Research Article

Drug Utilization Study and Monitoring of Adverse Events of Anti-cancer Drugs in a Tertiary Care Hospital of Bihar

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ABSTRACT

Chemotherapy is one of the integral components in the management of carcinomas. Significant variation in the response rate of individual anticancer drugs, availability of different regimens, and intolerability of combination regimens necessitate observation and evaluation of cancer chemotherapy. It has been found that the ADR profile of cancer chemotherapeutics is very less reported and the situation is even worse in India. Present study was conducted to delineate the various drugs used in carcinomas to find discrepancies, if any, between the actual and the ideal prescribing pattern of psychotropic drugs, to assess prevalence of various carcinomas and to assess adverse events. This was an observational and prospective study in which chemotherapy prescriptions and data regarding adverse event (patients complain, clinician report, laboratory data) were collected from out-patient department of Medical Oncology. Their prescriptions were collected and they were screened for adverse events of grade 1-4 of CTC version 5. Descriptive analysis was done to analyse and compare the results. Most of the patients were of age group 46-60 (39.08). Gall bladder cancer was mostly found in age group 61-70. Hodgkin's lymphoma and germ cell tumour were mostly found in younger patient. Cisplatin (15.13%), Gemcitabine (13.38%) and Carboplatin (11.40%) were mostly prescribed drugs. 20.56% of all adverse event were haematological. Most of the grade 3 adverse events were haematological. More recent developments in the availability of anticancer drugs which include molecular-targeted therapy such as targeting the proteins with abnormal expression inside the cancer cells should be utilized judiciously. Nevertheless, an early detection of these ADRs may help in minimizing the damage by either modifying the dose or changing the offending agent.

Keywords: Cancer, Chemotherapy, Drug utilization study, Adverse events, Prescriptions.

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INTRODUCTION

Cancer is a group of diseases characterized by the unchecked proliferation and spread of abnormal cells that can lead to death if left unchecked. It is a very debilitating condition that contributes significantly to the overall burden of disease. One in eight deaths worldwide is due to cancer. Cancer is associated with more deaths than the combined hazard of AIDS, tuberculosis and malaria. [1]

Chemotherapy is one of the integral components in the management of carcinomas. It is used alone or in combination with other modalities of management (radiotherapy, surgery). Chemotherapy alone or as a component of multimodality approach has been shown not only to be effective but curative too in certain cases of squamous cell head and neck carcinoma, small cell and non-small cell lung carcinoma, breast carcinoma, cervix carcinoma, uterine carcinoma and colorectal carcinoma.[2]

Setting standards and assessing the quality of care through performance review should become part of everyday clinical practice.[3] It oversees the observance of standards of medical treatment at all level of health care delivery system. It deals with the retrospective evaluation of medical care through the analysis of clinical records; to provide full benefits of medical knowledge effectively and rationally. [4]

The prescription pattern of anticancer drugs has changed significantly in the recent years because of better understanding of pathophysiology of carcinomas as well as introduction of newer drugs. Significant variation in the response rate of individual anticancer drugs, availability of different regimens, and intolerability of combination regimens necessitate observation and evaluation of cancer chemotherapy.

Drug utilization studies are a pre-requisite for the formulation of drug policies. This review identifies the problems that arise from drug usage in health care delivery system and highlights the current approaches to the

rational use of drugs. The World Health Organization (WHO) defines drug utilization study as the marketing, distribution, prescription and use of drugs in a society, considering its consequences, either medical, social and economic.[5]

Data of utilization patterns of drugs at out-patient departments of tertiary care teaching hospitals and analysis of that data is a very beneficial measure to formulate guidelines for improving the pattern of prescriptions aligned to rationality & effective outcome of the treatment with cost effectiveness. [6]

Measurement of drug use in health facilities not only describes drug use patterns and prescribing behaviour but also helps in the identification of factors responsible for the practice of poly-pharmacy and the problems associated with it. [7] Keeping this in mind, present study was conducted to delineate the various drugs used in carcinomas to find discrepancies, if any, between the actual and the ideal prescribing pattern of psychotropic drugs and to assess prevalence of various carcinomas.

Cytotoxic drugs do not distinguish between healthy and cancerous cells. Any proliferating cells exposed to these agents are killed, causing significant adverse drug reactions (ADRs) in patients. [8]

Adverse effects related to cancer chemotherapy significantly increase the cost of health care, as well as increased morbidity and mortality. This leads to further deterioration in the condition of the patient. Also, the adverse effect profile of anti-cancer drugs may differ in the Indian population due to many genetic and ethnic differences. [9]

It has been found that the ADR profile of cancer chemotherapeutics is very less reported and the situation is even worse in India. [10]

MATERIALS AND METHODS

This was an observational and prospective study in which chemotherapy prescriptions and data regarding adverse event (patients complain, clinician report, laboratory data) were collected on Monday and Thursday (twice a week only) from out-patient department of Medical Oncology between February 2019 to July 2019. The study protocol was approved by the institutional ethics committee and complied with International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki. All patients were provided written informed consent according to local guidelines.

Inclusion Criteria:

- Between 15 years to 70 years age group of all gender.
- Patient receiving Anticancer drugs with a diagnosis of cancer illness as per ICD 10 criteria. [11]

Exclusion Criteria:

- Patients below 15years or above 70 years of age
- Pregnancy
- Breastfeeding
- AIDS
- Recipient of any organ transplant or rheumatological condition on immuno-suppressive therapy
- Patients with expected survival <12 week

261 patients completed their follow-up at the end of the study. Their prescriptions were collected and they were screened for adverse events of grade 1-4 of CTC version 5.[12]

Statistical Analysis: Results obtained from this study were presented in tabular form and data were interpreted by using Microsoft Excel 365 software. Descriptive analysis was done to analyse and compare the results.

RESULTS

Table 1: Distribution of Neoplastic disorders based on age groups.

S. No.	Neoplastic Disorders	Age Group				Total
		16-30	31-45	46-60	61-70	
1.	Breast cancer (%)	03 (4.17)	18 (25.00)	39 (54.17)	12 (16.67)	72 (100.00)
2.	Gall bladder cancer (%)	03 (6.12)	10 (20.41)	15 (30.61)	21 (42.86)	49 (100.00)
3.	Lung cancer (%)	02 (3.70)	07 (12.96)	22 (40.74)	23 (42.59)	54 (100.00)
4.	CLL (Chronic Lymphocytic Leukemia) (%)	00 (0.00)	04 (17.39)	08 (34.78)	11 (47.83)	23 (100.00)
5.	Ovarian cancer (%)	02 (15.38)	03 (23.08)	04 (30.77)	04 (30.77)	13 (100.00)
6.	Carcinoma cervix (%)	02 (18.18)	03 (27.27)	04 (36.36)	02 (18.18)	11 (100.00)
7.	Prostate cancer (%)	00 (0.00)	02 (18.18)	05 (45.45)	04 (36.36)	11 (100.00)
8.	Hodgkin's lymphoma (%)	05 (62.50)	02 (25.00)	01 (12.50)	00 (0.00)	8 (100.00)
9.	Germ cell tumour (%)	04 (80.00)	01 (20.00)	00 (0.00)	00 (0.00)	5 (100.00)
10.	Colorectal cancer (%)	03 (20.00)	06 (40.00)	04 (26.67)	02 (0.00)	15 (100.00)
Total (%)		**24 (9.20)**	**56 (21.46)**	**102 (39.08)**	**79 (30.27)**	**261 (100.00)**

Most of the patients were of age group 46-60 (39.08). Gall bladder cancer was mostly found in age group 61-70. Hodgkin's lymphoma and germ cell tumour were mostly found in younger patient.

Table 2: Utilisation of Anticancer Drugs in 261 prescriptions

Name of Drug	No of Drug utilized	% of Drug Utilized
Paclitaxel	43	9.43
Nab paclitaxel	06	1.32
Docetaxel	25	5.48
Doxorubicin	38	8.33
Cisplatin	69	15.13
Cyclophosphamide	32	7.02
Epirubicin	06	1.32
Gemcitabine	61	13.38
Carboplatin	52	11.40
Pemetrexed	14	3.07
Etoposide	19	4.17
Oxaliplatin	26	5.70
Chlorambucil	11	2.41
Rituximab	04	0.88
Bendamustine	03	0.66
Bicalutamide	01	0.22
Bleomycin	12	2.63
Vinblastine	08	1.75
Dacarbazine	08	1.75
Capecitabine	15	3.29
Bevacizumab	3	0.66
Total	**456**	**100**

Cisplatin (15.13%), Gemcitabine (13.38%) and Carboplatin (11.40%) were mostly prescribed drugs.

Table 3: Frequency of Different Adverse Events in Different Grade

Type of Adverse Event (AE)	Number of AE (All Grades)	% of AE	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	27	5.44	19	8	0	0
Vomiting	61	12.30	6	44	8	3
Diarrhoea	31	6.25	4	20	7	0
Constipation	9	1.81	3	4	2	0
Abdominal pain	15	3.02	11	2	2	0
Gastritis	16	3.23	3	11	2	0
Anorexia	32	6.45	28	4	0	0
Pruritus	13	2.62	4	9	0	0
Rash	32	6.45	3	23	5	1
Alopecia	34	6.85	21	13	0	0
Lymphocytopenia	21	4.23	3	12	5	1
Neutropenia	27	5.44	6	14	5	2
Anaemia	30	6.05	12	14	4	0
Thrombocytopenia	24	4.84	4	8	12	0
Impaired Liver Function	13	2.62	10	2	1	0
Dizziness	8	1.61	4	3	1	0
Insomnia	10	2.02	7	3	0	0
Myalgia	19	3.83	13	4	2	0
Neuropathy	45	9.07	27	11	7	0
Fever	14	2.82	8	4	2	0
Oedema	11	2.22	6	5	0	0
Cough	4	0.81	4	0	0	0
Total	**496**	**100**	**206**	**218**	**65**	**7**

20.56% of all adverse event were haematological. Most of the grade 3 adverse events were haematological.

Table 4: Frequency of Adverse Events among Different Anticancer Drugs/Regimen (irrespective of grade).

Adverse Event	Number of Adverse Event	% of Adverse Event
Paclitaxel	13	2.62
Nab Paclitaxel	17	3.43
Docetaxel	32	6.45
Doxorubicin	3	0.60
Doxorubicin + Cyclophosphamide	30	6.05
Cisplatin + Paclitaxel	23	4.64
Doxorubicin + Docetaxel	21	4.23
Cyclophosphamide + Epirubicin	8	1.61
Gemcitabine + Carboplatin	22	4.44
Gemcitabine + Cisplatin	26	5.24
Carboplatin + Paclitaxel	46	9.27
Carboplatin + Pemetrexed	28	5.65
Carboplatin + Etoposide	17	3.43
Etoposide + Cisplatin	16	3.23
Gemcitabine	3	0.60
Gemcitabine + Oxaliplatin	39	7.86
Chlorambucil	7	1.41
Cyclophosphamide	7	1.41
Rituximab + Bendamustine	24	4.84
Bicalutamide	5	1.01
Docetaxel + Triptorelin	37	7.46
Docetaxel + Leuprolide	22	4.44
Etoposide + Bleomycin + Cisplatin	11	2.22
Cisplatin + 5 Fluorouracil	14	2.82
Etoposide	4	0.81
Capecitabine	21	4.23
Total	**496**	**100**

Most of the adverse events were found in patients prescribed with carboplatin + paclitaxel (9.27%), Gemcitabine + Oxaliplatin (7.86%) and Docetaxel + Triptorelin (7.46%).

DISCUSSION

The purpose of this study was to evaluate the prescription pattern and safety of anti-cancer drugs. In the department of medical oncology, most patients presented with the diagnosis of breast cancer and lung cancer followed by Carcinoma gall bladder. Deepa et al. found in their study that breast, cervix and tobacco-related cancers were majorly reported. [13]

Majority of patients in our study were elderly. Hodgkin's lymphoma and germ cell tumour were found mainly in younger patients. Kamlekar et al. found in their study that around 66.14% cancer patients were above the age of 50 years. [14] Manichavasagam et al. found that majority of cancer cases was evident in the age groups between 55 to 65 years. The age wise distribution of the patient in their study showed that there was higher incidence of cancer in this age group.[15] Same sort of observation is reported by other authors. [108-111]

Several mechanisms have been proposed for explaining how vulnerability of cancer increases with age. [17] Aging makes an organism susceptible to cancer due to hormonal disturbance increase in number of loci of chronic proliferation, and the decline in the immune surveillance. Exposure to infectious agents or creation of pro-oncogenic tissue microenvironment with increasing age can promote the development of cancer. [18]

Cisplatin, Gemcitabine and Carboplatin were mostly prescribed drugs. The paclitaxel and carboplatin combination were the most commonly prescribed double drug combination regimen in our study.

Preferring carboplatin with other anticancer drugs is due to its low neurotoxic profile than cisplatin, and also carboplatin protects nerves from paclitaxel-induced neuropathy, and work with great efficacy and safety in treatment of metastatic breast cancer. [19] The same combination regimen was preferred by Pentareddy et al. in his prescription-based study for treating carcinoma of

breast, urogenital carcinoma. [20] The gemcitabine and carboplatin are the best synergistic drugs for treating biliary tract/gallbladder carcinoma in females due to low genotoxic profile.[21] Here, in our study, this combination was preferred to treat gall bladder carcinoma. The same carboplatin was successfully used in the treatment of lung cancer in males with pemetrexed due to its high safety margin and less haematological toxicity followed by carboplatin and paclitaxel combination in head and neck cancers. The same combination was followed by Pentareddy et al.[20] for treating lung 66.66%, head and neck cancers consistently matching with our study.

An average of 1.71 anti-neoplastic medications was written in the prescriptions. Since, no prescription had more than five drugs, we can say that polypharmacy was avoided. Polypharmacy can lead to poor compliance, drug interactions, adverse drug reactions, under-use of effective treatments and medication errors. [22] Similarly, an average number of 1.97 and 1.78 cytotoxic medications per prescription was reported in the institutional studies in India and Nepal, respectively. [23]

Most of the adverse events were haematological (20.56%) followed by vomiting (12.30%) and neuropathy (9.07%). Among haematological adverse events, anaemia was found in 6.05% of patients.

Cancer chemotherapy damages rapidly dividing cells of bone marrow resulting in myelosuppression thus affecting white blood cells, platelets and red blood cells. This myelosuppression leads to a lowering of immunity and thus patients on cancer chemotherapy are at a high risk for developing various infections. Nausea and vomiting are prominent with most cytotoxic agents and is caused mainly due to direct stimulation of chemoreceptor trigger zone.

Most of the adverse events were found in patients prescribed with carboplatin + paclitaxel, Gemcitabine + Oxaliplatin and Docetaxel + Triptorelin. Sharma et al. found in their study that platinum compounds, nitrogen mustards, taxanes, antibiotics and 5-fluorouracil. This is in accordance with reports from other similar studies. [24,25]

Most of the adverse events belonged to grade 1-2 of CTCAE. Most of gastro-intestinal adverse events were of grade 1-2 whereas most of the grade 3 adverse events were haematological. A meta-analysis of 46 studies including 12,808 cancer patients treated with approved PD1/PD-L1 inhibitors reported a global incidence of any grade AEs of 26.8% and of severe grade (grade ≥3) AEs of 6.1%.[26]

Our study had certain limitation also. Cost of drugs and relation of prescribing to the socio-economic status of the patient was not included in our study. Our study also didn't include user characteristics (e.g., socio-cultural parameters and attitudes towards drugs), prescriber characteristics (e.g., specialty, education and factors influencing therapeutic decisions). Patients were not followed for the success or failure of the therapy. Causality assessment of Adverse events were not done.

CONCLUSION

Classical chemotherapeutic drugs directly target the DNA of the cell, but mutations enable the cell to develop resistance. More recent developments in the availability of anticancer drugs which include molecular-targeted therapy such as targeting the proteins with abnormal expression inside the cancer cells should be utilized judiciously. Cancer chemotherapeutic agents have a high propensity to cause ADRs as they are toxic to rapidly dividing cells in the body. Nevertheless, an early detection of these ADRs may help in minimizing the damage by either modifying the dose or changing the offending agent. There is a great need to set up an effective ADR monitoring and reporting system in all hospitals and also create awareness among health care professionals regarding the importance of this system.

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