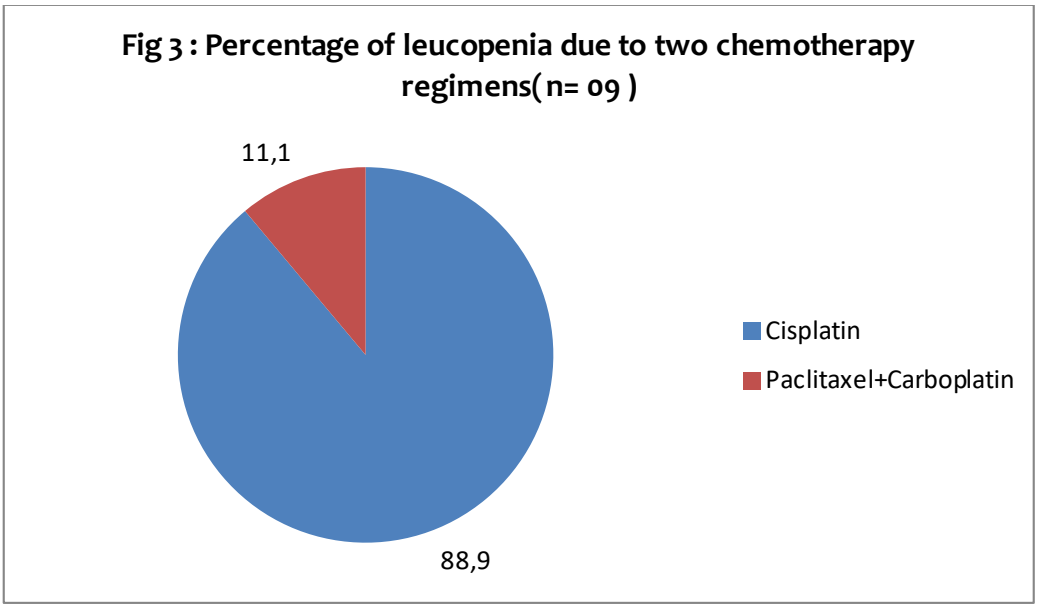
Fig 3 : Percentage of leucopenia due to two chemotherapy regimens(n= 09)
11,1
88,9
Cisplatin
Paclitaxel+Carboplatin

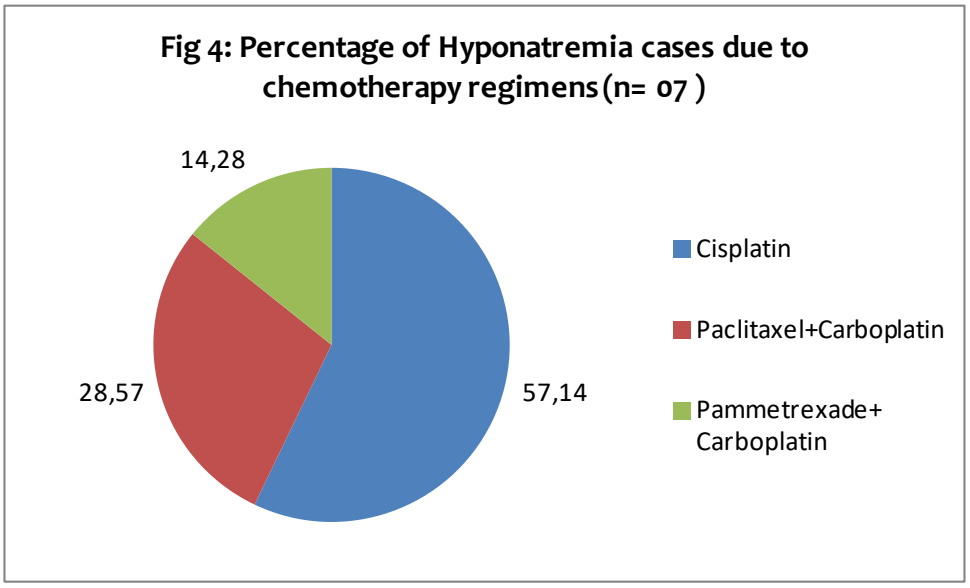
Fig 4: Percentage of Hyponatremia cases due to chemotherapy regimens (n= 07)
14,28
28,57
57,14
Cisplatin
Paclitaxel+Carboplatin
Pammetrexade+ Carboplatin