ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Incidence of Adverse Drug Reactions in Patients on Cancer Chemotherapy in a Tertiary Care Teaching Hospital.

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ABSTRACT

To assess the incidence of ADRs and their causal relationship to chemotherapeutic agents and to evaluate the severity and preventability of the ADRs. Patients above 18 years of age, on cancer chemotherapy were included. ADRs experienced by patients were identified and categorized using National Cancer Institute Common Terminology Criteria version 3.0 Questionnaire. The causality assessment of suspected ADRs was done using WHO and Naranjo's scales, severity assessment of ADRs using Hartwig and Siegel scale and preventability of ADRs using Schumock and Thornton scale. Results: The study was conducted in 109 patients (46 males, 63 females; mean age 53.75±12.75 years). Majority of the patients had breast cancer. Dry mouth and taste disturbances, were major ADRs found in 82.50% patients, dermatological ADRs alopecia, eczema and acne in 68.80%, hematological ADRs in 52.20%, and the least were the constitutional symptoms and renal ADRs (9.10% each). Causality assessment of ADRs using WHO scale identified 70.50% ADRs as Possible, 25.9% as Probable and only 1 ADR had a "Certain" causal link with the drug. Naranjo scale identified 61.4% ADRs as Probable, 36.6% as Possible and only one ADR had a "Definite" causal link with the drug. Severity assessment showed 65.90% as mild, 34.86% as moderate and none as severe ADRs. Nausea, vomiting, anorexia, fever, decrease in hemoglobin and neutrophil count were definitely preventable, diarrhea and constipation were probably preventable and the rest were not preventable. By implementing the ADR monitoring and reporting system, safe use of medications can be achieved.

Keywords: cancer, chemotherapy, adverse drug reactions, causality, severity, preventability.

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ISSN: 0975-8585

INTRODUCTION

Adverse drug reactions (ADRs) are a cause of significant morbidity and mortality and a major limitation in the provision of healthcare to patients and majority of the ADRs are believed to be preventable [1]. Cancer chemotherapeutic agents mainly affect the rapidly growing cells, such as blood cells, hair cells, germ cells and the cells lining the oral cavity and the gastrointestinal tract. Cancer chemotherapeutic drugs are often associated with several ADRs and the safety profile of each drug varies. Chemotherapeutic drugs have a range of side effects that depend on the type of medications used causing great physical and psychological burdens to the patient and their caregivers [2]. Common ADRs include depression of the immune system, resulting in potentially fatal infections, fatigue, thrombocytopenia, nausea and vomiting and alopecia. Damage to specific organs may occur, leading to cardiotoxicity, hepatotoxicity, nephrotoxicity, ototoxicity and encephalopathy [3].

The possible methods for preventing significant ADRs are monitoring, screening, closer laboratory test monitoring, patient risk assessment and patient counseling. It is essential that the health care professionals have a thorough knowledge about the adverse effects of the drugs including its predictability and reversibility, frequency and severity, predisposing factors, causal relationship to dosage and duration of treatment and prevention [4].

A study was conducted to identify the prevalence of suspected ADRs in patients on various cancer chemotherapeutic regimens, the causal relationship of the identified ADRs with the cancer chemotherapeutic drug regimens prescribed, the severity and the preventability of the ADRs.

MATERIALS AND METHODS

A prospective study was conducted to assess the incidence of ADRs in patients admitted in the oncology wards of a 1700 bedded University hospital to receive chemotherapy from 2nd cycle, with the approval of the Institutional Ethics committee and the consent of the patients. Data including patient demographics, types and stages of cancer, cancer chemotherapeutic regimens given and co-medications prescribed, pre-medications given before chemotherapy were obtained from patient medical records and the direct interview of the patients. The ADRs experienced by the patients were graded by using National Cancer Institute Common Terminology Criteria version 3.0 for adverse reactions [5]. The ADRs were also distributed according to age, gender and system affected.

The causal relationship between the suspected ADRs and the drugs was assessed using WHO [6] and Naranjo's scales [7]. The severity assessment of suspected ADRs was done using Hartwig and Siegel scale [8] and the preventability of suspected ADRs was assessed using Schumock and Thornton scale [9].

WHO causality assessment scale is recommended by the Uppsala Monitoring Centre, a WHO collaborating Centre for International Drug Monitoring. The scale is used for the evaluation of causal relationship of drugs to its adverse effects. If there is a direct causal link between the drug and the ADR, then the reactions is pertained to be 'certain' with the drug. If the reaction is unlikely to be attributed to a disease or other drugs, then the reaction is pertained to be 'probable' with the drug. If the reaction could also be explained with another drug or disease and the information on the drug withdrawal may be lacking, then the reaction is pertained to be 'possible' with the drug. If the event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) and disease or other drugs provide plausible explanations, then the reaction is 'unlikely' with the drug.

The Naranjo's Algorithm, a questionnaire designed by Naranjo, et al. comprises of objective questions with responses yes, no or do not know. Scores are given accordingly and the drug reaction can be classified as definite, probable or possible. If there were any previous conclusive reports on this reaction, then a score of +1 is given to that particular question; if the answer to this question is either no or don't know then a score of 0 is given. If the adverse event appeared after the suspected drug was administered, then a score of +2 is given; if the answer to this question is no or don't know then a score of -1 or 0 is given respectively. If the adverse reaction improved when the drug was discontinued or a specific antagonist was administered, then a score of +1is given; a score of 0 is given if the answer to this question was either no or don't know. If the adverse reaction reappeared when the drug was re-administered, then a score of +2 is given; a score of -1 or 0 is

given if the answer to this question was no or don't know respectively. If there are alternative causes (other than the drug) that could on their own have caused the reaction, then a score of -1 is given; if the answer to this particular question is no or don't know then a score of +2 or 0 is given respectively.

The modified Hartwig and Siegel scale classifies severity of ADR as mild, moderate or severe with various levels according to factors like requirement for change in treatment, duration of hospital stay and disability produced by the adverse drug reaction. If the ADR requires no change in the treatment with suspected drug then it is classified under severity of MILD level-1. If the ADR requires that suspected drug be withheld, discontinued or otherwise changed, no antidote is required or other treatment is required and there is no increase in length of stay, then it is classified under severity of MILD level-2. If the ADR requires that suspected drug is withheld, discontinued, otherwise changed and/or an anti-dote or other treatment is required, there is no increase in length of stay, then this is classified under MODERATE level-3 or any level 3 ADR that increases length of stay by at-least one day then it is classified under MODERATE level-4a. If the ADR is the reason for admission then it is classified under MODERATE level-4b. If any level 4 ADR that requires intensive medical care then it is classified under SEVERE level-5. If the ADR causes permanent harm to the patient, then it is classified under SEVERE level-6. The ADR directly or indirectly leads to the death of patient, and is classified as SEVERE level-7.

The modified Schumock and Thornton scale classifies ADRs as definitely preventable, probably preventable and not preventable based on a set of questions for each level.

Statistical Analysis

Chi-square test was used to analyse the severity of ADRs with age, gender, history of drug allergy, co-morbidity, concurrent radiation therapy and past surgical history. A P value of <0.05 was considered significant.

RESULTS

The study included 109 patients (46 (42.30%) males, 63(57.70%) females; mean age 53.75±12.75 years). Majority of the patient population (41.20%) were in the age range of 45-60years. 36.6% patients aged 60 years and above; 16.5% patients were in the age range of 30-45 years and 6% patients were in the age of below 30 years. History of drug allergy was reported by 2 patients.

Table 1: Type and Stage of Cancer

Type of cancer	Stage I	Stage II	Stage III	Stage IV	No. of Patients(N= 109)	%
Breast	0	9	16	5	30	27.52
Lung	0	1	3	3	7	6.42
Colorectal	0	3	3	5	11	10.09
Cervical	0	1	3	3	7	6.42
Ovarian	1	0	7	3	11	10.09
Gastro-Intestinal	0	2	6	4	16	14.67
Head& Neck	0	2	3	2	7	6.62
Prostate	0	2	0	0	2	1.83
Urinary bladder	0	1	2	0	3	2.75
Testis	0	0	0	1	1	0.91
Lymphoma	2	3	3	1	9	8.25
Leukemia	0	2	0	0	2	1.83
Others	0	1	2	0	3	2.75

*Others: Endometrial Cancer, Gall bladder, Pancreas

Table 1 depicts the types and stages of cancer of the study population. Majority of the (27.5%) patients were diagnosed with breast cancer stages 2 to 4, followed by 14.67 % with, gastric cancer stages 2 to 4, 10.09% with colorectal cancer stages 2 to 4, 10.09% with ovarian cancer stages 1, 3 and 4 and rest of the cancer types accounting to less than 10% each. Most of the patients were in stage III cancer (44.03%).

Diabetes was the co-morbidity found in majority of the patients (29 patients, 26.6%) followed by hypertension in 27 patients (24.8%) and the rest were coronary artery disease in 3 patients (3%), tuberculosis, asthma, chronic kidney disease and thyroid nodule in less than 5% of the population. Aluminum hydroxide gel was drug co-prescribed in 107 (98.16%) patients, followed by domperidone in 105 (96.3 %) patients, dexamethasone in 97 (88.9%) patients, pantoprazole in 97 (88.99%) patients and Megestrol acetate in 91(88.99%) patients.

Table 2: Chemotherapeutic Agents Prescribed

DRUG	No of patients (N=109)	%
Paclitaxel	40	36.60
Capecitabine	30	27.50
Cyclophosphamide	25	22.90
Cisplatin	20	18.30
Doxorubicin	17	15.50
Carboplatin	15	13.70
Gemcitabine	15	13.70
Docetaxel	15	13.70
5-Flourouracil	14	12.80
Vincristine	10	9.30
Epirubicin	10	9.30
Etoposide	10	9.30
Zoledronic acid	9	8.30
Oxaliplatin	6	5.50
Prednisolone	6	5.50
Vinorelbine	5	4.60
Becaivizumab	4	3.70
Daunorubicin	2	1.80
Methotrexate	2	1.80
Flutamide	1	0.90
Trabectidine	1	0.90

Table 2 explains the cancer chemotherapeutic drugs given for the study population. Paclitaxel was the most commonly prescribed chemotherapeutic agent for 40 (36.6%) patients, followed by capecitabine for 30 (27.5%) patients, cyclophosphamide for 25 (22.9%) patients and the least prescribed was Trabectidine (1patient and 0.92%).

Table 3 describes the various cancer chemotherapeutic regimens prescribed for study population based on the type of cancer. Taxol, Anthracycline and Cyclophosphamide (TAC) regimen was given for 21 (70%) breast cancer patients; platinum based regimen was given for 6 (85.7%) patients with lung cancer; platinum based regimen for gynecological and gastro intestinal cancers, of which ovarian cancer and colorectal cancer were predominant respectively.

Of 109 patients, gastrointestinal ADRs were the major group of ADRs found in about 90 (82.50%) patients, followed by dermatological ADRs in 75 (68.8%) patients, hematological ADRs in 57(52.2%) patients, and the least were the constitutional symptoms and renal ADRs in 10 (9.1%) patients each. Alopecia was the most common ADR in 66 (60.5%) patients among all the dermatological ADRs, followed by eczema in 10 (9.1%) patients and acne in 7 (6.4%) patients. Other dermatological ADRs were expressed in less than 5% of the total population. Of these gastrointestinal ADRs, dry mouth was the most reported ADR in 39 (35.8%) patients, followed by taste disturbances and anorexia in 37 (33.9%) patients. The incidence of nausea and vomiting was found in 31 (28.4%) patients and 25 (22.9 %) patients respectively. Based on the blood level monitoring, it was found that 55(50.4%) patients receiving the chemotherapy had decreased hemoglobin levels (less than 10g/dl). The WBC count was reduced to less than 4000cells/cu mm in 10 (9.10%) patients only. The

ISSN: 0975-8585

constitutional symptoms like insomnia, tiredness and fever occurred in less than 10% of the patient population. Dyspnea was the most common respiratory ADR reported by 37 (33.9%) patients, followed by cough in 25 (22.9%) patients and the least reported was nasal obstruction in 4 (3.70%) patients. Burning micturition was the renal ADR reported by 11(10.10%) patients followed by the urinary retention in 9 (8.25%) patients. Tinnitus was experienced by about 31.20% of the patients and oral candidiasis was reported by less than 1% of the total patients (Table 4).

Table 3: Chemotherapy Regimens Prescribed

Cancer type	Type of Cancer	Chemo-Regimen	No of Patients	%
	Breast (n=30)	TAC	21	70.0
		Capecitabine based	8	26.7
		Carbopaltin + Gemcitabine	1	3.3
	Lung (n=7)	Platinum based	6	85.7
		Erlotonib + Capecitabine +Etoposide	1	14.23
	Colorectal (n=11)	Platinum + 5-Flurouracil (5-FU)	7	63.6
		Becavizumab based	4	36.4
Gynecological cancer (n=19)	**Cervical**	Taxol based	7	36.8
	Ovarian	Paclitaxel + Carboplatin	7	36.8
		Doxo+Carboplatin	3	15.7
		Trabectidine	1	5.2
	Endometrial	Doxorubicin +Cisplatin	1	5.2
Gastrointestinal cancer (n=18)	**Esophageal**	Cisplatin+5-FU	4	22.2
		Etoposide+ Capecitabine	2	11.1
	Gastric	Taxol +Platinum	7	38.9
		Etoposide+Capecitabine	2	11.1
	Liver	Doxorubicin +Cisplatin+ Capecitabine	1	2.7
	Gall Bladder	Cisplatin+ Gemcitabine	1	2.7
	Pancreatic	Gemcitabine+Carboplatin	1	2.7
Head and Neck cancer (n=7)	**Oral Cavity**	Taxol+Cisplatin+5-FU	4	57.1
	Larynx	Taxol+Cisplatin+5-FU	1	14.3
	Glottis	Taxol+Carboplatin	1	14.3
	Pharynx	Cisplatin+5-FU	1	14.3
Urological Cancer (n=6)	**Prostate**	Taxol+Prednisolone +Zoledronic	2	33.3
	Urinary Bladder	Gemcitabine based	3	50.0
	Testicular	Etoposide+cisplatin	1	16.7
Hematological (n=11)	**Lymphoma**	CHOP	7	63.6
		ABVD	2	18.2
	Leukemia	ALL Protocol	2	18.2

The ADRs observed in the study population with various chemotherapeutic regimens were as follows: Alopecia and dry mouth were the most common ADRs that occurred in 16(76.19%) breast cancer patients on TAC regimen, followed by taste disturbances in 14 (66.6 %) patients, abdominal discomfort and anorexia in 13 (61.9%) patients. 5(86.6%) patients with lung cancer who were on platinum based regimen had vomiting as predominant ADR followed by diarrhea in 3 patients, Vomiting and constipation (4patients each, 57.14%) were the major ADRs in 4 patients each on platinum and 5 flurouracil regimen for colorectal cancer followed by nausea and diarrhea in 3 patients each. Tinnitus was major ADR observed in 4 (57%) patients with ovarian cancer on paclitaxel and carboplatin regimen followed by abdominal discomfort, diarrhea and dyspnea in 3patients each. Alopecia and abdominal discomfort (4patients each, 57.14%) were more pronounced ADRs in 4 (57%) patients each with gastric cancer on paclitaxel and platinum regimen. Anorexia, constipation and dyspnea succeeded them. 3 patients on Taxol, cisplatin and 5-Flurouracil regimen for carcinoma of oral cavity developed alopecia. Alopecia, dry mouth, cough and dyspnea were the ADRs reported by 3(50%) patients with carcinoma of urinary bladder on gemcitabine based regimen. Taste disturbance was the most enunciated ADR in 6 (85.7%) lymphoma patients receiving CHOP as the chemo-regimen.

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Table 4: System Wise Distribution OF ADRs

SYSTEM	SYMPTOMS	No of patients (N=109)	Total No. of Patients	%
Dermatological	Eczema	10	75	68.80
	Acne	7		
	Rashes	4		
	Itching	4		
	Alopecia	66		
	Injection site reaction	2		
	Numbness in legs	2		
	Hyperpigmentation	3		
Gastro Intestinal	Abdominal discomfort	36	90	82.50
	Dry mouth	39		
	Nausea	31		
	Vomiting	25		
	Taste disturbances	37		
	Anorexia	37		
	Diarrhea	29		
	Constipation	33		
Hematological	Hb decreased (<10)	55	57	52.20
	WBC decreased (< 4000)	10		
	Neutrophil decreased (<1000)	3		
Constitutional	Tiredness	7	10	9.10
	Fever	8		
	Sleeplessness	9		
Respiratory	Cough	25	42	38.50
	Dyspnea	37		
	Nasal Obstruction	4		
Renal	Urinary Retention	9	10	9.10
	Burning Micturition	11		
	Dysuria	4		
Neurological	Tinnitus	34	34	31.2
Infectious	Oral candidiasis	1	1	1

Causality assessment done for 577 ADRs experienced by 109 patients based on WHO causality assessment scale found that 421(70.5%) ADRs had a “Possible”, 155(25.9%) ADRs had a “Probable” and only 1 ADR had a “Certain” causal link with the drug i.e. numbness of the legs caused by Capecitabine (Table 5).

The causality assessment based on Naranjo’s scale showed that 367(61.40%) ADRs had a “Probable”, 219 (36.6%) ADRs had “Possible” and only 1 ADR had a “Definite” causal link with the drug (Table 6).

The classification of severity of the ADRs experienced by the patients using Hartwig and Seigel scale showed that 71 (65.9%) patients had ADRs categorized as mild and 37 (34.86%) patients had ADRs categorized as moderate. No severe ADRs were observed (Table 7).

Preventability of the ADRs based on Schumock and Thornton Scale showed that only ADRs like nausea, vomiting, anorexia, fever, decrease in hemoglobin, decrease in WBC and reduction in neutrophil count were definitely preventable. ADRs like diarrhea and constipation were probably preventable and the rest of ADRs were not preventable (Table 8).

The most common and more pronounced adverse drug reactions were graded in accordance with the NCI-CTC version 3.0. Most of the ADRs were categorized under grade 1 with a less percentage being classified under grade 2 and 3. Grade 4 adverse drug reactions were not observed in the study (Table 9).

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Table 5: Causality Assessment of ADRs by WHO Scale

ADR	CERTAIN	PROBABLE	POSSIBLE	UNLIKELY	TOTAL
Eczema		3	7		10
Acne		1	6		7
Rashes		2	2		4
Itching		1	3		4
Alopecia		40	26		66
Injection site reaction			2		2
Numbness in legs	2				2
Hyperpigmentation		1	2		3
Abdominal discomfort		10	26		36
Dry mouth		12	27		39
Nausea		2	29		31
Vomiting		7	15	3	25
Taste disturbances		8	29		37
Anorexia		10	27		37
Diarrhoea		5	24		29
Constipation			33		33
Hb decreased (<10)		5	40	10	55
WBC decreased (<4000)			10		10
Neutrophil decreased			3		3
Tiredness		2	5		7
Fever		3	5		8
Sleeplessness			9		9
Headache			12		12
Other regions		1	3		3
Cough		10	15		25
Dyspnea		12	25		37
Nasal Obstruction			4		4
Urinary Retention		2	7		9
Burning Micturition		5	6		11
Dysuria			4		4
Tinnitus		12	15	7	34
Oral candidiasis		1			1
Total	2	155	421	20	597

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Table 6: Causality Assessment by Naranjo's Scale

ADR	DEFINITE	PROBABLE	POSSIBLE	UNLIKELY	TOTAL
Eczema		4	6		10
Acne		5	2		7
Rashes		1	3		4
Itching		3	1		4
Alopecia		50	16		66
Injection site reaction			2		2
Numbness in legs	2				2
Hyperpigmentation		1	2		3
Abdominal discomfort		16	12	8	36
Dry mouth		20	19		39
Nausea		22	18		31
Vomiting		15	10		25
Taste disturbances		29	8		37
Anorexia		30	7		37
Diarrhoea		14	15		29
Constipation		17	16		33
Hb decreased (<10)		45	4	6	55
WBC decreased (<4000)		6	4		10
Neutrophil decreased			3		3
Tiredness		4	3		7
Fever		6	2		8
Sleeplessness		5	4		9
Headache		3	9		12
Other regions		2	1		3
Cough		16	9		25
Dyspnea		18	15	3	37
Nasal Obstruction			4		4
Urinary Retention		1	8		9
Burning Micturition		4	7		11
Dysuria		3	1		4
Tinnitus		27	7		34
Oral candidiasis			1		1
TOTAL	2	367	219	17	597

Table 7: Severity Assessment by Hartwig and Seigel Scale

Severity	Male	Female	No of patients (N=109)	%
Mild	33	38	71	65.10
Moderate	13	24	37	33.90

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Table 8: Preventability by Schumock and Thornton Scale

DEFINITE	PROBABLE	NOT PREVENTABLE
Nausea	Diarrhea	Acne
Vomiting	Constipation	Rashes
Anorexia		Itching
Hb decreased (<10)		Alopecia
WBC decreased (<4000)		Injection site reaction
Neutrophil decreased		Numbness in legs
Fever		Hyperpigmentation
		Abdominal discomfort
		Dry mouth
		Taste disturbances
		Tiredness
		Sleeplessness
		Cough
		Dyspnea
		Nasal Obstruction
		Urinary Retention
		Burning Micturition
		Dysuria
		Tinnitus
		Oral candidiasis

Table 9: Grading of the Most Common ADRs
(As per the grading guidelines in NCI-CTC)

ADR	Grade1	Grade2	Grade3	Grade 4
Alopecia	36	30	0	0
Diarrhea	28	1	0	0
Vomiting	16	9	0	0
Hb decrease	38	10	7	0
WBC decrease	6	4	1	0
Neutrophil decrease	4	3	0	0

Patients' demographic data (age and gender), drug allergy, concurrent radiation therapy and underlying disease were analyzed to see their association with the occurrence of three common ADRs alopecia, vomiting and decrease in hemoglobin levels. There was significant association between gender and alopecia of grade 1 and grade 2, 3 (P = 0.003) (Table 10). Underlying disease (P = 0.02) and concurrent radiation therapy (P = 0.04) had significant association with vomiting grade 1 and grade 2, 3 (Table 11). The hematological ADR (Hemoglobin decreased) did not have statistical significance with any of the factors (Table 12).

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Table 10: Factors Associated With the Dermatological ADR (Alopecia)

Gender	Grade 1*	Grade 2,3*	p value
Male	12	20	0.003*
Female	24	10	
Age			
≤45 years	10	6	0.46
>45 years	26	24	
Drug Allergy			
Yes	1	1	0.89
No	35	29	
Underlying disease			
Yes	14	13	0.71
No	22	17	
Concurrent radiation therapy			
Yes	0	2	0.11
No	30	28	
Surgical History			
Yes	26	25	0.28
No	10	5	

grading according to the NCI-CTC
*p < 0.05 significant

Table 11: Factors Associated With the Gastrointestinal ADR (Vomiting)

Gender	Grade 1*	Grade 2,3*	p value
Male	6	3	0.83
Female	10	6	
Age			
≤45 years	0	1	0.17
>45 years	16	8	
Drug Allergy			
Yes	2	0	0.26
No	14	9	
Underlying disease			
Yes	9	1	0.02*
No	7	8	
Concurrent radiation therapy			
Yes	0	2	0.04*
No	16	7	
Surgical History			
Yes	8	2	0.17
No	8	7	

grading according to NCI-CTC
* A p value of < 0.05 is considered significant

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Table 12: Factors Associated With the Hematological ADR
(Hemoglobin decreased)

Gender	Grade 1	Grade 2, 3	p value
Male	17	8	0.87
Female	21	9	
Age			
≤45 years	5	4	0.33
>45 years	33	13	
Drug Allergy			
Yes	1	0	0.49
No	37	17	
Underlying disease			
Yes	14	11	0.055
No	24	6	
Concurrent radiation therapy			
Yes	0	1	0.19
No	38	16	
Surgical History			
Yes	11	9	0.08
No	27	8	

grading according to the NCI-CTC

DISCUSSION

The most common ADRs with clinical manifestations found in the present study were gastrointestinal [90 patients (82.50%)] and cutaneous [75patients (68.80%)] ADRs. Comparison of the observations on incidence of ADRs in the present study with those reported by other studies is expressed in table 13.

Table 13: Comparison of ADRs with Literature

ADR	Present Study	Llopis-Salvia, et al,[1][10]	Vanessa Miranda, et al, [11]	Surendiran, et al, [12]
	Alopecia	Neutrophil decreased	Neutrophil Reduced	Nausea
More	Hb decreased	Hemoglobin decreased	Mucositis	Alopecia
	Dry mouth	Platelets reduced	Nausea	Anorexia
	Taste disturbances	Mucositis	Vomiting	Vomiting
	Anorexia	Diarrhea	Constipation	Taste Distrubances
	Abdominal discomfort	Vomiting	Abdominal Pain	Diarrhea
	Tinnitus	Neuropathy	ATRA syndrome	Constipation
	Constipation	Infection	Arterial Hypertension	Tinnitus
	Nausea	Alopecia	Cerebrovascular Ischemia	Hypocalcemia
Less	Vomiting	Hypersensitivity	Hypersensitivity	Dizziness

Cancer imposes a great physical and psychological burden to the patients and their caregivers. Overall, 109 cancer patients were enrolled in the study. Most of the patients were females (57.70%). Average age of the patients was about 53 years and most of them were in the age group of 45-60years (41.20%). About 44.90% of the patients had diabetes (26.61%) as the predominant co-morbidity, followed by hypertension (24.77%). These underlying diseases may further increase the risk of ADR while receiving chemotherapy.

The present study did not limit to specific type of cancer like Yoshihiro Shibata, et al, [13] and Aziza Khanam, et al, [14] which majorly concentrated only on colorectal cancer and breast cancer respectively. The present study did not concentrate on any specific chemotherapeutic agent or regimen like a study done by Galvão, Flávio Henrique Ferreira, et al, [15] or Surendiran, et al, [12] who majorly concentrated on specific chemotherapeutic agents like Gemcitabine and Cisplatin respectively.

All the patients in the present study received the same pre-medications. This consisted of Palanosetron, Pheniramine Maleate, Dexamethasone or Hydrocortisone and Pantoprazole which reduced the incidence of nausea and vomiting to a great extent.

Adverse drug reactions

The most common ADRs identified with clinical manifestations in the present study were gastrointestinal (82.50%) and cutaneous (68.80%) whereas in the study done by Venissa Miranda et al, [11] the most common adverse drug reactions with clinical manifestations were hematologic and gastrointestinal. Similarly a study done by Llopis-Salvia et al, [10] reported that the hematological adverse drug reactions (71.50%) were more intense than gastrointestinal (11.40%) and cutaneous (1.2%) which is different from the present study. This can be attributed to the use of the colony stimulating factors along with the chemotherapy

Of the cutaneous adverse drug reactions experienced by the patients, alopecia (60.50%) was predominant, followed by eczema (9.1%) and acne (6.4%). This is in accordance with the study done by Noor Kamil et al, [16] which reported that alopecia was the single most common (64.30%) adverse effect. This study also suggested that pigmentary changes were the second most common (18.2%) adverse effect but this is contrary to the present study where the pigmentary changes occurred only in 2.75% of the patient population.

Gastrointestinal ADRs were the most common (82.50%) among all adverse drug reactions, of which dry mouth was found in 35.80% patients, followed by anorexia and taste disturbances in 33.90% patients each. This is in accordance to the study done by Venissa Miranda et al, [11] which reported that mucositis/stomatitis as the most common gastrointestinal adverse drug Reaction followed by diarrhea and vomiting. But in the present study the incidence of nausea (28.40%) and vomiting (22.90%) was very less. This is attributed to the use of good premedications and other co-prescribed anti-emetics.

The incidence of anorexia (33.90%) was very less in the current study. This is due to the use of the drug Megesterol Acetate. The present study also monitored the blood sugar levels which showed that 28 patients (25.60%) had increase in their blood sugar levels (>120mg/dl) with no history of Diabetes Mellitus. This is attributed with the use of steroids and Megesterol acetate during chemotherapy.

Of 109 patients in the study, 55 patients (50.40%) had hemoglobin count less than 10gm/dl and only 3 patients (2.75%) had neutrophil count less than < 40%. This is contrary to the study done by Llopis-Salvia et al, [10] which reported 60.5% of patients had a reduced neutrophil count and hemoglobin count was reduced only in 10.6% of the patients. This can be attributed to the use of prophylactic colony stimulating factors along with the chemotherapy.

A causality assessment was done for ADRs experienced by 109 patients based on WHO causality assessment scale and it was found that most of the ADRs were under the category of “Possible” (70.50%) followed by “Probable”(25.90%) and only 1 ADR had a “Certain” causal link with the drug i.e. numbness of the legs caused by Capecitabine. When the same causality assessment was done by using the Naranjo’s scale, most of the ADRs were found to have “Probable” (61.40%) followed by “Possible”(36.60%) and only 1 ADR had a “Definite” causal link with the drug. This is accordance to the study done by Surendiran, et al, [12] which reported that based on WHO causality scale 69% were “Possible” and 31% were “Probable” reactions, but when the causality assessment was done using Naranjo’s scale 62% were “Probable” reactions and 38% were “Possible” reactions. This change in the causal relationship could be due to the more objective nature of the Naranjo’s algorithm.

In this study, an attempt was also made to assess the association between the patient demographics (age, gender), disease (underlying disease) and medication (drug allergy and concurrent radiation therapy). The association between these factors and the three most common ADRs of the study population (Alopecia,

vomiting and decrease in hemoglobin levels) were assessed. It was found that the gender had significant association with alopecia and underlying disease and concurrent radiation therapy had significant association with vomiting. To our knowledge, this was the first report given in Indian population on the association of the above mentioned factors on incidence of ADRs.

In this study, only 22% of ADRs were preventable as per Schumock and Thornton Scale which in consistence with those reported in literature. There is an urgent need to implement prevention strategies to reduce the considerable burden of ADRs. Given the wide variety of drugs implicated, and a huge array of ADRs that were identified affecting almost every organ system in the body, prevention is likely to require complex multi-faceted intervention strategies.

CONCLUSION

Chemotherapy has high potential to cause ADRs in cancer patients. Most of the ADRs in this study were mild and hence they do not affect the treatment. Majority of the patients receiving cancer chemotherapy had co-morbid conditions. These underlying diseases may promote the incidence of ADR while receiving chemotherapy. The incidence of nausea and vomiting was very less in the present study. Strategies to prevent CINV were effective. The occurrence of neutropenia was very less when compared to other studies. The prophylactic colony stimulating factors used were beneficial. There was a decrease in incidence of anorexia due to the use of megesterol acetate.

This study demonstrated that monitoring for of chemotherapy related ADRs in a cancer ward is feasible, and can facilitate quality improvement initiatives, as well as potentially improve patient care. Measures to improve detection and reporting of ADRs should be taken to enhance our understanding of nature and impact of these ADRs. By implementing the ADR reporting and monitoring system, Pharmacists can promote drug safety and there by assist healthcare professionals for a better patient care.

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