Original Article

Potential Drug Interactions in Hospitalized Hematologic Cancer Patients: New Update with New Chemotherapy Regimens

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Received: 10-02-2024.
Revised: 11-04-2024.
Accepted: 12-06-2024.
Published: 08-08-2024.

ABSTRACT

Objective: This cross-sectional study aimed to assess the frequency of potential drug–drug interactions (DDIs) and demographic correlates of moderate and major DDIs among patients with hematologic cancer at a referral hematology hospital in Iran. **Methods:** In this study, for 6 months, all patients suffering from hematologic cancers admitted to the tertiary oncology hospital, Omid, Isfahan, were considered. Data from all medications prescribed to patients during hospitalization were analyzed using the online Lexicomp® drug interaction checker, recording all interactions classified by risk level: C, D, or X. **Findings:** A total of 674 DDIs were detected in 109 patients. The prevalence of treatments with at least one clinically relevant interaction was 95%, being 57.9% for those at level C and 31.5% for levels D and X. According to the frequency, the main interaction was between aprepitant and corticosteroids, followed by the interaction between aprepitant and vincristine. The most common interaction between antineoplastic agents was between doxorubicin and cyclophosphamide. In terms of mechanism, most of DDIs (54.9%) were pharmacodynamics. Only the number of administered medications was associated with DDI occurrence. **Conclusion:** Potential DDIs of moderate to major severity are common among patients with hematologic malignancies. This underscores the importance of implementing different strategies to mitigate this clinically significant risk.

Keywords: *Cancer, chemotherapy, drug–drug interactions, hematologic malignancy*

Introduction

Drug–drug interactions (DDIs) probably happen frequently in daily clinical practice due to the increase in polypharmacy trends and life expectancy worldwide.[1,2] DDIs could be associated with significant morbidity or fatal adverse events and even can lead to lessening the therapeutic impacts of medications. Additionally, it can also weaken patients' drug adherence and outcome of treatment.[3-5]

DDI is defined as interference in the clinical or pharmacological effect of a drug due to co-administration or co-exposure to another drug.[6,7]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrpp

DOI: 10.4103/jrpp.jrpp_40_24

Historically, DDIs can be subdivided into three types: pharmacokinetic, pharmacodynamic, and pharmaceutical interactions.[1,4,7] During pharmacokinetic interactions, absorption, distribution, metabolism, or exertion of one medication alters the optimal pharmacologic effects of another drug or substance. Most of the pharmacokinetic interactions are mediated through the inhibition/induction

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How to cite this article: Gholipourshahraki T, Aria A, Sharifi M, Moghadas A, Moghaddas A. Potential drug interactions in hospitalized hematologic cancer patients: New update with new chemotherapy regimens. J Res Pharm Pract 2024;12:115-22.

of cytochrome P450 enzymes.[4,5] The second type of drug interaction, the pharmacodynamic interaction, refers to an interaction in which one drug changes another's pharmacologic effect as a synergetic, additive, or antagonistic effect.[3,4] In pharmaceutical interactions, chemical or physical incompatibilities between two drugs can take place.[7]

Cancer patients are uniquely susceptible to drug interactions. This population often receives multiple medications during their treatment to manage their malignancies, comorbid conditions, and chemotherapy toxicities.[1,3,6] The incidence of potential DDIs in cancer patients ranges from 27% to 92% in numerous centers depending on different therapeutic approaches, types of malignancies, and methods of DDIs detection.[8-11] The high rate of drug interactions has led researchers to conduct numerous studies in this field. For example, in a study performed by Ismail *et al*. in patients suffering from cancer, 78% of patients encountered at least one drug interaction.[8] In a similar study of 141 hospitalized nonhematologic cancer patients, 80.8% of patients encountered potential DDIs during their hospitalization.[10] In a recent study evaluating the prevalence of potential drug interactions in patients with breast cancer, at least one potential drug interaction was identified in 92% of patients.[9] Studies showed that most drug interactions are related to nonantineoplastic medications.[1,10,12-14] Despite a high prevalence of potential DDIs in cancer patients, the magnitude of this problem is mainly unknown.[15]

Generally, risk factors for DDIs in cancer patients were reported to be advanced age, renal and/or hepatic insufficiency, malnutrition, malabsorption, and differences in pharmacogenetic characteristics of individuals.[1,15,16] Furthermore, the number of administrated medications and comorbidities can increase the risk of DDIs.[7] In a study by Song and Oh, the patient's type of cancer, such as breast cancer or hematologic malignancy, regardless of age group, was independently associated with the occurrence of DDIs.[17] Theoretically, the pharmacokinetics of medications may be changed in cancer patients as a result of drug absorption impairment due to gastrointestinal mucositis, infection or malnutrition, low levels of serum binding proteins, and generalized edema consequently leading to variation in the volume of distribution and finally alteration in metabolism and exertion of medications.[1,7] In addition, antineoplastic medications have a narrow therapeutic index that could make patients more susceptible to DDIs.[3,5]

Indeed, DDIs in cancer patients can be concealed by physiological alteration in the body owing to cancer and its complications or other baseline comorbidities, as well as adverse effects of chemotherapy regimens. Of note, the identification of potentially harmful medications in concurrent drug administration is a matter of debate.[2] The importance of safety medication prescription, validation, and administration are necessary, especially in cancer patients who are suffering from numerous complications. Furthermore, by considering the possible negative impact of DDIs on cancer patient management as well as the paucity of data in terms of identification of potential DDIs in this special population, we decided to design a cross-sectional study aimed to assess the frequency of potential DDIs as well as the correlation of moderate and major DDIs with patients' demographic characteristics exclusively among patients with hematological cancer at a referral hematology hospital in Iran.

Methods

We performed a retrospective cross-sectional study in Omid Hospital, a referral tertiary-care teaching hospital, in Isfahan, Iran, from May 2019 to July 2019. All adult patients who were suffering from hematologic malignancies and were undergoing treatment with two or more antineoplastic or nonantineoplastic medications (either intravenous and/or oral) were included. We did not include outpatients' information, and also in the absence of the required information, the patient profile was excluded. The protocol of this study was approved by the Medical Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1395.3.491). Written consent was signed by all enrolled patients before data gathering. Patients who did not want to cooperate and did not fill out the consent form were excluded from the study.

The designed data collection sheets were prepared by the main investigator according to similar studies[4,5,18] to collect all necessary items and achieve the planned goals of the study.

The first part of the data collection checklist included the patient's demographic information including age, sex, type of cancer, medical and drug history, last date of chemotherapy, intention to treat cancer, length of hospital stay, type of regimen prescribed (chemotherapy or supportive care), and history of drug allergies.

The second part was designed to collect data on the dose and duration of antineoplastic and nonantineoplastic drugs administered simultaneously during hospitalization. Hospital records of patients and drug order forms were used for data extraction. There was no e-drug prescribing system with a medical decision support system in our hospitals for data collection assistance. We did not extract any drug due to special

dose or treatment purposes (prophylaxis, empirical, or preemptive) for further analyses.

Each patient's medication administered concurrently at any point during the hospitalization was collected and considered for potential DDIs analysis. Drug interaction analysis including classification of the severity and DDIs level of evidence as well as their pharmacologic mechanism were checked with the online Lexicomp® drug interaction checker.[19] The pharmaceutical interactions were beyond the study's purpose and were not supported by the software.

Several studies have shown the sensitivity and specifying of Lexi-Interact by 87%–100% and 80%–90%, respectively.[20,21] A DDIs risk rating according to A, B, C, D, or X was assigned to each interaction. The lowest risk is related to Group A interaction. As the interactions progress to X, the intensity of the interaction risk increases, indicating an urgent need to consider the drug administration changes before any DDIs happens. Generally, A and B interactions are not clinically significant and were not considered for our study endpoints and analyses. Table 1 shows other criteria for classifying drug interactions in terms of severity and definition of reliability rating based on Lexi-Interact software. We also considered only major and moderate interactions according to severity rating for statistical analysis and we excluded all minor severity interactions due to lack of clinical significance.

Categorical variables, as well as the reliability scores and DDIs' severity, were noted as a percentage and continuous variables and presented in terms of mean ± standard deviation. Logistic regression analysis was applied to identify the correlation between potential DDIs with patient's age, gender, number of prescribed drugs, hospitalization duration, and sort of cancer. Predictors were considered to be statistically significant if the $P < 0.05$. All statistical analysis was carried out by the Statistical Package for the Social Sciences (SPSS) software version 23 (SPSS Inc., Chicago, IL, USA).

Table 1: Lexi-Interact software drug–drug interaction's severity and reliability rating classification

Classification	Definition
Severity	
Major	These complications can lead to permanent injury, treatment failure, and even hospitalization or death
Moderate	Medical intervention is required to treat the complications. Although, it does not have the major criteria
Minor	Tolerable effects in most cases without the need for medical intervention
Reliability rating	
Excellent	It was reported by numerous randomized clinical trials or 1 randomized clinical trial plus at least >2 case reports
Good	It was reported by a single randomized clinical trial plus fewer than 2 case reports
Fair	It was reported by >2 case reports or <2 case reports in addition to other supporting evidence
Poor	It was reported by <2 case reports with no other supporting data

Results

A total number of 109 hospitalized patients suffering from different types of hematologic malignancies were enrolled in this cross-sectional study. Given the complexities of clinical outcomes' diagnosis and the retrospective nature of the study, it is challenging to differentiate between disease complications, drug side effects, and drug interactions in this study. Therefore, the main focus of this study was the evaluation of potential DDIs occurrence rather than the clinical consequences report. The patient's baseline clinical and demographic characteristics are shown in Table 2. The mean patients' age was 48.98 ± 17.5 years (range from 15 to 84 years), with the majority of patients between 36 and 45 years. More than half of the patients (75%) were male, and the most common malignancy was acute myeloid leukemia (33%). The average length of hospitalization was 7.94 ± 6.38 days (range: 2–31). On average 12.36 ± 4.727, medications were administered (range: 3–27) in a total of 1374.

A total number of 1347 medications were prescribed during the study follow-up. In general, among antineoplastic drugs, vincristine was the most prescribed

Table 2: Demographic characteristics of enrolled patients (*n*=109)

Characteristics	Value
Sex	
Male	75 (68.8)
Female	34 (31.2)
Age (years)	48.98±17.5 (15–84)
Administered medications	12.36±4.727 (3–27)
Duration of ward stay (days)	7.94±6.383 (2–31)
Pathological diagnosis	
Hematologic malignancies	
Acute myeloid leukemia	33 (30.3)
Acute lymphoblastic	23 (21.1)
Leukemia	8 (7.3)
Chronic lymphocytic leukemia	
Multiple myeloma	8 (7.3)
Hodgkin lymphoma	3 (2.8)
Diffuse large B-cell lymphoma	24 (22.0)
Others	10 (9.2)

Data are presented as *n* (%), or mean±SD (range), where applicable. SD: Standard deviation

drug (27 cases). Pantoprazole was also the most commonly prescribed nonantineoplastic drug (79 cases). After screening and evaluating the data from 109 enrolled patients, 674 DDIs were detected. Based on the mechanism, 54.9% and 45.1% of DDIs were classified as pharmacodynamics and pharmacokinetic, respectively. Among total DDIs, 57.9% were classified in category C interaction. Of these, 72 interactions (10.7%) and 161 interactions (23.9%) were assigned to categories B and D of interaction, respectively. We even recorded 51 (7.6%) cases of category X interaction, of which 13 (25.4%) cases were related to the DDI of fluconazole and aprepitant and 5 (9.8%) cases were subsequently associated with the interaction of promethazine and metoclopramide.

Regarding the severity, 41.5% of interactions were major, and 58.4% were moderate. The level of evidence of detected DDIs is shown in Figure 1. As can be seen in Figure 1, the fair rating was the most repetitive reliability rating (76.3%).

According to the frequency, the main interaction was the interaction between aprepitant and corticosteroids (including dexamethasone and hydrocortisone) in this study. Since the interaction of aprepitant with corticosteroids can occur with all systemic corticosteroids and is related to their pharmacological classification, the interaction of aprepitant with dexamethasone or hydrocortisone was classified and analyzed in one category. It was noted that aprepitant may increase serum concentrations of systemic corticosteroids. As aprepitant is a potent inhibitor of liver enzymes, theoretically, co-administration of aprepitant with various agents can lead to an increase in the plasma level of other drugs. However, the clinical consequences of this plasma level increase have not been defined yet. This interaction accounts for 7.5% of the total 674 potential DDIs, followed by the interaction between aprepitant and vincristine (3.11%). Since aprepitant is a moderate inhibitor of CYP3A4, it can reduce vincristine metabolism and increase its effects. The most common interaction between two antineoplastic medications was the administration of doxorubicin and cyclophosphamide concurrently in 19 cases (2.8%). Cyclophosphamide can exacerbate the cardiotoxicity of anthracyclines (including doxorubicin). These effects may be additive or synergistic. The 10 most detected DDIs are shown in Table 3 in detail.

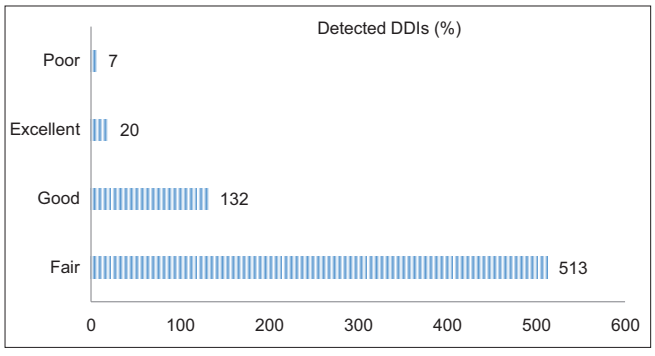

Figure 1: Reliability rating of detected drug–drug interactions (n = 674) according to Lexi-Interact online. DDIs: Drug–drug interactions

In terms of the number of drug interactions, we identified one drug interaction in 17 patients (15.6%). We also identified two interactions and three interactions, in 8 (7.3%) and 3 (2.8%) patients, respectively. In terms of frequency, after one drug interaction, five drug interactions were identified in 11 patients (10.1%) and eight drug interactions in 10 patients (9.2%). The highest drug interaction detected was 23, which was detected in only one patient (0.9%).

The results of logistic regression analysis showed a positive correlation between the total number of prescribed medications and the incidence of drug interaction [Table 4]. Other variables were not detected to be significant predictors for DDIs.

Discussion

In this short-term cross-sectional study, a total number of 109 patients with hematologic malignancies were screened for potential DDIs during hospitalization. According to our findings, more than 90% (91.7%) of patients who were suffering from hematologic malignancies and related complications were exposed to at least one potential DDIs. The pharmacological drug classes that were responsible for drug interactions in our study were mostly azole antifungals, corticosteroids, and neurokinin-1 (NK-1) receptor antagonists. We detected the potential drug interaction between aprepitant and corticosteroids as a most repeated DDIs. Furthermore, the most probable interaction among oncology drugs was between cyclophosphamide and doxorubicin. Based on the results of the regression analysis, the occurrence of DDIs was directly associated with the total number of drugs prescribed during hospital stay.

Due to a lack of information on cancer patients, this type of study will be influential in expanding our knowledge of the epidemiology and possible severity of DDIs in cancer patients. It is essential to identify potential risk factors for pharmacotherapy such as drug interactions and polypharmacy, especially in cancer patients, to change treatment protocols and introduce new drugs.

More than 90% (91.7%) of patients suffering from hematologic malignancies and related complications were exposed to at least one potential DDIs, which

Table 3: The 10 most frequently detected drug interactions (*n*=674)

Drug–drug interaction	Frequency	Percent	Interaction category	Severity	Reliability	Probable mechanism
Aprepitant + corticosteroids*	51	7.6	D	Major	Fair	Aprepitant may increase the serum concentration of corticosteroids (systemic)
Aprepitant + vincristine	21	3.1	C	Moderate	Fair	Aprepitant may increase the serum concentration of Vincristine
Doxorubicin + cyclophosphamide	19	2.8	C	Major	Fair	Cyclophosphamide may enhance the cardiotoxic effect of anthracyclines
Aprepitant + doxorubicin	15	2.2	D	Major	Fair	Aprepitant may increase the serum concentration of doxorubicin
Fluconazole + aprepitant	13	1.9	X	Moderate	Good	Fluconazole may increase the serum concentration of aprepitant
Promethazine + chlorpheniramine	12	1.8	C	Moderate	Good	Anticholinergic drugs may increase the adverse effects of other anticholinergic drugs
Fluoroquinolones** + corticosteroids	11	1.6	C	Moderate	Good	Corticosteroids (systemic) may increase the toxic effect of quinolones. Specifically, tendonitis and tendon rupture risk may be enhanced
Spironolactone + potassium chloride	10	1.5	D	Major	Fair	Potassium salts may enhance the hyperkalemic effect of spironolactone
Fluconazole + dexamethasone	8	1.2	C	Moderate	Fair	Fluconazole may decrease the metabolism of dexamethasone
Pethidine + granisetron	7	1.0	C	Moderate	Fair	Granisetron may enhance the serotonergic effect of pethidine

*Corticosteroids in this study included dexamethasone and hydrocortisone, **Fluoroquinolones in this study included ciprofloxacin and levofloxacin

Table 4: Drug–drug interaction in association with demographic characteristics and clinical factors in multiple regression analyses

Variants	Patients without DDIs	Patients with DDIs	OR (95% CIs)	*P*
Sex			7.88 (1.70–36.47)	0.67
Male	7 (9.58)	67 (90.42)		
Female	2 (5.71)	33 (94.29)		
Cancer type			1.02 (0.979–1.04)	0.81
Acute myeloid leukemia	1 (2.94)	33 (97.06)		
Acute lymphoblastic leukemia	1 (4.34)	22 (95.66)		
Chronic lymphocytic leukemia	2 (25)	6 (75)		
Multiple myeloma	3 (37.5)	5 (62.5)		
Hodgkin's disease	0	3 (1		
Diffuse large B-cell lymphoma	1 (4.34)	22 (95.66)		
Others	1 (9.09)	10 (90.91)		
Age (year)	50.44±15.44 (27–76)	48.85±17.74 (15–84)	1.27 (1.008–1.59)	0.84
Hospitalization (day)	6±2.59 (1–9)	8.12±6.59 (1–30)	1.18 (0.82–1.69)	0.642
Number of drugs	6.77±1.64 (4–10)	12.86±4.59 (3–27)	1.84 (1.25–2.72)	<0.001

Data are presented as *n* (%), or mean±SD (range), where applicable. SD: Standard deviation, OR: Odds ratio, CIs: Confidence intervals, DDIs: Drug–drug interactions

was a considerable amount in comparison with other similar studies[14,22,23] or as high as the others.[8,10] For example, in a large recently published study by Ismail *et al.* in Pakistan with 678 cancer patients receiving chemotherapy from two tertiary care hospitals, the results showed that the overall DDIs prevalence was about 78% and the majority of patients encountered 1–2 potential DDIs (39.2%).[8] Although the method of study was very similar to our investigation, there were numerous differences in some parts. First, in the Ismail *et al*.'s study,[8] the population was included patients with any type of cancer (hematological and solid cancer) in any range of age, of which 101 patients belonged to under 10-year-old age group. Second, contrary to our study, Micromedex Drug-Reax® software was used to evaluate potential drug interactions. The present study examined the status of hospitalized patients with underlying hematologic malignancies, regardless of the reason for hospital admission or the treatment protocol.

Due to different studies' design and methodology, the accurate comparison among different studies[8,14,22] is not accurate. For instance, the pattern and type of chemotherapy drugs and other treatment regimens such as preventive anti-nausea regimens varied among patients suffering from solid tumors in the study by Moghaddas *et al.*[10] Therefore, the results of studies involving solid tumor patients may not be generalizable to patients suffering from hematologic malignancies. Few reports have addressed the prevalence of DDIs only in patients suffering from hematologic malignancies.[14,22,23] Fernández de Palencia Espinosa *et al*.[7] investigated potential drug interactions in hospitalized hematological cancer patients. This article used different drug interaction checkers, such as Micromedex® and Drug Interactions databases® to examine the potential DDIs leading to the prevalence of 74.1% and 56.8%, respectively. Despite the difference in the prevalence of DDIs, the analyzed results of the study showed that azole antifungals, antiemetic medications, and corticosteroids were among the most common drugs that cause DDIs in cancer patients. In a similar manner to our study, different studies have confirmed that the number of prescribed medications is the predictor of potential DDIs by applying multivariate analysis.[10,23]

Another similar study evaluated potential DDIs in patients with hematologic malignancies. According to the results of this cross-sectional study,[14] 86.84% of patients showed at least one DDI; however, they used two different drug interaction checkers for identifying DDIs and they also considered minor interaction in the DDIs category for their analysis. The difference in DDIs frequency may arise from differences selected population, study method and design, DDIs screening method, and used drug interaction checker. In another study in the same hospital investigating the potential DDIs in cancer patients who were suffering from solid tumors exclusively, the prevalence of potential DDIs was estimated to be 80.8%,[10] revealing that the center prescription system was suffering from a lack of drug interaction checker before drug administration. However, it should be mentioned that the theoretical potential interactions do not necessarily prohibit the concomitant use of many drugs together. For example, the administration of aprepitant as an antiemetic agent in chemotherapy regimens is a strong liver enzyme inhibitor and has the potential of DDIs with many prescribed cancer management medications; however, due to the short duration of prescription (only for 3 days), the clinical consequence of aprepitant drug interaction is negligible.

More than half (58.4%) of the DDIs in the present study were found to be moderate, which is similar to other studies reported in the same range.[10,18,24] In a similar study by Ataei *et al.*,[14] 441 potential cases of DDIs were identified among 76 patients and 62% of drug interactions had moderate severity. In another study conducted in 2010,[25] 1359 cases of drug interactions were identified among 426 cancer patients with the highest frequency of moderate severity drug interaction category.

According to similar studies,[11,15,26] most of the diagnosed DDIs in the current study were attributed to nonantineoplastic medications. In congruent with the previous studies,[11,15,26] azole antifungals, corticosteroids, and NK-1 receptor antagonists were the most common classes of medications responsible for detected DDIs. The results arose from the fact that most of the patients suffering from hematologic malignancies were hospitalized due to complications from their disease or treatment such as fever and neutropenia or mucositis and they needed numerous nonantineoplastic medications for complication management.[11,27] A similar trend has been described by Richelmann *et al.*[13] who noted that approximately 13% of reported DDIs have occurred by antineoplastic agents versus 87% with nonantineoplastic medications.[11] In addition, in another cross-sectional study,[28] of the 1850 potentially identified potential DDIs, only 11 were related to neoplastic medication interactions.

The level of interference reliability was fair for many of the detected DDIs, indicating that these interactions were reported only based on case reports and there were no reliable randomized clinical trials behind. On the other words, there is a paucity of evidence for the clinical risks of most detected interactions. The most common DDIs detected in our investigation were the interaction between: 1) corticosteroids and aprepitant, 2) aprepitant and vincristine, 3) aprepitant and doxorubicin, 4) doxorubicin and cyclophosphamide. All of these DDIs were assessed to have fair reliability of the supporting evidence. Results showed that 51 detected DDIs were classified in class X, of which 13 and 4 cases were related to the intervention of the aprepitant with fluconazole and voriconazole, respectively. Azole antifungals can increase the serum concentration of aprepitant by inhibiting cytochrome 3A4. Although aprepitant was one of the most widely used drugs in the present study, its clinical significance may not be well known due to the limited duration of prescription.

In an analysis of individual safety reports during the last 20 years collected by the WHO Global Database,[29] 3766 case reports of drug interactions from 47 countries indicated that the dominant interaction mechanisms were pharmacodynamics (41%), pharmacokinetics (25%), and a combination of both (16%), respectively. Furthermore, 18% of the remaining DDIs had an unknown

mechanism. In our study, more than half of the DDIs were pharmacodynamics (54.9%), which was contrary to a previous similar study in adult cancer patients who had reported pharmacokinetic mechanisms as the most commonly detected DDIs.[4] This discrepancy among the results of different types of studies can be attributed to different inclusion criteria for population selection and administrated medications during study follow-up.

In our study, the highest reported DDIs among antineoplastic medications were detected between cyclophosphamide and doxorubicin, which was not similar to the results of a study conducted by Hadjibabaie *et al*.[4] in an adult oncology-hematology center in Iran. A case report has recommended that doxorubicin may increase the risk of cyclophosphamide-induced bleeding cystitis. However, an *in vivo* study has shown that cyclophosphamide may reduce the formation of doxorubicin inactive metabolites and enhance the cytotoxicity induced by the anthracycline drug class.[30] Although the risk rating category of doxorubicin and cyclophosphamide is C class and the severity of interaction is categorized as major, but optimum dose of combination for these two frequently administrated chemotherapy drugs was extracted from clinical trials. It means that this combination can be prescribed for cancer treatment in assigned optimum doses without any worries. It is worth mentioning that the clinical importance of the interaction has not yet been established in therapeutic doses used in chemotherapy regimens.

According to similar studies in adult oncology patients, we have identified the number of prescribed drugs during hospitalization accounted for DDI incidence. Numerous similar studies[5,10] have addressed the impact of polypharmacy on inducing drug interactions as the most identified reason. Riechelmann *et al*.[11] noted that the cancer type and the pharmacological symptoms were also associated with DDIs in patients with malignancy.[11]

Here are some strategies to reduce the risk of potential DDIs. For instance, medication database development, computerization of physician orders in connection with electronic program screening, the participation of clinical pharmacists in prescription, distribution, as well as prescribing and patients' follow-up along with patients' close monitoring for severe DDIs, avoiding polypharmacy, routine monitoring of the level of medications, especially those with narrow therapeutic effects, and changing from prescribing high-risk drugs to safer replacements. Preventive strategies include improving the knowledge and education of health-care professionals about clinically important DDI via constant teaching of medical and nursing students besides holding seminars or journal clubs.[4,5]

Our study had some impediments. First, this investigation was performed in just a single hospital with a restricted example size. The limitation of sample size may influence the factual intensity of our analysis and also make it impossible to perform separate statistical tests for various cancer types. Second, we just utilized a drug interaction checker for the detection of potential DDIs. To decrease the probability of overestimating clinical DDIs, an intensive pursuit of the significant writing and information bases, alongside the assessments of a multidisciplinary group of masters including hematologists, oncologists, and clinical medication specialists, is pivotal. Third, the absence of patients' follow-up and physical condition monitoring disabled us from distinguishing the clinical consequence of the potential DDIs occurrences.

In conclusion, this study demonstrated that the prevalence of DDIs in hospitalized patients suffering from hematologic malignancies was remarkable. Most identified interactions in terms of mechanism and severity were in the pharmacodynamic and moderate categories, respectively. The risk of DDIs appears to increase significantly as the number of prescribed drugs increases. Nonantineoplastic medications were responsible for most of the detected DDIs. Careful monitoring of the patients, especially those who have polypharmacy in their drug list, is recommended for the early prevention of adverse clinical outcomes accounting for drug interactions, especially those drug combinations that were involved by cytotoxic drugs. Because few studies have merely addressed the incidence of drug interactions in patients suffering from hematologic malignancies, multicenter, prospective, and standardized studies to evaluate the actual clinical effects are required.

Authors' Contribution

Administrative support: A. Moghaddas and M. Sharifi. Collection and assembly of data: T. Gholipourshahraki, A. Aria and A. Moghaddas. Data analysis and interpretation: T. Gholipourshahraki, A. Moghaddas, A. Aria and M. Sharifi. All authors contributed to the conception and design of the study, provision of the study patients, manuscript writing, and final approval.

Financial support and sponsorship

This study was part of an Iranian Pharm. D thesis that has been supported by Isfahan University of Medical Sciences (Grant Number: 395491).

Conflicts of interest

There are no conflicts of interest.

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