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ORIGINAL ARTICLE

Potential drug–drug interactions at a referral hematology–oncology ward in Iran: a cross-sectional study

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Abstract
Purpose To assess the pattern and probable risk factors for moderate and major drug–drug interactions in a referral hematology–oncology ward in Iran.
Methods All patients admitted to hematology–oncology ward of Dr. Shariati Hospital during a 6-month period and received at least two anti-cancer or non-anti-cancer medications simultaneously were included. All being scheduled anti-cancer and non-anti-cancer medications both prescribed and administered during ward stay were considered for drug–drug interaction screening by Lexi-Interact On-Desktop software.
Results One hundred and eighty-five drug–drug interactions with moderate or major severity were detected from 83 patients. Most of drug–drug interactions (69.73 %) were classified as pharmacokinetics. Fluconazole (25.95 %) was the most commonly offending medication in drug–drug interactions. Interaction of sulfamethoxazole-trimethoprim with fluconazole was the most common drug–drug interaction (27.27 %). Vincristine with imatinib was the only identified interaction between two anti-cancer agents. The number of administered medications during ward stay was considered as an independent risk factor for developing a drug–drug interaction.
Conclusions Potential moderate or major drug–drug interactions occur frequently in patients with hematological malignancies or related diseases. Performing larger standard studies are required to assess the real clinical and economical effects of drug–drug interactions on patients with hematological and non-hematological malignancies.

Keywords Drug–drug interactions · Hematology–oncology ward · Hematological malignancies · Iran

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Introduction

Drug–drug interaction (DDI) is defined as the pharmacological or clinical response to the administration of a drug combination that a second drug modifies the patient's response to an initial drug [1, 2]. DDIs could be a significant cause of morbidity and mortality because they may result in adverse events, decrease in therapeutic effects of a drug, enhancement of drug toxicity, and accordingly, patient adherence and treatment outcome [3]. It has been estimated that DDIs are responsible for 20–30 % of all

drug side effects, of which 70 % need clinical attention and 1–2 % cases lead to life-threatening situations [4].

DDIs can be subdivided into 3 groups of pharmacodynamics, pharmacokinetics, and pharmaceuticals. In pharmacodynamics interaction, one drug modulates the pharmacologic effect of another drug as an additive, synergistic, or antagonistic approach. Pharmacokinetics interaction occurs when a drug alters the absorption, distribution, metabolism, and/or excretion of another drug. Pharmacokinetic interactions are most often mediated through influencing cytochrome P450 enzymes. Pharmaceuticals interaction encompasses chemical and/or physical incompatibility between 2 drugs when mixed with each other [5].

The clinical effects of DDIs in general medicine have been investigated extensively. Large surveys have found that about 60 % of inpatients in general medical wards [6, 7] and 16–47 % of patients in emergency departments were at risk of potential or developed clinically relevant DDIs [8, 9]. An analysis of more than 5 million prescriptions in the French national health care system in 1999 revealed that 2 % of outpatients were exposed to either absolutely or relatively contraindicated drug combinations [10]. In an observational, descriptive study at department of internal medicine in Norway, 132 out of 732 (about 18 %) deaths were associated, either directly or indirectly, with DDIs [11].

Theoretically, patients with cancer are particularly vulnerable to DDIs because they frequently take numerous medications concurrently to manage their malignancy, chemotherapy-induced toxicities, cancer-associated syndromes, and other co-morbid illnesses such as pain, nausea, vomiting, and depression. Narrow therapeutic index of anti-cancer agents, their inherent toxicity, and alteration in their pharmacokinetic parameters due to impaired absorption, volume of distribution, and excretion could compromise their interaction profile [12]. Unfortunately, there is much little available clinical data about the occurrence and pattern of interactions in patients receiving anti-cancer therapy. The aim of this study was to evaluate the pattern and probable risk factors for moderate and major DDIs in a referral hematology–oncology ward in Iran.

Methods

All patients admitted to a 24-bed hematology–oncology ward of Dr. Shariati Hospital during a 6-month period from early October 2011 to late March 2012 were recruited into this cross-sectional study. Dr. Shariati Hospital is multispecialty, tertiary, teaching health care center affiliated to Tehran University of Medical Sciences, Tehran, Iran. No specific inclusion–exclusion criteria were implemented for selection of patients. Any patient who received at least 2 anti-cancer or non-anti-cancer medications simultaneously during ward stay was considered eligible. The Institutional Review Board (IRB) and the Medical Ethics Committee of the hospital approved the study. Informed consent was obtained from all patients or their families.

Demographic data (age and sex), final diagnosis, laboratory findings about kidney and liver function [aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, and creatinine], and all being scheduled rather than as needed medications including anti-cancer and non-anti-cancer drugs that were both prescribed and administered during hematology–oncology ward stay were collected from their medical charts (drug kardex and drug order sheet) by a clinical pharmacist. Medications administered concurrently at any point during ward stay regardless of their initial dose or probable dose alterations and treatment strategy (prophylaxis, empirical, or pre-emptive) were considered for DDI analysis. DDI screening was performed by the Lexi-Interact On-Desktop software version 1.3.11.04.18 [13]. According to the results of several studies that have evaluated the accuracy of DDI screening programs, Lexi-Interact software has both acceptable sensitivity (87–100 %) and specificity (80–90 %) [14–16]. Definitions for severity and reliability rating of DDIs by Lexi-Interact software are shown in Table 1. Due to lack of clinical significance, interactions of minor severity were excluded and only major or moderate interactions were considered eligible for further analysis. Regarding mechanism of action, DDIs were classified as either pharmacokinetics or pharmacodynamics. Pharmaceutical interactions were not investigated because they were beyond the scope of our study and were not supported by the software. Medication classes responsible for detected DDIs were categorized by third level pharmacological subgroup of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) Index 2012 of the World Health Organization Collaborating Center for Drug Statistics Methodology [17]. Regular ECG monitoring was performed in selected subjects whenever required such as presence of significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia) or underlying cardiac conduction defects. Similar to the definition used by Riechelmann et al. [18], an increase of 10 % or greater above the upper normal limit in the mean plasma levels of hepatic enzymes (AST $\leq$ 35 U/L, ALT $\leq$ 40 U/L, ALP $\leq$ 110 U/L, or bilirubin $\leq$22 μmol/L) or creatinine ($\leq$99 μmol/L) during ward stay was considered laboratory abnormality as an approximate index of liver and kidney dysfunction.

Statistical analysis

Categorical variables were expressed as percentage. Continuous variables were reported as mean ± standard

Table 1 Lexi-Comp drug interaction software classification criteria for drug–drug interactions

Classification	Definition
Severity	
Major	The effects of interaction may result in death, hospitalization, permanent injury, or therapeutic failure
Moderate	The effects of interaction may need medical interventions
Minor	The effects of interaction would be considered tolerable in most cases and need no medical intervention
Reliability rating	
Excellent	Multiple randomized clinical trials or single randomized clinical trial plus more than 2 case reports
Good	Single randomized clinical trial plus less than 2 case reports
Fair	More than 2 case reports or less than 2 case reports plus other supporting data, or a theoretical interaction based on known pharmacology
Poor	Less than 2 case reports with no other supporting data

deviation (SD). The possible association between the occurrence of DDIs and patients' age, sex, number of administered drugs during hematology ward stay, laboratory abnormality, and type of hematological malignancies or diseases was assessed by multivariate logistic regression analysis to calculate odds ratios (ORs) and their 95 % confidence intervals (CIs). *P* values less than 0.05 were considered to be statistically significant. Statistical Package for the Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA) was used for descriptive–statistical analyses.

Results

During a 6-month period, 132 patients were admitted to the hematology–oncology ward. Demographic and clinical characteristics of the study population are summarized in Table 2. More than half of the patients (54.55 %) were males. Newly diagnosed acute myeloid leukemia was the most common final diagnosis (34.09 %) followed by newly diagnosed acute lymphoblastic leukemia (16.67 %) and graft versus host disease (14.39 %). A total of 1651 medications were administered to the study population. Fluconazole (90.91 %), sulfamethoxazole-trimethoprim (71.97 %), allopurinol (69.69 %), imipenem (55.3 %), and vancomycin (49.24 %) were the 5 most common prescribed medications among 132 patients. The mean ± SD administered daily dose of fluconazole was 77.65 ± 88.31 mg

Table 2 Demographic and clinical characteristics of the study population ($n = 132$)

	n (%)
Sex	
Male	72 (54.55)
Female	60 (45.45)
Age (years)	
Mean ± SD	31.92 ± 15.37
Range	5–65
Administered medications	
Mean ± SD	12.54 ± 5.25
Range	5–23
Final diagnosis	
AML (new case)	45 (34.09)
ALL (new case)	22 (16.67)
GVHD	19 (14.39)
AML (relapsed)	16 (12.12)
ALL (relapsed)	11 (8.33)
Neutropenic fever	7 (5.3)
Aplastic anemia	3 (2.27)
Burkitt lymphoma	3 (2.27)
Non-Hodgkin lymphoma	2 (1.52)
TTP	1 (0.75)
ITP	1 (0.75)
Multiple myeloma	1 (0.75)
Pulmonary embolism	1 (0.75)

SD Standard deviation, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *GVHD* graft versus host disease, *TTP* thrombotic thrombocytopenic purpura, *ITP* Idiopathic thrombocytopenic purpura

(range 50–200 mg). Among 120 patients received fluconazole, prophylaxis against Candida infections was its major indication in 116 (96.7 %) cases. The remaining 4 (3.33 %) patients were taken fluconazole for empirically treatment of fungal infections. The 3 most frequent administered anti-cancer medication classes were antimetabolites [cytarabine (43.2 %)], anthracyclines (39.4 %), and corticosteroids (31.1 %). Prescribed anthracyclines included daunorubicin ($n = 31$), idarubicin ($n = 15$), doxorubicin ($n = 4$), and mitoxantrone ($n = 2$).

One hundred and eighty-five DDIs were identified from 83 patients. The frequency of at least one DDI was 62.88 % (83/132). The mean ± SD number of DDIs per patient was 1.4 ± 1.19. One DDI was detected in 31 (37.35 %) patients, 2 in 23 (27.71 %) patients, 3 in 16 (19.28 %) patients, 4 in 9 (10.84 %) patients, and 5 in 4 (4.82 %) patients. The severity of 114 (61.62 %) DDIs was considered as major and 71 (38.38 %) as moderate. Reliability rating (level of evidence) of detected DDIs is depicted in Fig. 1. Regarding mechanism, 129 (69.73 %) DDIs were classified as pharmacokinetics, 54 (29.19 %) as

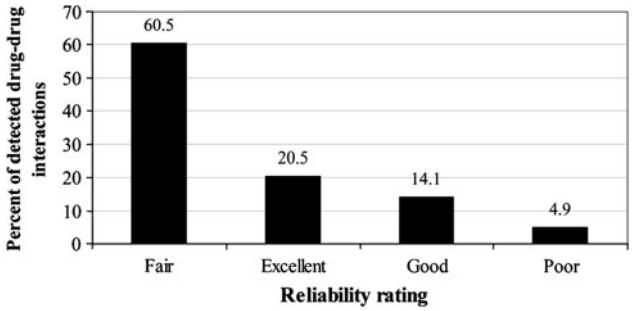

Fig. 1 Reliability rating of detected drug–drug interactions according to Lexi-Comp drug interaction software ($n = 185$)

pharmacodynamics, and the remaining 2 (1.08 %) had both pharmacokinetics and pharmacodynamics effects.

The characteristics of the 10 most frequent detected DDIs are given in Table 3. Interaction of sulfamethoxazole-trimethoprim with fluconazole was the most common DDI involving more than one-fourth (27.27 %) of detected DDIs. Fluconazole (25.95 %) was the most commonly offending medication followed by cyclosporine (11.35 %) and sulfamethoxazole-trimethoprim (9.73 %). The only identified interaction between 2 anti-cancer agents was vincristine with imatinib in one case in which imatinib could decrease the metabolism and enhance toxicity of vincristine. The detected interactions between anti-cancer and non-anti-cancer medications were as follows: arsenic trioxide with fluconazole ($n = 6$), arsenic trioxide with voriconazole ($n = 1$), arsenic trioxide with granisetron ($n = 1$), doxorubicin with cyclosporine ($n = 2$), and etoposide with cyclosporine ($n = 1$). Antimycotics for systemic use (31.35 %), immunosuppressants (13.51 %), and sulfamethoxazole-trimethoprim (9.73 %) were the most common medication classes responsible for detected DDIs (Table 4). No clinically significant rate-corrected QT (QTc) interval prolongation (over 500 ms) or torsades de pointes due to medications was detected in the study population.

A comparison between demographic, clinical, and paraclinical characteristics of patients with and without DDIs is shown in Table 5. According to multivariate logistic regression analysis, the number of administered medications during hematology–oncology ward stay was considered as an independent risk factor for developing a DDI (OR = 1.126, 95 % CI = 1.044–1.214, $P = 0.002$).

Discussion

According to the results of this cross-sectional study, more than half (62.88 %) of our patients with hematological malignancies or related diseases were exposed to at least one potential DDI. This rate is within the range reported from other similar studies. A systematic review about the epidemiology of DDIs in oncology patients was performed by Riechelmann et al. on relevant articles published up to April 2009. They demonstrated that the frequency of potential DDIs in oncology varied from 12 to 63 % [12]. In 2 other studies published later (both in 2011), the prevalence of DDIs in cancer and bone marrow transplant patients was reported to be 36 and 60 %, respectively [19, 20]. This wide variation in DDI frequency may be due to differences in study design and methodology (prospective vs. retrospective), method of DDI screening and detection, and study population and setting. For example, identification of potential DDIs in most relevant studies was

Table 3 The characteristics of the 10 most frequent drug–drug interactions detected in the study population ($n = 132$)

Drug-drug interaction	Probable effect (mechanism)	Severity	Reliability rating	Number of patients (%)
Sulfamethoxazole-trimethoprim + fluconazole	Fluconazole may decrease the metabolism of sulfamethoxazole-trimethoprim	Moderate	Fair	36 (27.27)
Granisetron + fluconazole	Fluconazole may enhance the QTc-prolonging effects of granisetron	Major	Fair	21 (15.91)
Cyclosporine + fluconazole	Fluconazole may decrease the metabolism of cyclosporine	Major	Excellent	12 (9.09)
Phenytoin + fluconazole	Phenytoin may decrease the serum concentration of fluconazole Fluconazole may increase the serum concentration of phenytoin	Major	Excellent	10 (7.58)
Cyclosporine + allopurinol	Allopurinol may increase the serum concentration of cyclosporine	Moderate	Poor	9 (6.82)
Methylprednisolone + phenytoin	Phenytoin may decrease the serum concentration of methylprednisolone	Major	Fair	7 (5.3)
Imipenem + ganciclovir	Ganciclovir may enhance the risk of imipenem-related seizures	Major	Fair	7 (5.3)
Arsenic trioxide + fluconazole	Fluconazole may enhance the QTc-prolonging effects of arsenic trioxide	Major	Fair	6 (4.55)
Cyclosporine + phenytoin	Phenytoin may increase the metabolism of cyclosporine	Moderate	Excellent	5 (3.79)
Atorvastatin + fluconazole	Fluconazole may decrease the metabolism of atorvastatin	Major	Excellent	4 (3.03)

Table 4 Medication classes responsible for detected drug–drug interactions categorized by therapeutic chemical (ATC) classification system of the World Health Organization ($n = 370$)

Code	Medication class	Medication(s)	*n* (%)
J02A	Antimycotics for systemic use	Voriconazole, itraconazole, fluconazole	116 (31.35)
L04A	Immunosuppressants	Cyclosporine, tacrolimus, sirolimus, mycophenolic acid	50 (13.51)
J01E	Sulfonamides and trimethoprim	Sulfamethoxazole and trimethoprim	36 (9.73)
N03A	Antiepileptics	Phenytoin, valproic acid	30 (8.11)
A04A	Antiemetics and antinauseants	Granisetron, aprepitant	26 (7.02)
M04A	Antigout preparations	Allopurinol	15 (4.05)
H02A	Corticosteroids for systemic use, plain	Methylprednisolone, prednisolone	14 (3.78)
L01X	Other antineoplastic agents	Arsenic trioxide, imatinib	9 (2.43)
J05A	Direct acting antivirals	Ganciclovir, adefovir dipivoxil	9 (2.43)
J01D	Other beta-lactam antibacterials	Imipenem	8 (2.16)
A12A	Calcium	Calcium carbonate	5 (1.35)
L02A	Hormones and related agents	Ethinylestradiol and levonorgestrel	5 (1.35)
C10A	Lipid modifying agents, plain	Atorvastatin, gemfibrozil	5 (1.35)
A02B	Drugs for peptic ulcer and gastro-esophageal reflux disease	Omeprazole	4 (1.08)
A02A	Antacids	Magnesium hydroxide	4 (1.08)
B01A	Antithrombotic agents	Dabigatran etexilate, clopidogrel	4 (1.08)
C09A	ACE inhibitors, plain	Captopril	3 (0.81)
N05A	Antipsychotics	Haloperidol	3 (0.81)
H01C	Hypothalamic hormones	Octreotide	3 (0.81)
N05B	Anxiolytics	Alprazolam	2 (0.54)
L01C	Plant alkaloids and other natural products	Vincristine, etoposide	2 (0.54)
V03A	All other therapeutic products	Sodium polystyrene sulfonate	2 (0.54)
A06A	Laxatives	Sorbitol	2 (0.54)
C03D	Potassium-sparing agents	Spironolactone	2 (0.54)
J01F	Macrolides, lincosamides, and streptogramins	Azithromycin	2 (0.54)
L01D	Cytotoxic antibiotics and related substances	Doxorubicin	2 (0.54)
C08C	Selective calcium channel blockers with mainly vascular effects	Amlodipine	1 (0.27)
G03X	Other sex hormones and modulators of the genital system	Danazol	1 (0.27)
H03A	Thyroid preparations	Levothyroxine sodium	1 (0.27)
A03F	Propulsives	Metoclopramide	1 (0.27)
G04B	Other urologicals, antispasmodics	Tolterodine	1 (0.27)
J04A	Drugs for treatment of tuberculosis	Isoniazid	1 (0.27)
M01A	Anti-inflammatory and antirheumatic products, non-steroids	Indomethacin	1 (0.27)

performed by Drug Interaction Facts software which we do not have access to that.

Above three-fifths (61.62 %) of DDIs in the present study were determined to be major. In contrast, other studies in cancer patients reported that more than half of detected DDIs were moderate [18–21]. Different criteria for classification of severity of DDIs by various drug interaction softwares could explain this discrepancy. For instance, interaction between phenytoin and corticosteroids was classified as major by Lexi-Interact software [13] while the severity of the same interaction was determined to be moderate by Micromedex Drug-Reax [20] as well as Drug Interaction Facts softwares [18].

In accordance with other studies [18–20], the majority of detected DDIs (173/185, 93.51 %) in the current survey are attributed to non-anti-cancer medications. A cross-sectional study undertaken at the Princess Margaret Hospital, Toronto, Canada, reported that among 276 identified potential DDIs from 109 ambulatory cancer patients receiving systemic anti-cancer therapy, 240 (87 %) involved non-antineoplastic drugs; most were antihypertensive agents, aspirin, warfarin, or anticonvulsants [18]. Similar results were observed by Kannan et al. [19]. Interestingly, in a retrospective study in hospitalized patients with solid or hematological malignancies who had not received anti-cancer drugs in the previous 4 weeks,

Table 5 Demographic, clinical, and paraclinical characteristics of patients with and without a drug–drug interaction ($n = 132$)

	Patients with DDI ($n = 83$)	Patients without DDI ($n = 49$)	OR (95 % CI)	*P*
Sex				
Male, *n* (%)	51 (61.45)	27 (55.1)	0.71 (0.33–1.529)	0.381
Female, *n* (%)	32 (38.55)	22 (44.89)		
Age (years)				
Mean ± SD	35.01 ± 15.29	32.86 ± 14.53	1.013 (0.988–1.039)	0.297
Range	5–69	7–65		
Type of hematological malignancies or diseases				
AML, *n* (%)	39 (46.99)	19 (38.78)	0.865 (0.591–1.265)	0.454
ALL, *n* (%)	20 (24.09)	14 (28.57)		
GVHD, *n* (%)	14 (16.87)	6 (12.24)		
Others, *n* (%)[a]	10 (12.05)	10 (20.41)		
Laboratory abnormality				
Yes	33 (39.76)	13 (26.53)	1.599 (0.703–3.635)	0.263
No	50 (60.24)	36 (73.47)		
Number of administered medications during ward stay				
Mean ± SD	14.2 ± 4.92	10.96 ± 5.92	1.126 (1.044–1.214)	0.002
Range	5–30	2–27		

DDI drug–drug interaction, *OR* odds ratios, *CI* confidence interval, *SD* standard deviation, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *GVHD* graft versus host disease

[a] Including neutropenic fever ($n = 7$), aplastic anemia ($n = 3$), burkitt lymphoma ($n = 3$), non-Hodgkin lymphoma ($n = 2$), thrombotic thrombocytopenic purpura ($n = 1$), idiopathic thrombocytopenic purpura ($n = 1$), multiple myeloma ($n = 1$), and pulmonary embolism ($n = 1$)

medications such as opioids, dexamethasone, furosemide, anticonvulsants, non-steroidal anti-inflammatory drugs, and low molecular weight heparins were considered as the most frequent drugs involved with DDIs [21].

In congruent with similar studies in cancer patients [18–20], pharmacokinetics was determined as the major mechanism of DDIs in our survey. This might be due to the fact that fluconazole was the most common medication involved in identified DDIs. Unlike these findings, analysis of 3,766 case reports of drug interactions from 47 countries during the past 20 years in the WHO Global Individual Case Safety Report database, VigiBase showed pharmacodynamics as the predominant mechanism of interaction (41 %); while pharmacokinetics accounted for 25 % and a combination of both types (pharmacodynamics and pharmacokinetics) accounted for 16 % of reported DDIs; for the remaining 18 % of DDIs, the mechanism of interaction was unidentified [22].

Fluconazole as the most commonly offending medication in DDIs at the present study could be partially attributed to the fact that it was the most common prescribed medication in our patients. In line with this, Guastaldi et al. [20] reported fluconazole as one of the 3 most commonly medications involved with potential DDIs in bone marrow transplant patients. Fluconazole as the azole of choice for prophylaxis against Candida infections in neutropenic patients [23] is the inhibitor of human cytochrome P450 (CYP) system, particularly CYP2C9, CYP2C19, and to lesser extent, CYP3A4 and could potentially interact with different medication classes such as corticosteroids, immunosuppressants, benzodiazepines, statins, anticoagulants, and anti-infectives [24]. Noting that fluconazole seems to have a dose-dependent effect on the CYP450 enzyme system. Therefore, at antifungal prophylaxis doses (<200 mg daily), its inhibitory effect on the metabolism of other medications appears not to be so profound and clinically significant [25]. This might be the case in the current investigation because the daily dose of fluconazole given to all our patients as prophylaxis or empirically treatment for fungal infections ranged from 50 to 200 mg.

Interaction between calcineurin inhibitor immunosuppressants (cyclosporine and tacrolimus) and concomitantly administered medications could adversely affect quality of life and clinical outcome in bone marrow transplant recipients. Since calcineurin inhibitors are extensively metabolized by the CYP3A4, co-administration of potent inducers of this isoenzyme such as phenytoin can decrease the level of calcineurin inhibitors and potentially increase the risk of GVHD [20, 26]. A number of case reports and pharmacokinetics studies have implicated the reduced cyclosporine blood levels among transplant patients taking phenytoin concurrently [27–29]. Therefore, close level monitoring and adjusting the dose of calcineurin inhibitors accordingly are mandatory [26]. In contrast to phenytoin,

triazoles antifungals can inhibit the metabolism and increase the level and potential toxicity of calcineurin inhibitors. Thus, it is generally recommended a 50–60 % reduction in the dose of calcineurin inhibitors when starting itraconazole [26] while the dose of cyclosporine should be reduced by 1/2 and tacrolimus by 1/3 on initiating voriconazole [30]. However, dose reductions in cyclosporine and tacrolimus are unnecessary when these agents are administered intravenously or doses less than 200 mg daily fluconazole are given [26].

Interaction between sulfamethoxazole-trimethoprim and fluconazole was identified as the most common DDI in the present study. Fluconazole, a strong inhibitor of CYP2C9, could significantly decrease the metabolism and increase the serum level of sulfamethoxazole-trimethoprim as a CYP2C9 substrate [24, 25]. This might lead to an increase in the risk of concentration-dependent sulfamethoxazole-trimethoprim adverse reactions such as nausea, vomiting, rash, fever, and myelosuppression [31]. In contrast, inhibition of sulfamethoxazole hydroxylamine formation, a reactive intermediate metabolite of sulfamethoxazole partially involves in its toxicities, by fluconazole demonstrated in healthy volunteers [32] as well as HIV-infected subjects [33] might be effective in preventing or decreasing sulfamethoxazole-trimethoprim adverse reactions, especially in HIV patients.

Among the 10 most frequent DDIs detected in our survey, interaction between arsenic trioxide with fluconazole was considered as the only DDI between an anti-cancer and non-anti-cancer medications. However, no clinically significant QTc prolongation or torsades de pointes was detected in patients receiving these medications simultaneously. Arsenic trioxide as a standard drug in the treatment of newly diagnosed or relapsed acute promyelocytic leukemia has been associated with significant QTc interval prolongation and symptomatic torsades de pointes in 35 and 1–3 % of patients at therapeutic doses, respectively [34]. Risk factors for QTc interval prolongation and torsades de pointes due to QTc-prolonging agents include female sex, age over 65 years, electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia), underlying heart disease, higher concentrations of offending medication, and concurrent use of another QTc-prolonging drug [13]. Patients with cancer are particularly at increased risk of these cardiac arrhythmias due to receiving numerous medications and high prevalence of electrolyte abnormalities [35]. Serum levels above 1 μmol/L have been demonstrated to increase the risk of cardiac conduction defects caused by arsenic trioxide [34]. Despite no formal DDI studies have been performed, Lexi-Interact software has been recommended that highest risk QTc-prolonging agents such as arsenic trioxide should not be administered concomitantly with any other QTc-prolonging agents such as fluconazole [13].

In our study among different administered anthracyclines, interaction between doxorubicin and cyclosporine was identified in 2 patients. Doxorubicin as a prototype of anthracyclines has been used for the treatment of a wide range of hematological as well as non-hematological malignancies since the late 1960s [36]. Doxorubicin is metabolized predominantly by the liver CYP system to its major active and potentially toxic metabolite, doxorubicinol [37]. The mechanism of cyclosporine interaction with doxorubicin appears to be dual because cyclosporine both inhibits doxorubicin transport by P-glycoprotein as well as CYP3A-mediated metabolism [13]. According to a case report, coma and tonic–clonic seizures were developed following administration of a chemotherapy regimen containing doxorubicin in a patient under chronic cyclosporine treatment [38]. A study in patients with small-cell lung cancer demonstrated an average of 48 and 443 % increase in doxorubicin and doxorubicinol area under the curve, respectively, as well as myelosuppression after initiating cyclosporine [39]. Other clinical studies have similarly reported increase in doxorubicin serum concentrations, toxicity, and/or reduced dose requirements with concurrent cyclosporine administration [40, 41]. This interaction has been drawn great attention as a potential beneficial means for reversing tumor resistance to doxorubicin [42].

Among the different studied demographic, clinical, and paraclinical characteristics of patients, only the number of administered medications during hematology–oncology ward stay was significantly associated with development of a DDI. It is in accordance with other studies particularly in cancer [18, 19, 43] and other conditions requiring complex treatments [8, 44], indicating that increasing the number of medications was an independent risk factor for occurrence of DDIs. As stated before, patients with cancer take numerous medications concurrently to manage their malignancy, toxicities, cancer-associated syndromes, and other co-morbid illnesses. Types of cancer (brain vs. genitourinary tumors) as well as medication indications (to treat co-morbid conditions vs. supportive care) have been identified as other probable risk factors for DDIs in patients with malignancies [18].

Several direct and indirect preventive strategies could be contributed in minimizing the risk of DDIs. Direct approaches include the development of medication databases and computerized physician order entry linked to screening electronic programs that assist health care professionals in detection of potentially life-threatening and lethal drug combinations, participation of clinical pharmacists in prescription, dispensing as well as administration of medications and patient follow-up, identification and close monitoring of patients at considerable risk for serious DDIs, regular level monitoring of medications with

narrow therapeutic index, avoiding polypharmacy, and switching from high risk medications to safer alternatives. Enhancing alertness and knowledge of health care professionals about common and clinically significant DDIs by teaching medical students, residents, as well as nursing staff and helding workshops and journal clubs are considered as indirect preventive approaches [12, 18, 20].

The present study has a number of limitations. First, it was conducted in a single center; thus, the results might be vulnerable to center bias and cannot be extrapolated to other related settings. Second, the methodology of the current survey did not allow us to determine the real clinical consequences of most of these potential DDIs. To our knowledge, only 2 studies have been investigated real DDIs in cancer patients [11, 45]. Third, screening and detection of DDIs were only based on single software rather than a comprehensive searching of relevant literature and databases along with opinions of a multispecialty team including hematologist–oncologists and clinical pharmacists. Therefore, at least a number of detected DDIs might not be clinically valuable. Interactions of major or moderate severity were considered eligible in this study to reduce the probability of overestimating not clinically significant DDIs. However, the level of evidence of about three-fifths (60.54 %) of detected DDIs in our survey was fair which means that they had no well-documented literature background such as randomized clinical trials and only based on anecdotal case reports.

In conclusion, potential moderate or major DDIs occur frequently in patients with hematological malignancies or related diseases. Most of detected DDIs had pharmacokinetics mechanism and classified as major regarding severity. Interaction of sulfamethoxazole-trimethoprim with fluconazole was the most common DDIs and fluconazole identified as the most frequent offending medication in DDIs. Majority of detected DDIs were among non-anticancer medications. The number of administered medications during ward stay was as an independent risk factor for developing a DDI. Large, multi-center, prospective, standard studies are warranted to assess the real clinical as well as economical impacts of DDIs on patients with various hematological and non-hematological malignancies.

Conflict of interest The authors declare that they have no competing interests.

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