J Young Pharm, 2016; 8(3): 220-224
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Original Article

Exploring Troublesome Symptom and Problems Experienced by Cancer Patients Undergoing Chemotherapy

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ABSTRACT

Objective: The objective of this cross-sectional, non interventional 8-months observational study was to investigate the prevalence, type and risk factors of Drug related problem (DRPs) in cancer patients admitted to the Oncology Department of Guru Gobind Singh Medical College, Faridkot, Punjab. **Methods:** A cross-sectional 8 months study was conducted from January to August 2015 at the Oncology Department of Guru Gobind Singh Medical College, Faridkot, Punjab. A total of 283 cancer patients were recruited in the present investigation analysis. **Results**: A total of 283 cancer patients participated in this current study, out of which 135 (47.70%) were males and 148 (52.30%) were females. Adverse drug reactions (ADRs) were the most common DRP, nausea and vomiting was the most common ADR (155). Female subjects experienced more DRPs 56% as compare to 44% in male cancer survivors. **Conclusion**: This study showed that DRPs were common in our setup and the risk factors associated with DRPs were female gender, number of medications, Body mass index and extremes age (in year) ranges. Early detection and timely intervention is the key to ensure a better therapeutic outcome.

Key words: Cancer Chemotherapy, Drug Related Problems, Adverse drug reactions, Drug-drug interactions, Cytotoxic agents, Oncology.

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DOI: 10.5530/jyp.2016.3.9

INTRODUCTION

With increase in number of available drugs, drugs combinations and drug users as well as more complex drug regimens lead to more side effects and drug interactions, complicated follow-up and compromised compliance of therapy.[1]

To study the overall problem burden of drug therapy/administration need a broader coverage of this crisis which is much beyond then merely ADR monitoring or drug morbidity or mortality in different setup. To look after this hazard a common term was coined called "Drug related problem" (DRP). A DRP can be defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[2] DRPs are classified in subgroups including: Need additional drug therapy, unnecessary drug therapy, ineffective drug, too low or too high dosage, adverse drug reactions, and noncompliance.[3] Drug related problems (DRPs), which includes adverse drug reactions (ADRs), unnecessary drug therapy, inappropriate choice of drugs, and untreated conditions, has been reported in up to 25% of hospitalized patients and lead to substantial morbidity and mortality.[4] Drug toxicity is also a major limitation in providing healthcare to patients and as it affects the patient's recovery as well as the economy of healthcare.[5]

Cancer chemotherapy is best state of affairs where we can extract so many relevant information regarding Drug related problems as it is a very composite blend of low safety margin drugs and need a prolong strict compliance to follow. Cytotoxic agents have a narrow therapeutic window and a complex pharmacologic profile. The more complex drug therapy is the higher the risk of experiencing DRPs such as adverse effects, interactions, medication errors, and non-adherence. Furthermore, cancer itself increases the need for more medications like use of anticancer drugs often results in the use of other agents to reduce or prevent side-effects of the anticancer treatment, thereby increasing the interaction potential. In oncology patients, pharmacokinetic parameters can be altered by the disease itself or due to malnutrition, reduced levels of serum-binding proteins, edema, or hepatic and/or renal dysfunction, therefore more at risk for drug interactions.[6] The common late-effects mostly in childhood malignancy therapy includes growth related effects, hormonal issues, infertility issues, cognitive effects, renal insufficiency, cardiac effects and at worse may leads to second cancers.[7]

Therefore it must be the goal of all health care providers to minimize treatment-associated risks as much as possible in these patients. A more comprehensive study of DRPs in hospitalized patients would provide valuable insights for the healthcare professionals trying to reduce the incidence of DRPs.[8]

However there is scarcity of data on comprehensive DRPs among hospitalized patients and above published information of DRP in cancer chemotherapy is very-very rare. So far, most studies published had addressed either the problem of drug-related admissions to hospitals or focused only on adverse drug reactions (ADRs) among hospitalized patients. Therefore, the aim of this study was to investigate the prevalence, type and risk factors of DRPs in cancer patients admitted to the Oncology Department of Guru Gobind Singh Medical College, Faridkot, Punjab.

MATERIALS AND METHODS

A cross-sectional 8 months study was conducted from January to August 2015 at the Oncology Department of Guru Gobind Singh Medical College, Faridkot, Punjab. A total of 283 cancer patients were recruited in the present non-interventional, prospective clinical investigation analysis. Before the subjects were asked to participate, a formal written consent was obtained from all of them. The following inclusion criteria were outlined in advance before recruiting patients for study:

1. Diagnosed with cancer and visiting the institution to receive chemotherapy.

Table 1: Demographic Profile of cancer patients

BASIC DEMOGRAPHIC	GROUP (n=283)	Number (%)
SEX	Male	135 (47.70)
	Female	148 (52.30)
Age	10-19	12 (4.24)
	20-29	16 (5.63)
	30-39	65 (22.96)
	40-49	79 (27.91)
	50-59	63 (22.26)
	60-69	25 (8.83)
	70-79	16 (5.65)
	80 and above	07 (2.47)
Education	Illiterate	168 (59.36)
	1-5	18 (6.36)
	5-10	60 (21.20)
	11-12	30 (10.60)
	Graduate	12 (4.24)
	Post graduate	12 (4.24)
Family History	Present	30 (10.60)
	Absent	253 (89.39)
Type of Cancer	Breast Cancer	68 (24.02)
	Urogenital Cancer	63 (22.26)
	Head & neck thorax	60 (21.20)
	GIT Cancer	46 (16.25)
	Connective, Blood	25 (8.83)
	Others	21 (7.42)
Stages of cancer	No signs and symptoms 1-2	97 (34)
	Stationary state 3	144 (51)
	local invasion 4	34 (12)
	Metastasis and terminal stage	08 (03)
No. of Drug prescribed	<5	97 (34.27)
	5>	186 (65.72)
Body mass Index in kg/m^2	Low BMI(<18.5)	97 (34.27)
	Normal BMI(18.5-25)	186 (65.2)

Table 2: Classification and Sex wise distribution of load of DRPs in patient

Classification of DRPs	Total Number of DRP Occurrences (n = 813]	Number of DRP Occurrences in Male	Number of DRP Occurrences in Female
Adverse drug reaction	725 (89.18%)	303 (41.8%)	422 (58.21%)
Dosing problem	06 (0.73%)	4 (66.67%)	2 (33.33%)
Inappropriate drug chart	08 (0.98%)	3 (37.5%)	5 (62.5%)
Unnecessary drug therapy	12 (1.48%)	8 (66.67%)	4 (33.33%)
Needs additional therapy	47 (5.78%)	30 (63.83%)	17 (36.17%)
Drug-drug interaction	15 (1.85%)	6 (40%)	9 (60%)

2. No history of other chronic disease such as diabetes or heart disease.
3. No known mental problem or being treated with psychotropic drugs.
4. Patent's voluntary readiness to participate in study.

A total of 283 heterogenous cancer patients receiving chemotherapy were interviewed and socio-demographic variables, past medical history, medication history, number of drugs prescribed, current diagnosis, type of adverse effects, laboratory values, vital signs, and current medications information were collected in a specially designed data collection Performa from the patient's medical records and verbal communication.

The identification and categorization DRPs and concern data was compiled according to using a Pharmaceutical Care Network Europe (PCNE) version 5.01 and modification by Ruths *et al* as shown in Table 2.[1] The causes of DRPs were found from the subject case sheets and through a structured questionnaires response from cancer patients. Two standard reference books were used to measure the drug appropriateness usage, drug interactions, adverse reactions, drug choice problem and contra-indications.

Causality Assessment of ADR: ADR monitoring and its causality assessment were done with WHO and Naranjo causality assessment tool. The

Table 3: Factors associated with DRPs in two groups (with/without DRP)

Variable	Number of patients with DRPs (group-1)	Number of patients without DRPs (group-2)	OR	P value
Age in years				
0-30	10 (35.7%)	18 (64.3%)		
30-60	150 (72.5%)	57 (27.5%)		0.000
> 60	27 (56.3%)	21 (43.8%)		
Gender				
Male	80 (59.3%)	55 (40.7%)		
Female	107 (72.3%)	41 (27.7%)	0.557	0.021
No. of Drug prescribed				
<5	54 (55.7%)	43 (44.3%)		
5>	133 (71.5%)	53 (28.5%)	0.5	0.008
Body mass Index in kg/m^2				
Low BMI(<18.5)	77 (79.38)	30 (30.92)	1.77	0.03
Normal BMI(18.5-25)	110 (59.14)	76 (40.86)		

Table 4: Causality and severity assessment of individual adverse drug reaction

Adverse Drug Reaction No.	WHO causality assessment scale		Naranjo's algorithm		Hartwig and Siegel Scale		
	Possible	Probable	Possible	Probable	Mild	Moderate	Severe
Total (725)	300	425	323	402	452	257	16

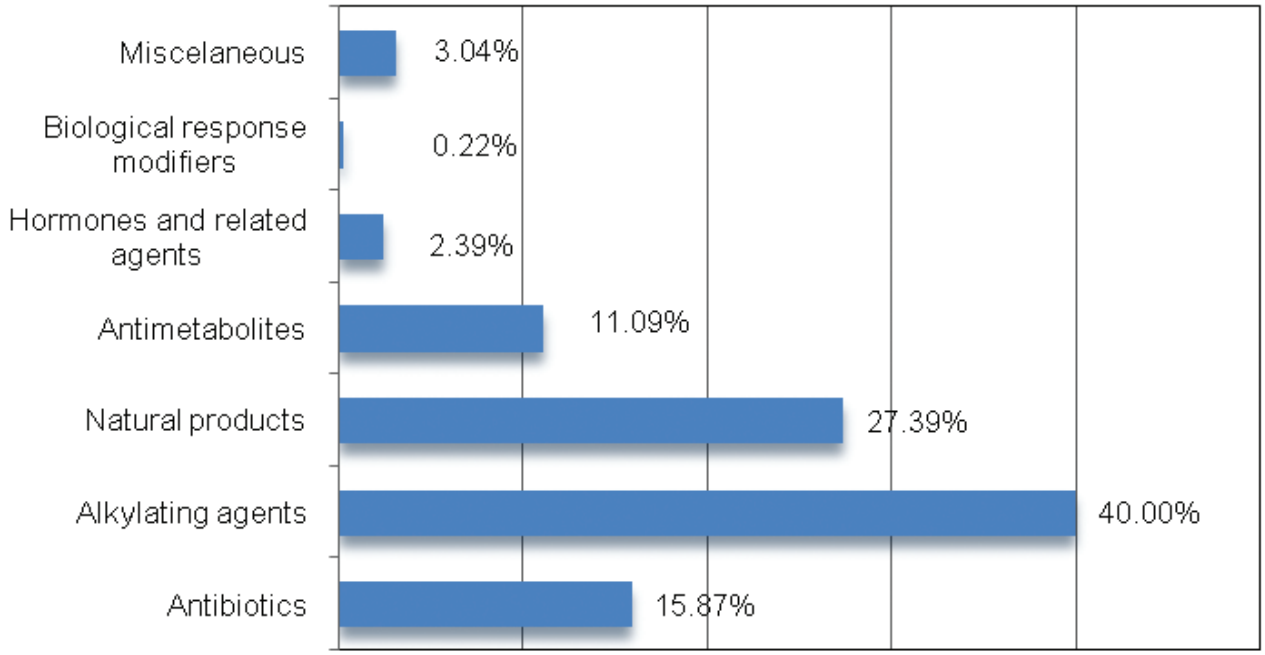

Figure 1: Cancer Chemotherapy anticancer drugs.

WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and causality is categorized into "certain," "probable," "possible," "unlikely," "conditional/unclassified" and "unassessable/unclassifiable." Naranjo algorithm has 10 objective questions with three options for answers - yes, no, do not know. Scores are given accordingly and the causality of the drug can be classified as "definite," "probable," "possible," and "unlikely.[9,10] Severity assessment was done with Hartwig Siegel severity scale.[11]

Statistical analysis

Baseline distinctiveness (demographic, cancer specific parameter) were summarized by descriptive statistics. Frequency, mean, percentages and standard deviation were calculated wherever appropriate. Association of DRPs with patient's age, gender, number of drug prescribed and body mass index was done with appropriate statistical test (ANOVA and Chi square test) All P-values ≤0.05 were considered as significant.

Ethical consideration: Ethical clearance was obtained from the Institutional ethical Review Board of Guru Gobind Singh Medical College, Faridkot, Punjab.

RESULTS

A total of 283 cancer patients were participated in this current study, 135 (47.70%) were males and 148 (52.30%) females. The mean age ± standard deviation was 49.05 ± 14.35 years (range 8 to 80 years) with leading age group being 40-49 years. The most prevalent malignancy was breast cancer 68 (29.4%), followed by Urogenital cancer 63 (22.26%) and Head and neck cancer 60 (21.2%). 144 (51%) patients were in stage three and 8 patents were in advance metastasis stage at the time of data collection. 65.2% of the patients had normal BMI with 37.27% having low BMI as shown in Table 1.

A total of 813 numbers of DRPs were observed in the present study, Table 2 shows the main classification of DRP and bifurcation of different variable according to male/female study population. ADRs were the most common DRPs noticed and nausea and vomiting were the most common ADRs (155). Among total DRPs observed 56% experienced by female subjects as compare to 44% in male cancer survivors.

A significance difference was noticed among two populations with/without DRPs with respect to Age in years, Gender, No. of Drug prescribed and Body mass Index shown in Table 3. Assessing the ADR profile of cancer patients observed a total 725 ADRs reported during study as shown in Table 4, Causality and severity assessment are shown in Table 4.

Chemotherapeutic agents: Anticancer drugs were mostly prescribed in combination (81.21%) and among combination, 5-FU and platinum based combinations were most commonly prescribed (30.45%). A detail group wise cancer chemotherapy utilization shown in Figure 1.

DISCUSSION

The frequent occurrence of DRPs among hospitalized patients is a routine occurrence and allied with diverse reasons and risk factors therefore Identification of these factors is crucial for the prevention and control of DRPs in an individual patient. Small number of studies from developed and middle income countries had identified the different classes of DRPs, the drugs involved with the respective class and various associated reasons and risk factors associated with DRPs.[12] Drug-related morbidities are a significant healthcare problem and great proportions are preventable.

We identified 813 DRPs in 283 patients which was comparable to study done in Netherland that showed 952 DRP in 546 patients.[13] But a higher number of DRPs was detected in this study when compared with another retrospective study done in Portugal that detected 43 DRP in 56 patients.[14] This variation indicates that as such comparisons are hampered by different settings, measurement methods and classification systems.

In this current study, nausea and vomiting occurred in 155 patients of which about 140 patients needed additional medication as an antiemetic when they subjected to highly emetic chemotherapy like platins and commonly prescribed antiemetics were Ondansetron (8-16 mg), Dexamethasone (20 mg) and Aprepitant (125 mg). Cisplatin was responsible for about 31% of the total ADRs that includes nausea, vomiting, peripheral neuropathy and nephrotoxicity. Cyclophosphamide, 5-fluorouracil, Paclitaxel and Adriamycin were found to be other important drugs to cause ADRs. The second more prevalent DRP in this study was additional therapy that occurred in 5.8% of the participants. A study in Thailand noticed low dose as a second more prevalent DRP in their study which occurred in 34.24% of the study population.[15] A similar study in Portugal also showed that the majority of interventions were related to the need to adjust dosages (53.5%) which is much higher than this study.[16]

Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents. Interactions with other medications can cause small changes in the pharmacokinetics or pharmacodynamics of a chemotherapy agent that could significantly alter its efficacy or toxicity.[16,17] In our study we observed 1.85% drug interaction to the total number of DRPs. While the exact incidence of Drug-drug interactions (DDI) is unknown in cancer patients, it has been estimated that about one-third of cancer outpatients are at risk of developing a DDI. Approximately 20% to 30% of all adverse events (AEs) are caused by interactions between drug.[18,19]

We observed inappropriate drug chart recorded in about 1% (08) of the participants, while Itchipruchyabun A *et al*. showed incomplete patient's data in 21 cases (30.88%).[15] These findings indicate as presence of patient chart registration or unclear order before starting a chemotherapy problem and it may affect therapeutic outcome. Unnecessary drug therapy was noticed in 12 (1.48%) patient's charts and mostly consists of prescription of antiemetics given while they were not important in the low and moderately emetic chemotherapy regimens.

The overall DRPs observed in female gender were higher than male subjects. which may be accounted to higher sensitivity in this gender to these effects. These mechanisms include hormonal changes in women and its effect on drug metabolism. Sex differences in fat composition and the impact on drug distribution may also play a role, as may the genomic constitutional difference that exists between men and women and the way in which this difference affects the levels of various enzymes involved in drug metabolism.[20,21]

CONCLUSION

This study showed that DRPs were common in our setup and noticed by other studies as well. The risk factors associated with DRPs observed by our finding includes female gender, number of medications, Body mass index and extreme age (in year) ranges. Cancer patients with above said risk factors are one of the groups who were most at risk of developing DRPs. Early detection and timely intervention is the key to ensure a better therapeutic outcome.

ACKNOWLEDGEMENT

We Acknowledge the Great Contribution of Cancer Patients in this present study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS USED

DRP: Drug Related Problems; **ADR:** Adverse drug reactions; **DDI:** Drug-drug interactions; **WHO:** World health organization.

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