

Evaluation of Drug Interactions in Hospitalized Patients with Malignancy

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ABSTRACT

Drug-drug interaction (DDI) occurs when the pharmacological effect of a drug is altered due to concomitant administration with other drugs. DDIs still remain a serious issue; thus, we conducted this retrospective study to evaluate DDIs prevalence in our care center.

Methods: All admitted patients with any kind of malignancies that received at least two medications from oncology and non-oncology classifications during six months were enrolled in this study. All relevant data including, patients' demographic information, diagnosis, hospitalization duration, and all administered medication during hospitalization were recorded. The DDI was assessed by using the latest version of Lexi-interact.

Results: Each patient received a mean number of 11.6 ± 4.7 medications. The number of non-oncology drugs demonstrated a remarkable correlation with the number of interactions ($P < 0.001$).

Whereas, the number of oncology drugs does not have any relation with the number of interactions ($P = 0.64$). Among the 763 detected DDIs during this study, the incidence of major, moderate and minor interactions were 31.2%, 61.4%, and 7.3%, respectively.

Conclusion: Our results highlighted the clinical significance of DDIs, considering that 104 (92%) patients had at least one DDI. The main reason that could have potentially contributed to this outcome is the complicated nature of cancer treatment and clinical management. We believe that using computer software to collect all prescribed and OTC collaboration of clinical pharmacists with oncologists can reduce the potential interactions prior to drug administration.

Keywords: Drug-drug interaction; Over-the-counter (OTC) drugs; Malignancy; Oncology

INTRODUCTION

By definition, a drug-drug interaction (DDI) occurs when the pharmacological effect of a drug is altered due to concomitant administration with other drugs. Subsequently, patients may either be deprived of desired therapeutic effect or experience adverse reactions due to increased toxicity of drug¹. DDIs are considered a major issue since it is estimated that they are the cause of 20-30% of adverse reactions². Cancer patients experience distressing physical and non-physical adverse reactions. DDIs evaluation in cancer patients is rather complicated since cancer

patients usually receive numerous medications from different pharmacologic categories. These medications may be prescribed for therapeutic goals such as chemotherapy agents or administered in order to alleviate their symptoms³. According to the World Health Organization (WHO) statistics, cancer is among the main causes of death globally⁴. Thus, the clinical importance of DDIs is further highlighted as a study reported that drug-drug interactions account for 4% of all deaths in cancer patients⁵. Old age proves to be a further vulnerability for cancer patients from DDIs. Because it is more likely

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for older patients to have comorbidities that may require further medication use⁶.

Drug-drug interactions are divided into three main subcategories: pharmaceutical, pharmacodynamic, and pharmacokinetic interactions⁶. Pharmaceutical interactions occur when two physiochemical non-compatible drugs are combined⁷. A pharmacokinetic interaction may occur while drug passes through absorption, distribution, metabolism, and excretion phases. While none of the major interactions were found in distribution and excretion phases, metabolism phase was considered as the position where most significant clinical DDIs laid. CYP oxidizing enzymes are the predominant metabolic route for most chemotherapy agents^{6,8}.

DDIs still remain a serious and possibly life threatening matter requiring adequate attention⁹. However, great efforts may be done in order to shed light on drug-drug interaction incidence and their clinical significance in cancer patients. The acquired data may result in better recognition and subsequently higher prevention rate of DDIs by healthcare professionals³.

We conducted this retrospective study in Shahid Ghazi hematology and oncology center affiliated to Tabriz University of Medical Sciences for a six month-period. The study aimed to evaluate the incidence of DDIs in our center and determine the seriousness of these interactions based on the probable clinical consequences.

MATERIALS AND METHODS

Study design

This cross-sectional observational study was done in a single tertiary adult cancer care center for a period of six months (October 2015 to March 2016).

We retrospectively evaluated the prevalence of DDIs in patients with any kind of malignancies who admitted to hospital and received at least two medications from oncology and non-oncology classifications during hospitalization. However, patients who referred to our center just for chemotherapy infusion session were excluded from the study.

Data collection

We gathered patients' relevant data including, demographic information, diagnosis, hospitalization

duration and clinical data based on pre-designed data collection forms.

We recorded all data regarding to medications that patients received during hospitalization period. As drug-food and drug-herb interactions are also a major clinical concern, they were not assessed in our study³.

In our center, medications had been prescribed with different purposes. Therefore, for better consideration we divided them into two subcategories: oncology drugs and non-oncology drugs.

Since it is possible to formulate two or more drugs in a single dosage form, we counted each pharmacologically active compound individually (e.g. sulfamethoxazole in combination with trimethoprim). However when patients received same medication with differently modified formulation, it was counted once (e.g., immediate and sustained release morphine).

After data collection process, we performed an analysis of patients' whole medication profile for potential DDIs.

Data analysis

This analysis was done using last available version of Lexi-interact, which is a trustworthy source according to studies that reported its sensitivity and specificity of 88-100% and 88-92%, respectively^{9,10}. Drug-drug interactions are classified by reliability rating based on the quantity of supporting scientific evidence. Severity rating which reflects potential consequences may arise due to interaction and risk rating as an indicator for both urgency level and necessary actions needed to react to an interaction. Risk rating is defined as following; A: No known interaction; B: No action needed, C: Monitor therapy, D: Consider therapy modification, X: Avoid combination.

Severity rating is defined as following: Major: may be life-threatening or capable to cause permanent injury, Moderate: may deteriorate patient's clinical status which could require medical intervention, Minor: may not need medical intervention in most cases due to insignificant outcome.

Statistical analysis

Data with normal distributions were analyzed with independent t-test. Continuous quantitative variables were expressed with mean \pm standard deviation (SD). Categorical variables were described with frequency and percentage. Chi-square test (or Fisher's exact test if needed) was used to compare qualitative results. Data with non-normal distributions were analyzed by the Mann-Whitney U test. Spearman's correlation coefficient was used to show the direction of association between two ranked variables or data with quantitative non-normal distributions. Zero-truncated Poisson regression was used to show count data with quantitative non-normal distributions for which the value zero cannot occur. P-values less than or equal to 0.05 were considered statistically significant. Statistical analysis was performed using the IBM SPSS statistics for Windows, version 21

Ethics

This study was approved by Research Ethics Committee of Tabriz University of Medical Sciences. All information obtained from patients' documents was confidential and not released by their identity.

RESULTS

From November 2015 to March 2016, 113 eligible patients were enrolled in this retrospective observational study. Patients' demographic information is shown in Table 1. Hospitalization duration ranged was from 1 to 51 days. The mean number of received medication for each patient was 11.6 ± 4.7 . There were 188 co-administration of drug which leads to 763 DDI during this study. From all DDI, 117 (15.3%) of them was related with chemotherapy agents. There was at least one DDI in 104 (92%) of patients. Patients DDI ranged from zero to 26, with mean of 6.6 ± 5.4 DDI for each patient. The incidences of potential severity of DDI were 31.2%, 61.4% and 7.3% in major, moderate and minor category, respectively. In addition, the incidence of DDI based on risk rating was 7.2%, 63.6%, 20.1% and 8.9% for B, C, D, and X category.

From all DDIs, fluconazole, granisetron and ciprofloxacin had more common DDI with the number of 191, 190 and 172, respectively. In

addition, the more common co-administration of drugs which leads to DDI was the combination of ciprofloxacin with dexamethasone or granisetron (in 40 patients). The incidence of DDI based on pharmacologic category was 227 with 5-HT₃ antagonist, 197 with azoles, 174 with fluoroquinolones, and 171 with corticosteroids. The more frequent DDIs with their mechanism are presented in Table 2. The relation between different co-administration of drugs with their DDI risk rating and hospitalization duration is presented in Table 3. Data showed that there are a significant relation between the number of both oncology and non-oncology drugs and the number of interactions with the hospitalization duration (Table 4). In addition, there is a remarkable relation between the number of interactions and the number of non-oncology drugs ($P < 0.001$). Whereas, the number of oncology drugs do not any relation with the number of interactions ($P = 0.64$).

The impression of different DDI risk rating in hospitalization duration adjusted with or without the type of malignancy (solid tumor or hematologic) is displayed in Table 5. As shown in Table 5, all types of DDI increase the hospitalization duration. It means DDI correlates with duration of hospitalization. The maximum effect is seen in DDI category C, which increases the hospitalization duration by 0.8 and 0.9 day (adjusted with or without the type of malignancy, respectively). Moreover, the absence of any DDI decreases the duration of hospitalization (reverse correlation). It should be mentioned that even one DDI can increase the hospitalization duration (Table 5).

Table 1: Patients demographic information

Variable		Average (Mean \pm SD)/Number%
Age (Year)*		50.4 \pm 17.2
Hospitalization Duration (Days)*		12.8 \pm 9.7
Number of administered medication*		11.6 \pm 4.7
Sex	Female	42 (37%)
	Male	71 (63%)
Malignancy	Solid	61 (54%)
	Hematologic	52 (46%)

Continuous variables are described in mean \pm standard deviation (SD).

Table 2: The more frequent DDIs with their mechanism

Drugs	Mechanism	Risk rating	Number	Severity
Ciprofloxacin Dexamethasone	Corticosteroids may enhance the adverse/toxic effect of Quinolone Antibiotics. Specifically, the risk of tendonitis and tendon rupture may be increased	C	40	Moderate
Ciprofloxacin Fluconazole	QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying) may enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents	B	37	Moderate
Fluconazole Dexamethasone	CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates.	C	36	Moderate
Fluconazole Pantoprazole	Fluconazole may increase the serum concentration of Proton Pump Inhibitors	C	22	Moderate
Furosemide Dexamethasone	Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics.	C	15	Moderate
Ciprofloxacin Prednisolone	Corticosteroids (Systemic) may enhance the adverse/toxic effect of Quinolone Antibiotics. Specifically, the risk of tendonitis and tendon rupture may be increased	C	9	Moderate
Fluconazole Diazepam	CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates	D	9	Moderate

Lexicomp-Interact, version 4.0.4, Wolters Clinical Drug Information

Table 3: The relation between different co-administration of drugs with their DDI risk rating and hospitalization duration

Drug combination	DDI risk rating	P
Ciprofloxacin + Fluconazole	B	<0.001
Fluconazole + Granisetron	B	<0.001
Acetaminophen + Ondansetron	B	0.021
Ciprofloxacin + Ondansetron	B	0.012
Granisetron + Ondansetron	B	0.039
Ciprofloxacin + Dexamethasone	C	<0.001
Arsenic + Granisetron	C	0.045
Fluconazole + Dexamethasone	C	<0.001
Fluconazole + Pantoprazole	C	<0.001
Furosemide + Allopurinol	C	0.009
Furosemide + Cisplatin	C	0.465
Furosemide + Dexamethasone	C	0.002
Furosemide + Prednisolone	C	0.023
Hydrocortisone + Amphotericin B	C	0.015
Hydrocortisone + Ciprofloxacin	C	0.004
Arsenic + Fluconazole	D	0.123
Fluconazole + Benzodiazepine	D	<0.001
Aprepitant+ Fluconazole	X / C	0.372

Variables are analyzed with Mann-Whitney U Test

Table 4: Correlation of hospitalization duration with number of interaction and oncology and non-oncology drugs

Correlation*	Hospitalization duration	
	Correlation Coefficient	P
Oncology drug number	0.205	<0.029
Non-oncology drug number	0.595	<0.001
Number of interaction	0.483	<0.001

*Nonparametric Correlations are analyzed with Spearman's rho

Table 5: The effect of different type of DDI in hospitalization duration

DDI	Cancer type	Hospitalization duration Correlation Coefficient	P value
Category B	Not adjusted	0.2921772	<0.001
	adjusted	0.3064627	<0.001
Category C	Not adjusted	0.9066975	<0.001
	Adjusted	0.8147116	<0.001
Category D	Not adjusted	0.603336	<0.001
	Adjusted	0.5666827	<0.001
Category X	Not adjusted	0.511629	<0.001
	Adjusted	0.3986374	<0.001
One DDI	Not adjusted	0.0581936	<0.001
	Adjusted	0.0487662	<0.001
No DDI	Not adjusted	- 0.8723346	<0.001
	Adjusted	- 0.8234069	<0.001

Variables analyzed by Zero Poisson test

DISCUSSION

Our results remarkably highlighted DDIs clinical significance, considering the fact that 104 (92%) patients had experienced at least one DDI. According to Lexi-Interact classification, moderate and major severity interactions accounted for 61.4% and 31.2% of all identified DDIs, respectively. Our findings meaningfully demonstrated higher incidence of DDIs compared to a similar study which reported that 46% of patients had at least one DDI, while 16% of them were major interactions⁹. We may be able to explain high incidence of DDIs with respect to previous studies. The main reason that could have potentially contributed to this outcome is the complicated nature of cancer treatment and clinical management. In general, cancer patients receive one or more anticancer medications as their treatment, either alone or in combination with radiotherapy and surgery¹².

However, health care professionals may decide to prescribe supportive care agents such as analgesics,

anticoagulants, antidepressants, antibiotics, antiemetics, corticosteroids, and other complementary medications in order to prevent any chemotherapy-related complications¹².

Moreover, a review concluded that as most cancer patients were in their 60's, there is a considerable risk of existing comorbidities such as chronic cardiovascular, gastrointestinal and rheumatologic illnesses¹³. Although, the median age of patients who enrolled in our study was 50.4 years, the mentioned chronic diseases were also highly probable in our patients which may have required further medication administration. On average, each patient received 11.6 medications during hospitalization period in our study, which is noticeably higher than similar studies. For instance, a systematic review of 64 patients with solid tumors found that each patient received a mean number of seven treatments⁶. In our study, pharmacological agents with prophylactic

targets such as antibiotics and antiemetics contributed to the majority of DDIs occurrence.

The mean length of stay for patients in our center was 12.8 days. We identified a relationship between prevalence of DDIs and length of hospitalization in cancer patients. As demonstrated by Table 5, in different risk rating categories, the hospitalization period is increased. Therefore, hospitalization period decreased in the absence of DDIs. Thus, as fewer clinical consequences of DDIs occurs, patients' quality of life as well as health care cost efficiency improves⁵.

These consequences that are reflected by numerous studies can be divided into sub-categories based on their pharmacologic effects. Since many chemotherapy agents can potentially cause gastrointestinal (GI) tract adverse reactions (including nausea and vomiting), a combination of these agents and other GI tract toxic drugs (such as corticosteroids and NSAIDs) could increase the intensity of toxicity^{9,14}. As a consequence of interaction between oral anticancer medications (e.g. capecitabine) and coumarins desired anticoagulant efficacy may be diminished and subsequently lead to hemorrhage⁹.

QT prolongation is a highly important symptom in cancer patients' clinical management. In addition to well-known QT prolongation effect of many chemotherapy agents, various supportive care medications (e.g. 5-HT₃ antagonists and fluoroquinolone antibiotics) could potentially prolong QT segment. Excessive prolonged QT may induce a rare but extremely fatal tachycardia called torsade de pointes^{15,16}.

CNS depressant agents (such as antidepressants, opioids, benzodiazepines) may be frequently prescribed in cancer care centers for therapeutic targets. However, additive CNS depression due to co-administration of these agents may increase falling risk up to 47%. As a result, cancer patients may be at higher risk of fractures due to falling⁹.

Cancer patients experience severe adverse reactions mainly due to chemotherapy agents' toxicity¹. However, it is believed that 20-30% of experienced adverse reactions are due to DDIs². These interactions are responsible for 4% of all deaths in cancer patients⁵. Therefore, a precise evaluation of

DDIs prevalence in cancer care centers and developing effective methods to prevent them are of great importance. Despite the fact that DDIs could lead to a wide range of clinical consequences, optimum prevention of DDIs in cancer care centers is still a challenging goal⁶.

First issue is that not all drug combinations are avoidable. In fact, their administration may be possible if dosage is properly adjusted and patients are subsequently monitored for adverse reactions⁹. However, with respect to chemotherapy agents' narrow therapeutic index, it is extremely difficult to modulate dosage without compromising the optimal balance between efficacy and side-effects¹. There arises another issue as the DDIs associated side-effects may be incorrectly attributed to intrinsic toxicity of chemotherapy agents⁶.

Third issue is that over-the-counter (OTC) and herbal drugs are often disregarded in the evaluation of DDI damaging potential. This issue mainly originates from patients' attitude because they do not require to report herbal and OTC drugs. Moreover, inadequate patient-specialist communication could also contribute into taking no notice of herbal and OTC drugs use⁵. Inefficient communications between health care professionals (i.g. oncologists and other specialists) is another notable issue⁹.

We believe the same way as numerous studies suggested that use of computer-based software to collect all prescribed drugs for patients along with OTC medications is the ideal way to detect potential interactions prior to drug administration. However, to be effective, it requires active collaboration between clinical pharmacists and oncologists⁵.

This study was conducted in a single care center by a retrospective approach. Therefore, our results may not be generalized to other cancer care centers. Although, various studies have evaluated OTC and herbal medications role in potential DDIs in cancer patients, we did not analyzed these medications in our study^{1,9}.

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CONCLUSION

Our data showed that 104 (92%) patients had at least one DDI. The complicated nature of cancer treatment, especially in hematologic malignancies, is the main reason of interactions. Using computer software to collect all prescribed and consumption information of OTC products, and collaboration of clinical pharmacists with oncologists can reduce the potential interactions prior to drug administration.

CONFLICT OF INTEREST

All authors declare no competing interests.

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