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Original Research Article

Assessment of causality and severity of various reported adverse drug reactions by different classes of anti-cancer drugs

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ABSTRACT

Background: Chemotherapy involves highly complex regimens and hence accounts to high susceptibility towards Adverse Drug Reactions. All antineoplastic drugs have potential to cause one or more Adverse Drug Reactions which may vary from mild to severe form. So the aim of this study was to determine the prevalence of Adverse Drug Reactions in patients treated with chemotherapy.

Methods: After getting approval from the Institutional Ethical Committee, the prospective observational study was conducted in the Department of Pharmacology in association with Department of Radiation Oncology and Department of Medicine, Government Medical College, Srinagar between April 2015 to October 2016. All patients of either sex and any age receiving anti-cancer drugs in the inpatient department of radiation oncology were included. The mean age of the study population was 51 years and 53.9% of them were males and 46.1% of them were females. The WHO-UMC system was used for assessment of case programme and case reports. The severity of adverse drug reactions was determined by using modified Hart wig and Siegel scale.

Results: Most of the reported ADR's were moderate to mild in severity according to modified Hart wig and Siegel scale. Most of the frequent ADR's were certain followed by probable and possible according to WHO-UMC causality assessment.

Conclusions: Antineoplastic 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. Measures need to be put into place to reduce the physical, emotional and economic burden on the patient due to adverse drug reactions. Therefore, there is a need for vigilant ADR monitoring to decrease morbidity and mortality due to ADR's which require further studies on large populations.

Keywords: Anti-cancer drugs, Chemotherapy, Hart wig and Siegel scale, WHO-UMC system

INTRODUCTION

ADRs are considered among the leading causes of morbidity and mortality causing hospital visits and admissions. In relation to mortality a landmark meta-analysis of 39 prospective studies found that ADRs resulting in medical care were the fourth to sixth highest cause of death in emergency services in United States, following only ischemic cardiopathy, cancer and stroke.[1,2]

Many reports have shown that there is an increase in the number of cancer cases in India every year. This increment in the incidence of cancer in India may be attributed to poor living standards, and due to inadequate medical facilities.[3,4] Chemotherapy is employed as part of a multimodal approach to the treatment of many tumors.[5] Chemotherapy regimens are immensely complex, and cancer patients are a susceptible population with little tolerance.[6] The magnitude of adverse drug reactions (ADR's) endured by oncology patients is colossal making

them almost synonymous with the treatment.[7] An adverse drug reaction (ADR) is a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis and treatment of disease or for modification of physiological function.[8] Adverse drug reactions are considered among the leading causes of morbidity and mortality causing hospital visits and admissions. 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. The normal tissues adversely affected by these drugs are those which are rapidly dividing: the bone marrow, gastrointestinal tract and hair follicles.

METHODS

After getting approval from the Institutional Ethical Committee, the prospective observational study was conducted in the Department of Pharmacology in association with Department of Radiation Oncology and Department of Medicine, Government Medical College, Srinagar and associated SMHS Hospital, between April 2015 to October 2016.

Inclusion criteria

All the patients of either sex and any age receiving anti-cancer drugs in the inpatient department of radiation oncology were included.

Exclusion criteria

Patients who did not give consent to participate in the study.

WHO-UMC Scale

The WHO-UMC system has been developed in consultation with National Centers participating in the programme for international Drug Monitoring and is meant as a practical tool for assessment of case programme for international Drug Monitoring, also for assessment of case reports. It is basically a combined assessment taking into account the clinico-pharmacological aspects of the case history and the quality of the documentation of the observation. This method gives guidance to the general arguments which should be used to select one category over another.

Severity of adverse drug reactions

The severity of adverse drug reactions was determined by using modified Hart wig and Siegel scale as given below:[9]

Mild

Adverse drug reactions which are self limiting and able to resolve over time without treatment and did not contribute to prolongation of length of stay

Table 1: Classification of ADRs as per WHO-UMC Scale.

Term	Description
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacolo-gically, pathologically) Event definitive pharmacologically or phenomeno-logical (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if necessary
Probable/ likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal maybe lacking or unclear.
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanation.
Conditional/ unclassified	Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination
Unassessible/ unclassifiable	Report suggesting an adverse reaction Cannot be judged because information is in sufficient or contradictory Data cannot be supplemented or verified.

Moderate

Adverse drug reactions are defined as those that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in < 24 hrs or change in drug therapy or specific treatment to prevent a further outcome.

Severe

Adverse drug reactions are those that were life threatening, producing disability and those that prolonged hospital stay or led to hospitalization or required intensive medical care.

Lethal

Adverse drug reactions are those that directly or indirectly contributed to patient's death.

Patient outcomes were reported as:

- Fatal
- Fully recovered (Patient fully recovered during hospitalization)
- Recovering (patient recovering, but not fully recovered during hospitalization)
- Unknown (not documented after initial report in chart)

Statistical methods

Data was entered in Microsoft Excel spread sheet. Data was summarized in the form of tables and graphs. Categorical variables were summarized as frequency and percentage.

RESULTS

Table 2 revels that most of the patients were in the age group of 50-60 years (30.1%) followed by age group of 40-50 years (27%). There were 76 (53.9%) males and 65 (46.1%) females in this study population.

Table 2: Distribution of the study population according to age and sex.

Age (years)	Frequency	Sex		Percent
		Male	**Female**	
≤10	1	1	0	0.7
11-20	1	0	1	0.7
21-30	3	1	2	2.1
31-40	23	8	15	16.3
41-50	38	16	22	27.0
51-60	43	28	15	30.1
61-70	27	17	10	19.1
71-80	5	5	0	3.5
Total	141	76	65	100

Table 3 revels by occupation, most of the patients were belonging to two groups, i.e. Housewives (44.7%) and farmers (17.5%) and out of 141 enrolled patients, one patient was a toddler of 1 ½ year age.

Table 3: Distribution of study population according to occupation.

Occupation	Frequency	Percent
Housewife	63	44.7
Farmer	25	17.5
Business man	19	13.5
Ex-govt. employee	12	8.5
Labourer	6	4.3
Carpenter	4	2.8
Pvt. Job	3	2.1
Govt. Employee	3	2.1
Student	2	1.4
Tailor	1	0.7
Driver	1	0.7
Blacksmith	1	0.7
Total	140	100

Table 4 indicates that Carcinoma colon 19.9% was the most common malignancy in the study population followed by carcinoma breast 16.3%, stomach 15.6%, lung 9.2%, ovary and rectum 6.4%.

Table 4: Distribution of study population according to cancer type.

Diagnosis	Frequency	Percent
CA Colon	28	19.9
CA Breast	23	16.3
CA Stomach	22	15.6
CA Lung	13	9.2
CA Ovary	9	6.4
CA Rectum	9	6.4
GE junction Growth	7	5.0
CA Pancreas	5	3.5
NHL	4	2.8
CA Gall bladder	3	2.1
CA Larynx	3	2.1
CA Esophagus	3	2.1
RCC	2	1.4
CA Testis	2	1.4
Retinoblastoma	1	0.7
CUPS	1	0.7
CA Ethmoid sinus	1	0.7
Rhabdomyosarcoma (hand)	1	0.7
Periampullary CA	1	0.7
CA Rectumandovary	1	0.7
CA Thyroid	1	0.7
CA Urinary Blader	1	0.7
Total	141	100

NHL = Non-Hodgkin's lymphoma; RCC = Renal cell carcinoma; CUPS = Carcinoma of unknown primary site

Table 5: Anticancer drugs used in study population.

Name of the regimen/ drug	Frequency	Percent
Folfox (5-FU, Oxaliplatin)	27	19.14
ECF (Epirubicin, cisplatin, 5-FU)	24	17.02
Paclitaxel+Carboplatin	11	7.80
Folfiri (5-FU, Irinotican)	7	4.96
Paclitaxel+cisplatin	5	3.5
Gemcitabine+cisplatin	5	3.5
Cisplatin+5-FU	5	3.5
Cisplatin+Etoposide	5	2.8
RCHOP (Rituximab, cyclophosphamide, doxorubicin, oncovin, prednisolone)	4	2.8
Docetaxel+capecitabine	4	2.8
Paclitaxel+Gemcitabine	4	2.8
Oxaliplatin+capecitabine	4	2.8
Docetaxel+Irinotican	3	2.1
Adriamicim+Cyclophosphamide	3	2.1
Gemcitabine+Oxaliplatin	3	2.1
Docetaxil+Carboplatin	2	1.4
Sunitinib	2	1.4
Paclitaxel	2	1.4
Docetaxel+cisplatin	1	0.7
Gemcitabine+Capecitabine	1	0.7
Adriamycin+Ifosphamide	1	0.7
Formorubicin+Cyclophosphamide	1	0.7
Oxaliplatin+Bevacuzumab+capecitabine	1	0.7
CAF (cisplatin, Apristar, 5-FU)	1	0.7
Paclitaxel+cisplatin+Ifosphamide	1	0.7
BEP (Bleomycin, Etoposide, cisplatine)	1	0.7
Pemetrexed+Carboplatin	1	0.7
Pemetrexed+cisplatin	1	0.7
Docetaxel+Doxorubicin+Cyclophosphamide	1	0.7
EC (Epirubicin, Cyclophosphamide)	1	0.7
Docetaxel+Cyclophosphamide	1	0.7
Bevacuzumab+Capecitabine	1	0.7
Cisplatin+Capecitabine	1	0.7
Trastuzumab	1	0.7
Adriamycin+Paclitaxel+Trastuzumab	1	0.7
DCF (doxorubicin, cisplatin, 5-FU)	1	0.7
Vincristine+Carboplatin+Etoposide	1	0.7
Irinotican	1	0.7
Gemcitabine	1	0.7
Total	141	100

Table 5 reveals that common regimens used in the study population were those of Folfox (19.14%), ECF (17.02%), Paclitaxel + Carboplatin (7.80%) and Folfiri (4.96%).

Table 6 shows that all enrolled (141) patients in the study population developed adverse drug reactions.

Table 6: Distribution of study population according to adverse drug reaction.

ADR	Frequency	Percent
Present	141	100
Total	141	100

Table 7 shows that gastrointestinal tract was the most common organ system involved by adverse drug reactions.

Table 7: Frequency of ADRs according to organ system involved.

System Involved	Number of ADR's	Percentage
Gastrointestinal	311	37.02
Musculoskeletal and connective tissue	181	21.54
Haematological	138	16.42
Skin and Sub-cutaneous tissue	109	12.97
Neurological	56	6.66
Infections	26	3.09
Others	12	1.42
Electrolyte imbalance	6	0.71
Renal	1	0.11
Total	840	100

Table 8 shows that as per the WHO-UMC scale for assessing causality of ADRs, among 840 adverse drug reactions, 39.28% were classified as certain, 34.04% were probable and 25.35% were possible.

Table 8: Causality assessment according to WHO-UMC Scale.

WHO-UMC scale category	Frequency	Percent
Certain	330	39.28
Probable	286	34.04
Possible	213	25.35
Unlikely	11	1.3
Total	840	100

Table 9 shows that ECF regimen accounted for 19.79% of adverse drug reactions followed by Folfox 18.69% and Paclitaxel + Carboplatin 8.09%.

Table 10 shows that most of the adverse drug reactions in the study population were in the age group of 40-50 years (29.76%) followed by 50-60 years (28.92%).

Table 9: ADR status in patients according to regimens/drug used.

Regimen/drug	No. of ADR's	Percent
ECF	166	19.79
Folfox	157	18.69
Paclitaxel + carboplatin	68	8.09
FOLFIRI	45	5.35
Paclitaxel + cisplatin	35	4.16
Cisplatin + 5-FU	30	3.57
Gemcitabine + cisplatin	27	3.21
Cisplatin + etoposide	27	3.12
Oxaliplatin + capecitabine	23	2.73
Paclitaxel + gemcitabine	23	2.73
Docetaxel + capecitabine	19	2.26
R-CHOP	18	2.14
Docetaxel + irinotican	18	2.14
Gemcitabine + oxaliplatin	16	1.90
Adriamycin + cyclophosphamide	13	1.54
Paclitaxel	12	1.42
Docetaxel + carboplatin	11	1.30
Pemetrexed + carboplatin	10	1.19
BEP	10	1.19
Gemcitabine + capecitabine	8	0.95
CAF	8	0.95
Oxaliplatin + bevacizumab + capecitabine	8	0.95
Sunitinib	8	0.95
Adriamycin + ifosfamide	7	0.83
Pemetrexed + cisplatin	6	0.71
Bevacizumab + capecitabine	6	0.71
Paclitaxel + cisplatin + ifosfamide	6	0.71
Gemcitabine	6	0.71
Docetaxel+ cisplatin	5	0.59
Cisplatin+ capecitabine	5	0.59
Trastuzumab	5	0.59
Adriamycin + paclitaxel + trastuzumab	5	0.59
Irinotican	5	0.59
Docetaxel+ cyclophosphamide	4	0.47
Formorubicin+ cyclophosphsmide	4	0.47
EC	4	0.47
Vincristine + etoposide + carboplatin	4	0.47
Docetaxel + doxorubicin + cyclophosphamide	4	0.47
DCF	4	0.47
Total	840	100

Table 11 shows that Adverse drug reactions were more common in males (50.95%) as compared to female (49.04%). Table 12 shows that 52.6% of the adverse drug reactions were moderate in severity, 45.2% were mild and 2.14% were severe.

Table 10: Distribution of study population according to age and ADR.

Age (years)	No. of ADR's	Percent
≤10	4	0.47
11-20	5	0.59
21-30	24	2.85
31-40	138	16.42
41-50	250	29.76
51-60	243	28.92
61-70	156	18.57
71-80	20	2.38
Total	840	100

Table 11: Distribution of study population according to sex and ADR.

Sex	No. of ADR's	Percent
Male	428	50.95
Female	412	49.04
Total	840	100

Table 12: Severity of ADR in the study population according to Hartwig and Siegel scale.

Severity of ADR	Frequency	Percent
Mild	380	45.2
Moderate	442	52.6
Severe	18	2.14
Total	840	100

Table 13 shows that Platinum group of drugs (Cisplatin, Carboplatin, Oxaliplatin) were responsible for most of the Adverse drug reactions followed by 5-FU and Taxanes (Paclitaxel and Docetaxel). ECF regimen caused 27.79% severe adverse drug reactions followed by 5-FU + cisplatin.

A total number of 141 patients were enrolled and followed during this period that were treated for different malignancies with different chemotherapeutic agents. Out of a total of 141 patients, there were 76 (53.9%) males and 65 (46.1%) females. In this study, most of the patients i.e. 43 (30.1%) were in the age group of 50-60 years. The maximum number of females were in the age group of 40-50 years while as the highest number of males were in the age group of 50-60 years.

Most of the patients were belonging to two groups, i.e. Housewives (44.7%) and farmers (17.5%) and out of 141 enrolled patients, one patient was a toddler of 1 ½ year age. Most common malignancy in this study was colon (19.1%), breast (16.3%) and stomach (15.6%). The common used antineoplastic drug regimens for the treatment of different malignancies were Folfox (19.4%), ECF (17.02%), Paclitaxel/ Carboplatin (7.80%), Folfiri (4.96%), Paclitaxel/ Cisplatin (3.5%), Gemcitabine/ Cisplatin (3.5%) and R-CHOOP (2.8%). The overall

prevalence of ADRs in this study was 100% i.e. all 141 enrolled patients developed one or more ADRs during the follow up.

Gastrointestinal tract was the most common organ system involved by adverse drug reactions. As per the WHO-UMC scale for assessing causality of ADRs, among 840 adverse drug reactions, 39.28% were classified as certain, 34.04% were probable and 25.35% were possible. ECF regimen accounted for 19.79% of adverse drug reactions followed by Folfox 18.69% and Paclitaxel + Carboplatin 8.09%.

Table 13: Severity of ADR'S according to regimens/ drug used.

Regimen/drug	Mild	Moderate	Severe	No. of ADR's
ECF	71	90	5	166
FOLFOX	70	87	0	157
Paclitaxel + carboplatin	31	36	1	68
FOLFIRI	18	26	1	45
Paclitaxel + cisplatin	17	18	0	35
Cisplatin + 5-FU	12	15	3	30
Gemcitabine + cisplatin	11	15	1	27
Cisplatin + Etoposide	13	14	0	27
Oxaliplatin + capecitabine	11	12	0	23
Paclitaxel + gemcitabine	13	10	0	23
Docetaxel + capecitabine	5	13	1	19
R-CHOP	12	6	0	18
Docetaxel + irinotican	8	10	0	18
Gemcitabine + oxaliplatin	10	6	0	16
Adriamycin + cyclophosphamide	6	5	2	13
Paclitaxel	3	9	0	12
Docetaxel + carboplatin	4	5	2	11
Pemetrexed + carboplatin	5	4	1	10
BEP	5	5	O	10
Gemcitabine + capecitabine	2	6	0	8
CAF	6	2	0	8
Oxaliplatin + bevacizumab/ capecitabine	4	4	0	8
Sunitinib	5	3	0	8
Adriamycin + ifosfamide	4	3	0	7
Pemetrexed + cisplatin	1	5	0	6
Bevacizumab + capecitabine	3	2	1	6
Paclitaxel + cisplatin + Ifosfamide	5	1	0	6
Gemcitabine	3	3	0	6
Docetaxel + cisplatin	1	4	0	5
Cisplatin + capecitabine	3	2	0	5
Trastuzumab	3	2	0	5
Adriamycin + paclitaxel + trastuzumab	3	2	O	5
Irinotican	2	3	0	5
Docetaxel + cyclophosphamide	1	3	0	4
Formorubicin + cyclophosphamide	3	1	0	4
EC	3	1	0	4
Vincristine + etoposide + carboplatin	0	4	0	4
Docetaxel + doxorubicin + cyclophosphamide	1	3	0	4
DCF	2	2	0	4
Total	380	442	18	840

Most of the adverse drug reactions in the study population were in the age group of 40-50 years (29.76%) followed by 50-60 years (28.92%). Adverse drug reactions were more common in males (50.95%) as compared to female (49.04%).52.6% of the adverse drug reactions were moderate in severity, 45.2% were mild and 2.14% were severe. Platinum group of drugs (Cisplatin, Carboplatin, Oxaliplatin) were responsible for most of the Adverse drug reactions followed by 5-FU and Taxanes (Paclitaxel and Docetaxel). ECF regimen caused 27.79% severe adverse drug reactions followed by 5-FU + cisplatin.

DISCUSSION

Adverse drug reactions significantly diminish quality of life, increase hospitalizations, prolong hospital stay and increase mortality.[10] The financial cost of Adverse drug reactions to health care system is enormous.[10] The ADR prevalence encountered that practically all patients receiving cytotoxic drugs suffer one or more Adverse drug reactions.[11,12] The present study was a prospective and observational study conducted by the department of pharmacology in collaboration with the department of radiation oncology and department of medicine between 1st April 2015 to October 2016 with the aim of finding out the frequency of adverse drug reactions among patients treated with anticancer drugs and to ascertain the causality and severity of these adverse drugs reactions. WHO-UMC scale was used for causality assessment and modified Hart Wig and Siegel scale was used to assess ADR severity. Out of a total of 141 patients, there were 76 (53.9%) males and 65 (46.1%) females. So, number of males was more than the number of females as is also found in the studies.[12,13] The overall prevalence of Adverse drug reactions in this study was 100% i.e. all 141 enrolled patients developed one or more Adverse drug reactions during the follow up. This is in accordance with the study.[11] Total number of 840 adverse drug reactions were noted in 141 patients and the average number of adverse drug reactions per patient was 5.95. Males were more affected by adverse drug reactions than females. Most of the adverse drug reactions were encountered in the age group of 40-50 years. The most common adverse drug reactions were loss of appetite 80.90%, nausea vomiting 72.3% and alopecia 50.73%. As per WHO - UMC scale 330 (39.28%) were certain, 286 (34.04%) were probable, 213 (25.35%) were possible and 11 (1.30%) were unlikely.According to Hart wig and Siegel scale for severity assessment out of 840 ADR's 442 (52.06%) were moderate, 380 (45.02%) were mild and 18 (2.14%)were severe.Platinum group of drugs were responsible for most of the adverse drug reactions followed by 5- Fluorouracil and Taxanes.

CONCLUSION

All antineoplastic drugs have potential to cause one or more adverse drug reactions, which may vary from mild to severe form as seen in the present study. These 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. Measures need to be put into place to reduce the physical, emotional and economic burden on the patient due to adverse drug reactions. Therefore there is a need for vigilant ADR monitoring to decrease morbidity and mortality due to ADR's which require further studies on large populations. The yield could be better if monitoring is focused on individual drugs or formulations and the monitoring team includes a committed oncologist. Patient tolerance is an important factor and there is a high need for patient councelling about the therapy and possible ADR's during treatment.

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