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A prospective interventional study on comorbidities, drug – drug interactions and its management among cancer

Estudio prospectivo de intervención sobre comorbilidades, interacciones farmacológicas y su manejo en pacientes con cáncer

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ABSTRACT

Introduction: Drug-Drug interactions (DDI) may cause considerable adverse drug reactions and potentially lead to an increased or decreased clinical effect of a given drug and increases the cost of management. Cancer patients are at high risk of such DDIs because they commonly receive a high number of drugs concomitantly, including other cytotoxic agents, hormonal agents, targeted agents, and supportive care agents among medication prescribed to treat comorbidities, especially for elderly patients. The objective of this study is to evaluate the incidence of comorbidities and the role of clinical pharmacist in preventing DDIs in a group of cancer patients.

Materials and Methods: A prospective – observational study was conducted in a multispecialty hospital for a period of 8 months among 100 cancer inpatients of oncology department. DDIs were analyzed using Medscape Drug Interaction checker.

Results: In this study, 65 DDIs were identified from 100 patients. Of all DDIs, 33.85% were major, 60% were moderate, and 6.15% were minor DDIs. Clinically significant (55.38 %) DDIs were reported and 69.44% of those were accepted and modified accordingly. Furthermore, we observed 50.77% of DDIs between co administered drugs. Elderly people (48%) have more co-morbidity such as diabetes (30%) and hypertension (17.81%).

Conclusion: This study concluded that DDIs are very common in cancer patients, particularly people with more co morbidities and using multiple medicines. Clinical pharmacist and physicians must work together to extend the practice of preventing DDIs on individual patient management to improve their quality of life.

Keywords: Drug-Drug Interactions; Cancer; Comorbidity

RESUMEN

Introducción: Las interacciones medicamentosas (DDI) pueden causar reacciones adversas considerables a los medicamentos y, potencialmente, pueden provocar un aumento o disminución del efecto clínico de un medicamento dado y aumentan los costos de administración. Los pacientes con cáncer tienen un alto riesgo de tales interacciones porque comúnmente reciben una gran cantidad de medicamentos concomitantes, incluidos otros agentes citotóxicos, agentes hormonales, agentes dirigidos y agentes de atención de apoyo entre los medicamentos prescritos para tratar las comorbilidades, especialmente en pacientes ancianos. El objetivo de este estudio es evaluar la incidencia de comorbilidades y el papel del farmacéutico clínico en la prevención de interacciones entre medicamentos en un grupo de pacientes con cáncer.

Materiales y métodos: se realizó un estudio prospectivo - observacional en un hospital de múltiples especialidades durante un período de 8 meses entre 100 pacientes hospitalizados con cáncer del departamento de oncología. Las interacciones de fármaco y fármaco se analizaron utilizando el comprobador de interacción de medicamentos de Medscape.

Resultados: En este estudio, se identificaron 65 interacciones de 100 pacientes. De todas las interacciones entre medicamentos, 33,85% fueron mayores, 60% fueron moderadas y 6,15% fueron interacciones menores. Se informaron interacciones clínicamente significativas (55,38%) y el 69,44% de ellas se aceptaron y modificaron en consecuencia. Además, observamos el 50,77% de las interacciones entre los fármacos coadministrados. Las personas mayores (48%) tienen más comorbilidad, como diabetes (30%) e hipertensión (17,81%).

Conclusión: este estudio concluyó que las interacciones entre medicamentos son muy comunes en pacientes con cáncer, especialmente en personas con más comorbilidades y que usan múltiples medicamentos. El farmacéutico clínico y los médicos deben trabajar juntos para ampliar la práctica de prevención de interacciones entre medicamentos en el manejo individual del paciente para mejorar su calidad de vida.

Palabras clave: interacciones con fármacos; cáncer; comorbilidad

INTRODUCTION

DDIs more commonly occur when consuming more drugs concomitantly, which may also cause considerable adverse drug reactions and potentially lead to an increased or decreased clinical effect of a given treatment [1- 3]. Cancer patients are at high risk of such DDIs because they commonly receive a high number of drugs concomitantly, including cytotoxic agents, hormonal agents, targeted agents, and supportive care agents among the medications prescribed to treat comorbidities. Particularly, elderly patients have high risk to develop DDIs due their physiological changes and comorbidies [4]. Maximum patients with cancer will develop at least one DDIs and it requires medical intervention [5].

Gastro intestinal effects, Central Nervous System depression and QT prolongation are the most reported DDIs among cancer patients. These potential DDIs are needed to be noticed by the physician and proper intervention should be initiated to improve the health quality of cancer patients. This can be achieved by healthy professional interaction between oncologist, pharmacist, and other health care team members [6, 7].

Clinical pharmacists have important role in the cancer management by checking DDIs before starting the chemotherapy for the successful usage of drugs and improve the quality life of the patient. Clinical pharmacist requires skills to identify and prevent DDIs which necessitates updating the knowledge about DDIs among cancer patients. Hence, the present study was aimed to assess the comorbidities, DDIs among cancer patients.

MATERIALS AND METHODS (SUBSECC LEVEL 1)

A prospective interventional study was carried out for an 8 month period (from August 2016 to March 2017) in a Tertiary Care Hospital with Institutional Ethical Committee approval (Ref no: 12/003). Patients of either gender >18 years and diagnosed with cancer were included in the study. Patients who were referred to oncology department for op consultation, patients who are not willing to participate, pregnant and lactating women were excluded from the study.

The data were collected from patients' treatment chart on a daily basis and recorded in the drug DDIs' data collection form. Medscape multidrug interaction checker tool was used to identify the pattern of DDIs. In Medscape, on entering the drugs one by one, the program lists the possible DDIs and categorizes DDIs according to their interaction effect. Medscape contains a separate tool for detecting DDIs known as the multidrug interaction checker tool and also classified the DDIs as major, moderate and minor [8]. Major DDIs may be life-threatening and/or require medical intervention such as liver failure, abnormal heart rhythms, certain types of allergic reactions etc...Moderate or minor DDIs may result in exacerbation of the patient's condition and may or may not require an alteration in therapy e.g. Nausea, vomiting, headaches and rashes, etc.

The entire drug DDIs were informed to the physician and management was provided based on the drug interaction tools. Descriptive statistics and chi – square test was used to show the significant interaction between the different class of drugs. Data analysis was carried out using the Statistical Package for Social Studies (SPSS) version 20.

RESULTS (SUBSECTION LEVEL 1)

Among 100 study participants, 65% of patients had drug – drug interaction in their prescriptions. In that, 53.85% of patients were males and 46.15% were female's patients. Most of the patients were in the age of above 60 years followed by 41 – 60 years and less than 40 years. Maximum of patients had history of comorbidities and 53.85% of patients had employment during study period. Diabetes mellitus was found to be the most common comorbidity along with cancer in both groups with and without DDIs.

The maximum duration of hospital stay was 6 days for cancer patients in the study population, even though, the majority of patients with and without DDIs stayed for 3 days to complete their chemotherapy cycles. Demographics of study participants were described in Table 1.

Table 1. Demographic details of study participants

Demographics	No of Patients (n=100)	
	With DDIs N=65	Without DDIs N=35
Gender Male	35(53.85)	19(54.29)
Female	30(46.15)	16(45.71)
Age 18-40 yrs	10(15.38)	6(17.14)
41-60 yrs	23(35.38)	13(37.14)
61-80 yrs	32(49.23)	16(45.71)
Occupation Employed	35(53.85)	19(54.29)
Unemployed	28(43.07)	15(42.86)
Student	2(3.08)	1(2.86)
Duration of Hospital stay 2	23(35.38)	12()
3	29(44.62)	15(42.86)
4	9(13.85)	5(14.28)
5	4(6.15)	2(5.71)
6	1(1.54)	1(2.86)
Comorbid conditions No comorbidity	18(27.69)	9(25.71)
DM	20(30.77)	10(28.57)
hypertension	9(13.85)	4(11.43)
DM & hypertension	3(4.61)	2(5.71)
asthma	2(3.08)	1(2.86)
psychosis	3(4.61)	1(2.86)
Other comorbidities	12(18.46)	6(17.14)

Among 100 patients, 35% had some uncommon type cancer like Non-Hodgkin lymphoma, pancreatic cancer...etc. and 25% had stomach cancer followed by ovarian (10%) and breast cancer (9%), which is displayed in Figure 1.

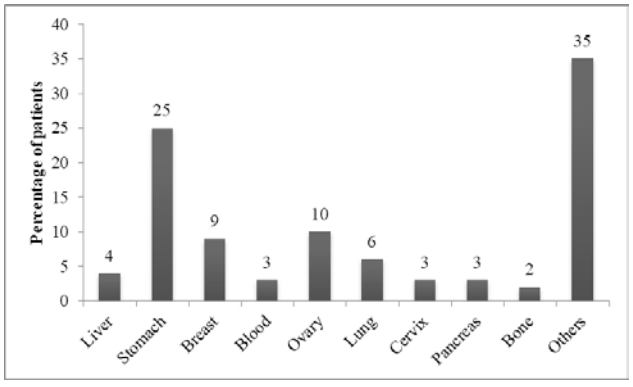

Figure 1. Distribution of patients according to the cancer site.

In multivariate analysis, the dependent variable like age, gender, hospital stay, comorbidity, and occupation doesn't affect significantly the occurrence of drug – drug interaction among cancer patients. The multivariate analysis results are described in Table 2.

Table 2. Multivariate analysis of dependent variables on occurrence of DDIs

Source	Dependent Variables	Type III Sum of Square	df	Mean Square	F	Sig.
Drug interaction	Hospital stay	.194	1	.194	.233	.630
	Age	.063	1	.063	.116	.735
	Gender	.000	1	.000	.002	.967
	occupation	.000	1	.000	.002	.967
	comorbidity	.009	1	.009	.044	.834

Table 3 shows the details of drug – drug interaction among all cancer patients. Out of 65 drug DDIs, 47.69% had one DDI, 30.77% had two types of DDIs and 18.46% had more than three type's DDIs in the treatment chart. Based on the severity of DDIs, 60% were moderate, 33.85% were major and 6.15% were mild. Clinically, significant DDIs were observed with 36 prescriptions. Out of 65 DDIs, 29 have theoretical DDIs which are not observed in cancer patients during the study period. All clinically significant DDIs were reported to the physician and 25 were accepted and 11 were not given priority or accepted.

Also, the study observed 24.62% of DDIs between anticancer drugs, 24.62% between anticancer and co-administered drugs, and 50.77% of DDIs between co-administered drugs as represented in Table 3. Major DDIs were significantly ($p<0.0001$) high in numbers (n=18) between co administered drugs which indicates comorbidities increased the risk of DDIs. Then, 60% of major DDIs and 28% of moderate DDIs were accepted by the physicians.

Table 3. Details of Drug – Drug Interaction among cancer patients

Details of Drug – Drug DDIs	No of Patients (%) n= 100(%)	P value
Drug DDIs Yes No	 72(72) 28(28)	0.000
No of DDIs per patient One DDIs Two interaction Three DDIs More than three DDIs	 31(47.69) 20(30.77) 9(13.85) 12(18.46)	0.000
Severity of DDIs Minor Moderate Major	 4(6.15) 39(60) 22(33.85)	0.000
Type of Interaction Anticancer-Anticancer Anticancer-Co-administered Co-administered - Co-administered	 16(24.62) 16(24.62) 33(50.77)	0.000
Observed of Interaction Clinically significant interaction Non-clinically significant interaction	 36(55.38) 29(44.62)	0.000
Reported to physician Yes No	 36(55.38) 29(44.62)	0.000
Acceptance of DDIs Yes No	 25(69.44) 11(30.56)	0.000

Details of Drug – Drug DDIs	No of Patients (%) n= 100(%)	P value
Acceptance based on severity Major Moderate Minor	 15(60) 7(28) 3(12)	0.00

Among anticancer drugs that cause drug interaction, cyclophosphamide (n=6) was found be the most common interacting drug in cancer patients. With co administered drugs, ondansetron (n=5), glimepiride & aceclofenac (n=4), and clonidine & levodopa (n=4) have shown more DDIs. QT interval prolongation, Hypotension, and was found to be the most common consequences of drug – drug interaction among cancer patients. The frequency and percentage distribution of clinically significant DDIs are summarized in Table 4.

Table 4. Severity of Drug – Drug Interaction based on the drug treatment

Type of interaction	Number of DDIs N (%)	Severity of interaction		
		Minor	Moderate	Major
Anticancer-Anticancer drugs	16(24.62)	2	14[a]	0
Anticancer-Co-administered drugs	16(24.62)	1	11[a]	4
Within Co administered drugs	33(50.77)[*]	1	14	18[*]

Figure 2 indicates the management of DDIs among cancer patients. Out of a total of 25 accepted drug DDIs, 54.5% (n=14) DDIs were managed through dose taper or reduction, 22.7% (n=6) DDIs were monitored closely, 9% (n=2) DDIs were treated by addition of new drug, and 13% (n=3) DDIs were managed by drug withdrawal or stoppage. During the study period, September '16 and January'17 got highest numbers of DDIs which was described in Figure 3.

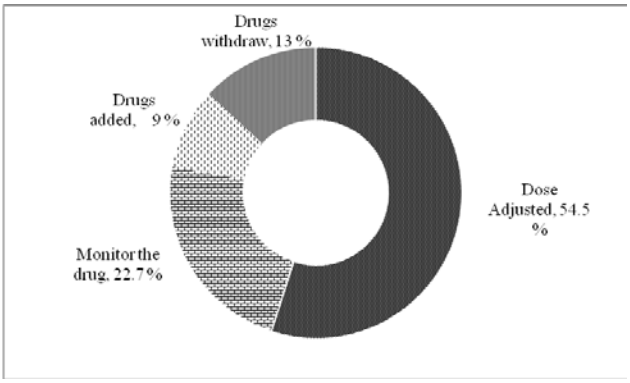

Figure 2. Management of accepted Drug –Drug Interactions

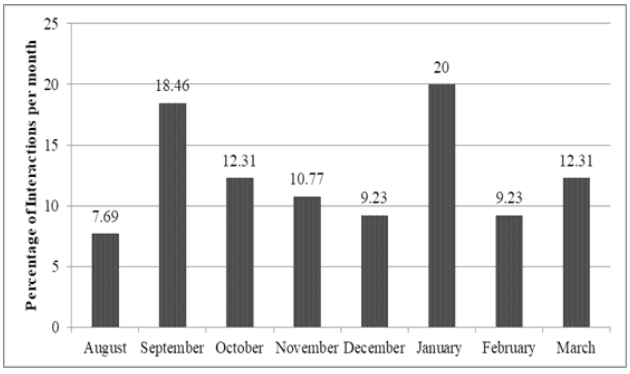

Figure 3. Month wise report of Drug – Drug Interactions

DISCUSSION

Cancer patients are more likely to develop drug – drug interaction due to treatment with multiple medication simultaneously. This study assessed the various comorbidities, DDIs and their management among cancer patients. In this population, male cancer patients were dominant compared to female patients, which is similar to previous reports shown by Van Leeuwen RW et al., which found high prevalence of cancer in male patients [9]. Age is an important factor to increase the chance of drug interaction due to multiple medications for comorbid conditions as well as age-related decline in hepatic and renal functions which reduces patient ability to metabolize and clear drugs [10,11]. This study results proved that advanced age group (>60 years) have more drug interaction than younger age. Furthermore, comorbid conditions associated with cancer might add number of medications to the drug chart of cancer patients. Our study results indicates that 72.31% of study participants had comorbidities and another study found that the median number comorbidities per patient was one and this means that all cancer patients suffered from at least one comorbidity. Stomach cancer was found to be the most common type of cancer in this population, which is further supported by earlier studies and suggests a high prevalence of stomach cancer among male population. But, contradictory to our study another study reported a high prevalence of cervical cancer in women [12].

The number of drug interaction per prescription in the present study was found to be the range of 1 – 5 and prescription with one drug interaction was highly significant ($p<0.0001$). But, former studies on patient care revealed that the increase in DDIs in the prescriptions occurs when

number of items per prescription increased with more than four drugs, thereby, also in the number of potentially interacting drug combinations per patient. Also, they found that a positive correlation exists between the incidence of DDIs and number of drugs prescribed. Generally, patients have several concurrent diseases and, consequently, the number of drugs used to treat them is greater. The greater the numbers of drugs have higher the possibility of DDIs [13].

Based on the severity, this study found that maximum DDIs were moderate and major; few DDIs were minor. Similarly, a study done by the team from a south Indian tertiary care teaching hospital in Chennai, Tamilnadu, reported that more than a 50% of cancer patients may be at risk of potentially moderate DDIs [14].

This study results shows that a high prevalence of moderate DDIs in cancer patients. But, anticancer drugs were not the primary source for drug interaction. The majority of DDIs are between different classes of co administered medications received for co-morbidities and cancer supportive care were more likely to be involved. It indicates that co administered drug have an impact or increase the occurrence of drug interaction in cancer patients.

In the same way, another study supported that the chemotherapeutic agents have lesser number of drug interaction compared to non-anticancer agents. Like other study reports, this study also confirms that cancer patients those have used drugs concomitantly to treat comorbidities have been identified as a risk factor for the occurrence major type of DDIs [15].

In 2008, a similar study conducted and reported by Wong CM et al, showed 21.7% clinically significant DDIs from the 184 DDIs that were identified [16]. The effect of drug interaction, which is described in database, and was clinically observed on daily basis of patient life, is known as clinically significant interaction. In this study, more than half of the DDIs were found to be clinically significant during the study period. The remaining DDIs that were not clinically observed with patients are called as theoretical DDIs. All significant DDIs were reported to the concern of physician for further management of drug interaction. In that, a small number of DDIs were not accepted due to non-serious reaction from the physician point of view.

Mostly, the accepted DDIs were managed with dose adjustment and few of them needed close monitoring of patients. Leape et al in 1999 observed that pharmacists often identified potential drug related DDIs and suggested dose corrections which was not accepted because the physician believed that the benefits of continue treatment outweighed the risk of DDIs [17].

Another finding in this study includes QT interval prolongation. This was frequently observed as an adverse outcome due to DDIs and cyclophosphamide was the most frequent anticancer drug involved in this DDIs. Equally, many other studies concluded that QT interval prolongation was found to be the most common DDI outcome in cancer patients [18]. On the other hand, a conflicting report by Mouzon A et.al suggested that Cisplatin was the most common anticancer drug responsible for DDIs because it was prescribed frequently in their study population [19]. All the patients with DDIs were well managed and got recover from adverse effects except those need monitoring closely. Even though not accepted, the qualities of life of patients were not affected considerably because of DDIs was not life-threatening in this study.

CONCLUSION

This study concludes that DDIs are very common in cancer patients, particularly in people with more co morbidities and using multiple medicines. Clinical pharmacists and physicians must work together to extend the practice of preventing DDIs on individual patient management to improve their quality of life.

Professional insight into the clinical consequences of DIs in cancer patients is not well known and further study need to be investigated. Physicians and clinical pharmacists must collaborate to extend the practice of identify DIs upon drug prescription, which includes the knowledge, awareness, and attentiveness during the use of anticancer drugs and supportive or co administered drugs.

There is an imperative need to tackle these DDIs in an organized and efficient manner and to provide this information to the healthcare professionals during patient care and it may improve the quality of health care provided to cancer patients. This can be achieved probably through specific teaching in oncology and could be put into practice to reduce medication related problems and optimize therapeutic treatments.

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