Ann Hematol (2014) 93:1913–1922
DOI 10.1007/s00277-014-2122-0

ORIGINAL ARTICLE

Pattern and associated factors of potential drug-drug interactions in both pre- and early post-hematopoietic stem cell transplantation stages at a referral center in the Middle East

Safoora Gholaminezhad · Molouk Hadjibabaie · Kheirollah Gholami · Mohammad Reza Javadi · Mania Radfar · Iman Karimzadeh · Ardeshir Ghavamzadeh

Received: 13 January 2014 / Accepted: 26 May 2014 / Published online: 7 June 2014

Abstract The aim of this study was to determine the pattern as well as associated factors of moderate and major potential drug-drug interactions (PDDIs) in both the pre- and early post-transplantation stages at a referral hematopoietic stem cell transplantation (HSCT) center. All adolescents and adults undergone HSCT within a 3-year period were screened retrospectively for potential moderate or severe PDDIs by the Lexi-Interact On-Desktop software. Among 384 patients, a total of 13,600 PDDIs were detected. The median (interquartile range) cumulative PDDIs burden was 41 (28). All (100 %) individuals experienced at least one PDDI. More than four fifths (81.8 %) of detected PDDIs were moderate. The predominant mechanism of PDDIs was pharmacokinetics (54.3 %). Interaction between sulfamethoxazole-trimethoprim and fluconazole was the most common PDDIs involving 95.3 % of the study population. More than three fifths (61.5 %) of detected PDDIs were caused by HSCT-related medications. No interaction was identified between two anticancer agents. Interactions of cyclophosphamide with phenytoin, busulfan with metronidazole, dexamethasone, or clarithromycin were the only detected PDDI between anticancer and non-anticancer medications. Type of HSCT and the numbers of administered medications were significantly associated with major PDDIs. The epidemiology, real clinical consequence, and economic burden of DDIs on patients undergone HSCT particularly around the transplantation period should be assessed further by prospective, multicenter studies.

Keywords Drug-drug interactions · Hematopoietic stem cell transplantation · Conditioning period · Early post-transplant stage

S. Gholaminezhad
Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
e-mail: snowy28_67@yahoo.com

M. Hadjibabaie · K. Gholami · M. R. Javadi · M. Radfar · I. Karimzadeh (✉)
Research Center for Rational Use of Drugs and Faculty of Pharmacy, Tehran University of Medical Sciences, 4th Floor, No. 92, Karimkhan Zand Avenue, Hafte Tir Square, Tehran 1584775311, Iran
e-mail: karimzadehiman@yahoo.com

M. Hadjibabaie
e-mail: hajibaba@tums.ac.ir

K. Gholami
e-mail: khgholami@sina.tums.ac.ir

M. R. Javadi
e-mail: javadirctex1351@yahoo.com

M. Radfar
e-mail: mania1352@yahoo.com

A. Ghavamzadeh
Hematology-Oncology and Stem Cell Transplantation Research Center, Department of Hematology-Oncology, Dr Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
e-mail: ghavamza@sina.tums.ac.ir

Introduction

Drug-drug interaction (DDI) is the modification of pharmacological or clinical response of an initial drug by another drug that is given concurrently [1]. It can be classified into three types including pharmacokinetics, pharmacodynamics, and pharmaceuticals [2, 3].

DDIs comprise a significant cause of morbidity and mortality in both inpatient and outpatient settings. This may be due to adverse events, decrease in therapeutic effects of a drug, enhancement of drug toxicity, and, accordingly, compromising patient adherence as well as treatment outcome caused by DDIs [2]. It has been estimated that DDIs account

for 20–30 % of all drug toxicities, of which, 70 % need clinical attention and 1–2 % cases lead to life-threatening situations.

Currently, hematopoietic stem cell transplantation (HSCT) is considered as the main therapeutic modality for several malignant as well as nonmalignant hematologic and genetic diseases. It can offer a cure or prolonging survival for affected individuals [4, 5]. According to the first global survey by the Worldwide Network for Blood and Marrow Transplantation, a total of 50,417 first HSCTs have been reported in 2006 [6]. Ghavamzadeh et al. reported 3,237 first HSCTs from March 1991 through April 2011 in the Hematology-Oncology and Stem Cell Transplantation Research Center, affiliated to Tehran University of Medical Sciences, as one of the largest centers in the Middle East [7].

Despite its clinical and economical benefits, HSCTs are associated with various drawbacks and complications such as drug toxicities and DDIs [7]. Similar to patients with hematologic or solid organ malignancies, those planned to receive HSCT are also susceptible to develop DDIs at both the pre- and post-transplantation stages. This has been attributed to many factors including: (1) narrow therapeutic index and inherent toxicity of anticancer agents; (2) co-administration of multiple medications in addition to anticancer agents to manage chemotherapy-induced toxicities; (3) cancer-associated syndromes and other co-morbid illnesses (e.g., pain, seizures, venous thrombosis, nausea, vomiting, and depression); and (4) alteration in the pharmacokinetic parameters of anticancer medications secondary to impaired absorption, volume of distribution, and excretion [2]. The likelihood and severity of DDIs can even become more serious in the conditioning and early post-HSCT periods because pharmacotherapy (especially the number and dose of medications) are generally more complex during these stages. Based on a cross-sectional study by Guastaldi et al. on 70 subjects undergone HSCT in a tertiary care hospital in Sao Paulo, Brazil, 60 % patients in the conditioning period had at least one potential DDI (PDDI) and 21.4 % individuals were exposed to at least one major PDDI [8]. A retrospective analysis of 84 nonmyeloablative HSCT recipients at days 2, 7, and 21 after allogeneic graft infusion demonstrated that 11 out of 187 (5.9 %) co-administered medications can potentially affect mycophenolic acid pharmacokinetics and more than four fifths (87 %) of patients were exposed to at least one mycophenolic acid-related pharmacokinetics PDDI [9].

In contrast to general medicine settings, much few studies have addressed various aspects of potential or real DDIs in patients with different hematologic and nonhematologic malignancies especially around the HSCT period. We conducted the current study to determine the pattern as well as associated factors of moderate and major PDDIs in both pre- and early post-transplantation stages at a referral HSCT center in the Middle East.

Methods

All adolescents and adults (age ≥13 years) with different hematologic and/or nonhematologic malignancies or diseases undergone HSCT at the Hematology-Oncology and Stem Cell Transplantation Research Center of Dr Shariati Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran, within a 3-year period from January 2009 to January 2012 were included into this retrospective study. The center encompasses three HSCT wards with 25 beds for adults and adolescents, one pediatric HSCT ward with 9 beds, and two hematology-oncology wards, each consisting of 12 beds. Our study was conducted only in three HSCT wards that admit adults and adolescents. Except for receiving at least two anticancers or non-anticancer medications simultaneously during the HSCT ward stay, no specific inclusion–exclusion criteria were implemented for patient recruitment. The Institutional Review Board (IRB) and the Medical Ethics Committee of the hospital approved the study. This study was in accordance with the 1975 Helsinki Declaration as revised in 2008.

A clinical pharmacist collected required data of patients from their medical records. They included demographic characteristics (age and sex), final diagnosis, type of transplantation, and duration of ward stay. Laboratory findings regarding kidney and liver function (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], bilirubin, and serum creatinine), and all being scheduled anticancer as well as non-anticancer agents regardless of their initial dose or probable dose alterations and treatment strategy (prophylaxis, empirical, or pre-emptive) were also registered. Medications administered on as-needed basis were not recorded. Lexi-Interact On-Desktop software version 1.3.11.04.18 was used to screen PDDIs. Sensitivity and specificity of Lexi-Interact software has been determined to be about 87–100 and 80–90 % by several studies, respectively [10–12]. Table 1 lists definitions for the severity and reliability rating of PDDIs by the Lexi-Interact software. Only interactions with major or moderate severity were taken into account. Those with minor severity were not considered eligible for further analysis. PDDIs were classified as pharmacokinetics, pharmacodynamics, both, and unknown based on their suggested mechanism of interaction. Pharmacodynamics interaction was defined as one drug modulates the pharmacologic effect of another drug in either increasing (additive or synergistic) or decreasing (antagonistic) approach. Changing the absorption, distribution, metabolism, and/or excretion of a certain drug by another drug was considered as pharmacokinetics interaction [13]. Since they were beyond the scope of our study and also not supported by the software, pharmaceutical interactions (chemical and/or physical incompatibility between two drugs when mixed with each other) were not analyzed. The

Table 1 Classification criteria for drug-drug interactions based on the Lexi-Comp Drug Interaction software

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

third level pharmacological subgroup of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) Index 2013 of the World Health Organization Collaborating Center for Drug Statistics Methodology were exploited to categorize class of medications that detected PDDIs were belonged to them [14]. Similar to the definition of Jaklič et al. [9], anticancer agents used in the conditioning regimen, those for the prophylaxis of graft versus host disease (GVHD) including calcineurin inhibitors (cyclosporine), sirolimus, mycophenolate mofetil, methotrexate, and corticosteroids (prednisolone and methylprednisolone), and antimicrobials were considered as HSCT-related medications. The cumulative PDDI burden was defined as the number of PDDIs identified for an individual subject during the HSCT ward stay. Agents given to prevent and/or treat chemotherapy-induced toxicities, cancer-associated syndromes, and other comorbidities including pain, seizures, venous thrombosis, nausea, vomiting, and depression were categorized as non-HSCT-related medications. Based on the definition used in the study by Riechelmann el al. [13] as well as our previous study [15], an increase of 10 % or greater above the upper normal limit in the mean plasma levels of hepatic enzymes (AST ≤35 U/L, ALT ≤40 U/L, ALP ≤110 U/L, or bilirubin ≤22 μmol/L as normal ranges) and serum creatinine (≤99 μmol/L as normal range) during ward stay was considered as hepatic and renal laboratory abnormalities, respectively.

Statistical analysis

All descriptive-statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as percentage. The Kolmogorov-Smirnov test was applied to analyze the distribution of continuous variables. Normally and non-normally distributed continuous data were expressed as the mean ± standard deviation (SD) and median (interquartile range), respectively. The total number of administered medications during ward stay in individuals received either allogeneic or autologous HSCT was compared by the independent t test. In contrast, comparing the number of detected PDDIs between patients with and without hepatic and renal laboratory abnormalities individually was conducted by the Mann–Whitney test. Multivariate logistic regression analysis was exploited to assess the possible association between only major PDDIs and different variables including patients' age, sex, number of administered medications during HSCT ward stay, duration of ward stay, final diagnosis, type of HSCT (allogeneic versus autologous), and hepatic or renal laboratory abnormality by calculating odds ratios (OR) and their 95 % confidence intervals (CI). P values less than 0.05 were considered to be statistically significant.

Results

Three hundred eighty-four patients who have undergone HSCT during the 3-year period were screened for PDDIs. Various demographic and clinical characteristics of the study population are summarized in Table 2. Above three fifth (63.5 %) of the cohort were males. The number of individuals received allogeneic HSCT was about twice higher than those undergone autologous HSCT (64.3 versus 35.7 %, respectively). Acute myeloid leukemia was the most frequent diagnosis (28.7 %), followed by Hodgkin's disease (15.6 %), multiple myeloma (12.8 %), and acute lymphoblastic leukemia (12.2 %). The cohort received a total number of 12,192 medications including anticancer and nonanti cancer agents. The mean ± SD numbers of administered medications per patient during ward stay was 31.8±4.96. The five most commonly prescribed non-anticancer medications among the cohort were fluconazole (97.7 %), sulfamethoxazole-trimethoprim (96.6 %), allopurinol (93.2 %), phenytoin (91.4 %), and acyclovir (89.1 %). The median (interquartile range) daily dose of fluconazole was 150 mg (50). The three most commonly administered anticancer medications during the conditioning stage were cyclophosphamide (64.3 %), busulfan (58.3 %), and melphalan (35.9 %). Conditioning regimens of the study population are listed in Table 3. Busulfan plus cyclophosphamide (43.5 %) was the most frequently given conditioning regimen, followed

Table 2 Demographic and clinical characteristics of the study population (n=384)

	n (%)
Sex	
Male	244 (63.5)
Female	140 (49.3)
Age (years)	
Median (interquartile range)	30 (23)
Range	13–65
Duration of ward stay (days)	
Median (interquartile range)	27 (7)
Range	8–75
Number of administered medications	
Mean ± SD	31.8±4.96
Range	19–45
Type of hematopoietic stem cell transplantation	
Allogeneic	247 (64.3)
Autologous	137 (35.7)
Final diagnosis	
Acute myeloid leukemia	110 (28.7)
Hodgkin's disease	60 (15.6)
Multiple myeloma	49 (12.8)
Acute lymphoblastic leukemia	47 (12.2)
Thalassemia	37 (9.64)
Non-Hodgkin's lymphoma	31 (8.07)
Aplastic anemia	22 (5.7)
Myelodysplastic syndromes	10 (2.6)
Chronic myeloid leukemia	6 (1.6)
Myelofibrosis	4 (1.04)
Chronic lymphocytic leukemia	3 (0.8)
Fanconi anemia	3 (0.8)
Others[a]	2 (0.52)

[a] Including acute undifferentiated leukemia (n=1) and Askin tumor (n=1)

by lomustine plus etoposide plus cytarabine plus melphalan (23.2 %).

Table 3 Conditioning regimens of the study population (n=384)

Conditioning regimen	n (%)
Busulfan, Cyclophosphamide	167 (43.5)
Lomustine, Etoposide, Cytarabine, Melphalan	89 (23.2)
Melphalan, Cyclophosphamide	37 (9.64)
Busulfan, Fludarabine, anti-thymocyte globulin	27 (7.03)
Cyclophosphamide, anti-thymocyte globulin	22 (5.73)
Busulfan, Cyclophosphamide, anti-thymocyte globulin	19 (4.95)
Melphalan, Fludarabine	12 (3.13)
Busulfan, Etoposide	11 (2.86)

Among 384 patients, a total of 13,600 PDDIs were detected. The median (interquartile range) cumulative PDDIs burden was 41 (28). All (100 %) individuals experienced at least one PDDI. Two hundred twenty-four (58.3 %) subjects developed only one PDDI. In contrast, 61 (15.9 %), 57 (14.8 %), and 42 (10.9 %) individuals were involved with concurrent two, three, and more than three PDDIs, respectively. Regarding severity, 11,129 (81.8 %) and 2,471 (18.2 %) PDDIs were identified as moderate and major, respectively. Reliability rating (level of evidence) of detected DDIs is listed in Table 4. More than two fifths (43.4 %) of detected PDDIs were fair. The predominant mechanism of detected PDDIs was pharmacokinetics (54.3 %). The remaining 32.8, 8.72, and 4.18 % PDDIs were categorized as pharmacodynamics, mixed (both pharmacokinetics and pharmacodynamics effects), and unknown, respectively.

Table 5 demonstrates different features of the 10 most common detected PDDIs. Interaction between sulfamethoxazole-trimethoprim and fluconazole (95.3 %), granisetron and fluconazole (92.9 %), and phenytoin and fluconazole (88.8 %) were among the most frequent PDDIs involving more than four fifth of the study population. Fluconazole was the most common causative medication involved with 12.9 % of all detected PDDIs, followed by phenytoin (7.66 %), cyclosporine (5.63 %), ciprofloxacin (3.77 %), and sulfamethoxazole-trimethoprim (3.04 %). No interaction was identified between two anticancer agents. In contrast, the following PDDIs were detected between anticancer and non-anticancer medications—cyclophosphamide with phenytoin (n=202), busulfan with metronidazole (n=4), busulfan with dexamethasone (n=2), and busulfan with clarithromycin (n=2). The mean ± SD time duration of co-administration of the above anticancer and non-anticancer medications involved in PDDIs was 2.3±0.68, 3.6±0.64, 2±0.81, and 4±1.19 days, respectively.

Medication classes responsible for detected PDDIs were summarized in Table 6. The three most frequent classes of medication responsible for detected PDDIs were antimycotics for systemic use, antiepileptics, and immunosuppressants. More than three fifths (61.5 %) of detected PDDIs were caused by HSCT-related medications. The remaining 38.6 % PDDIs were due to non-HSCT-related medications. Among 13,600 detected PDDIs, 210 (1.54 %) and 1,154 (8.49 %) were with the conditioning regimen agents and postgrafting immunosuppressive prophylaxis regimen medications, respectively.

Among the cohort, 89 (23.2 %) and 32 (8.33 %) individuals were involved with hepatic and renal laboratory abnormalities, respectively. The median (interquartile range) number of PDDIs did not differ significantly between patients with (40.5 [25.5]) and without (42 [28.8]) renal laboratory abnormalities (P=0.847). In contrast, subjects with hepatic laboratory abnormalities experienced significantly more PDDIs than those

Table 4 Reliability rating of detected drug-drug interactions (n=13,600)

Reliability rating (level of evidence)	n (%)
Fair	5,901 (43.4)
Good	5,524 (40.6)
Excellent	1,705 (12.5)
Poor	470 (3.46)

without hepatic laboratory abnormalities (45 [17] versus 39 [29], respectively; P=0.004).

Multivariate logistic regression analysis demonstrated that among studied variables, only the numbers of administered medications during ward stay (OR=1.08, 95 % CI=1.99–3.17; P=0.044) and the type of HSCT (OR=2.96, 95 % CI=1.26–4.98; P=0.013) were significant associated factors for major PDDIs (Table 7). The mean ± SD numbers of all administered medications during ward stay in patients undergone allogeneic HSCT was significantly higher than those received autologous HSCT (33.5±4.24 versus 28.6±4.63, respectively; P<0.001).

Discussion

In the present study, at least one moderate or major PDDI was identified in all (100 %) patients within the period of pre- and early post-HSCT. This rate is much higher than what was reported from oncology settings. According to Riechelmann et al., systematic review on the epidemiology of PDDIs in oncology published up to April 2009, 12 to 63 % of oncology patients were exposed to PDDIs [2]. Guastaldi et al. reported that more than half of the individuals (60.0 %) were involved with at least one PDDI [8]. In a retrospective study by Jaklič and colleagues, 73 out of 84 (87 %) nonmyeloablative HSCT recipients were exposed to at least one mycophenolic acid-related pharmacokinetics PDDI after allogeneic graft infusion [9]. This wide variation in the frequency of PDDIs can be attributed to the heterogeneity of study methodology, screening and detection method of PDDIs, and clinical setting. In this regards for example, in contrast to the study by Guastaldi et al. [8], we considered PDDIs in both the pre- and early post-HSCT periods without separating these two stages. Therefore, our cohort was inevitably more vulnerable to PDDIs, because their pharmacotherapy regimen and duration were further complex and lengthy. In addition, Guastaldi et al. exploited Micromedex Drug-Reax software to detect PDDIs [8].

Only about 1.5 % (210/13,600) of identified PDDIs in the current survey was attributed to anticancer medications and the remaining 98.5 % PDDIs were involved among non-anticancer agents. In line with our results, Riechelmann et al. reported that among 276 identified PDDIs from 109 ambulatory cancer patients under systemic anticancer therapy, 240 (87 %) and 36 (13 %) were involved non-anticancer and

Table 5 Features of the 10 most frequent drug-drug interactions detected in the study population (n=384)

Drug-drug interaction	Probable effect (mechanism)	Severity	Reliability rating	Time duration of co-administration, days (mean ± SD)	Number of patients (%)
Sulfamethoxazole-Trimethoprim+ Fluconazole	Fluconazole may decrease the metabolism of sulfamethoxazole-trimethoprim	Moderate	Fair	3.9±1.66	366 (95.3)
Granisetron+Fluconazole	Fluconazole may enhance the QTc-prolonging effects of granisetron	Major	Fair	3.6±1.5	357 (92.9)
Phenytoin+Fluconazole	Fluconazole may increase the serum concentration of phenytoin	Moderate	Excellent	4.3±1.76	341 (88.8)
Ciprofloxacin+Fluconazole	Fluconazole may enhance the QTc-prolonging effects of ciprofloxacin	Major	Good	3.4±1.95	286 (74.5)
Cyclosporine+Methotrexate	Cyclosporine may increase the serum concentration of methotrexate Methotrexate may increase the serum concentration of cyclosporine	Moderate	Good	3.8±0.42	242 (63.02)
Cyclosporine+Phenytoin	Phenytoin may increase the metabolism of cyclosporine	Moderate	Excellent	2.9±0.316	240 (62.5)
Cyclosporine+Allopurinol	Allopurinol may increase the serum concentration of cyclosporine	Moderate	Poor	2.8±0.42	221 (57.6)
Phenytoin+Cyclophosphamide	Phenytoin may increase the metabolism of cyclophosphamide	Major	Fair	2.3±0.68	202 (52.6)
Diazepam+Fluconazole	Fluconazole may decrease the metabolism of diazepam	Moderate	Good	6±1.5	177 (46.1)
Methylprednisolone+Phenytoin	Phenytoin may decrease the serum concentration of methylprednisolone	Major	Fair	2.5±1.18	68 (17.7)

Table 6 Classes of medications stratified by ATC/DDD Index 2013 responsible for detected drug-drug interactions in the study population (n=384)

Code	Medication class	Medication(s)	n
J02A	Antimycotics for systemic use	Fluconazole, Itraconazole, Voriconazole	1,815
N03A	Antiepileptics	Phenytoin, Valproic acid, Gabapentin	1,038
L04A	Immunosuppressants	Cyclosporine, Sirolimus, Methotrexate, Mycophenolic acid	1,030
J01M	Quinolone antibacterials	Ciprofloxacin, Ofloxacin	506
A04A	Antiemetics and antinauseants	Aprepitant, Granisetron	463
J01E	Sulfonamide and trimethoprim	Sulfamethoxazole and trimethoprim	408
N05B	Anxiolytics	Diazepam, Alprazolam, Chlordizepoxide, Clonazepam	352
M04A	Antigout preparation	Allopurinol, Colchicine	242
L01A	Alkylating agents	Busulfan, Cyclophosphamide	219
H02A	Corticosteroids for systemic use,	Betamethasone, Methylprednisolone, Prednisolone, Dexamethasone, Hydrocortisone	170
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease	Omeprazole, Pantoprazole, Sucralfate	153
J01F	Macrolides, Lincosamides and Streptogramins	Azithromycin, Clarithromycin, Erythromycin	116
N06A	Antidepressants	Sertraline, Citalopram, Nortriptyline, Trazodone, Fluoxetine, Clomipramine	71
L02A	Hormones and related agents	Ethinylestradiol and levonorgestrel	66
A12A	Calcium	Calcium carbonate, Calcium gluconate	51
B05X	IV solution additives	Magnesium sulfate, Sodium bicarbonate	50
C03D	Potassium-sparing agents	Spironolactone	41
N05A	Antipsychotics	Quetiapine, Haloperidol, Trifluoperazine, Chlorpromazine	26
R06A	Antihistamines for systemic use	Diphenhydramine, Promethazine	21
B02A	Antifibrinolytics	Tranexamic acid	20
C03C	High-ceiling diuretics	Furosemide	14
J01X	Other antibacterials	Metronidazole	12
C09A	ACE inhibitors, plain	Lisinopril, Enalapril, Captopril	12
C08D	Selective calcium channel blockers with direct cardiac effects	Diltiazem, Verapamil	11
C09C	Angiotensin antagonists	Losartan	10
A11C	Vitamin A and D combination of the two	Calcitriol, Vitamin D	10
C07A	Beta blocking agents	Propranolol, Sotalol, Metoprolol, Carvedilol	9
A02A	Antacids	Magnesium hydroxide	9
J01G	Aminoglycoside antibacterials	Amikacin	9
J01C	Beta-lactam antibacterials, penicillins	Tazobactam and piperacillin	9
J05A	Direct acting antiviral	Adefovir dipivoxil, Ganciclovir, Lamivudine	8
C10A	Lipid modifying agents, plain	Atorvastatin, Gemfibrozil	8
J01D	Other beta-lactam antibacterials	Imipenem, Ceftriaxone	7
C08C	Selective calcium channel blockers with mainly vascular effects	Amlodipine	6
B01A	Antithrombotic agents	Warfarin	4
H01C	Hypothalamic hormones	Octreotide	4
A03C	Antispasmmodics in combination with psycholeptics	Clidinium and chlordiazepoxide	3
C03E	Diuretics and potassium sparing agents in combination	Triamterene and hydrochlorothiazide	3
R03D	Other systemic drugs for obstructive airway disease	Theophylline	2
N05C	Hypnotics and sedatives	Zolpidem	2
A03F	Propulsives	Metoclopramide	1
H03A	Thyroid preparations	Levothyroxine	1

anticancer agents, respectively [13]. Similarly, our recently published study on hospitalized patients with hematological malignancies or related diseases implicated that 93.5 % of detected PDDIs were attributed to non-anticancer medications [15]. These findings highlight the importance of PDDIs among non-anticancer agents or between anticancer and

Table 7 Comparison of different demographic, clinical, and paraclinical characteristics of patients with and without major drug-drug interactions (n=384)

	Patients with major DDIs (n=319)	Patients without major DDIs (n=65)	OR (95 % CI)	P
Sex				
Male, n (%)	202 (63.3)	42 (64.6)	0.872 (0.446–1.71)	0.688
Female, n (%)	117 (36.7)	23 (35.4)		
Age (years)				
Median (interquartile range)	30 (22)	30 (27)	1.01 (0.982–1.03)	0.543
Range	15–65	13–62		
Duration of ward stay (days)				
Median (interquartile range)	27 (7)	27 (8)	1.01 (0.970–1.06)	0.541
Range	8–75	16–51		
Number of administered medications during ward stay				
Mean ± SD	32.9±5.01	27.7±4.63	1.08 (1.99–3.17)	0.044
Range	19–45	20–42		
Type of hematological malignancies or diseases				
Leukemic malignancies, n (%)	141 (44.2)	26 (40)	0.725 (0.448–1.17)	0.188
Nonleukemic malignancies, n (%)	151 (47.3)	25 (38.5)		
Nonmalignant hematologic diseases, n (%)	27 (8.46)	14 (21.5)		
Type of hematopoietic stem cell transplantation				
Allogeneic, n (%)	203 (63.6)	44 (67.7)	2.96 (1.26–4.97)	0.013
Autologous, n (%)	116 (36.4)	21 (32.3)		
Hepatic or renal laboratory abnormality				
Yes, n (%)	101 (31.7)	28 (43.1)	0.742 (0.384–1.44)	0.376
No, n (%)	121 (37.9)	21 (32.3)		

non-anticancer medications that are usually overlooked in the hematology-oncology and HSCT settings.

We identified allogeneic HSCT and the number of administered medications as independent associated factors of major PDDIs. The role of allogeneic HSCT in susceptibility to PDDIs can be justified by the fact that patients undergone allogeneic HSCT received significantly higher number of medications compared to those undergone autologous HSCT. This difference may be attributed to the administration of postgrafting immunosuppressive prophylaxis regimen against GVHD [16]. The present finding is in accordance with other studies particularly in patients with cancer that require complex treatments [13, 17]. In a study conducted by Guastaldi and Secoli in the day prior to bone marrow infusion, male gender, age between 40 and 49 years, and using four or more medications were significant risk factors of PDDIs between antimicrobial agents [18]. Some differences of our results with Guastaldi and Secoli about probable risk factors of PDDIs in HSCT patients could be explained by different stages of HSCT and classes of medications studied.

Similar to our previous investigation in hematology-oncology ward [15], interaction between sulfamethoxazole-trimethoprim and fluconazole was the most common PDDI within pre- and early post-HSCT stages in the present study. Fluconazole, by inhibiting CYP2C9, could significantly decrease the metabolism and increase the serum level of sulfamethoxazole-trimethoprim as a CYP2C9 substrate [19]. This PDDI can theoretically lead to an increase in the risk of concentration-dependent adverse reactions of sulfamethoxazole-trimethoprim such as nausea, vomiting, rash, fever, and myelosuppression [20]. Nevertheless, it is noteworthy that fluconazole is the moderate and weak inhibitor of CYP3A4 and CYP2C9, respectively in a dose-dependent manner [21]. In daily doses less than 200 mg of fluconazole, primarily used for the prophylaxis or empirical treatment of fungal infections similar to that observed in the current survey, its inhibitory effect on the metabolism of other medications such as sulfamethoxazole-trimethoprim appears not to be clinically significant in the HSCT setting [19].

Interaction between cyclosporine and phenytoin was among the most 10 frequent PDDIs in the present study. Similar finding was observed by Hadjibabaie et al. [15] as well as Guastaldi et al. [8] in the hematology-oncology and HSCT wards, respectively. As calcineurin inhibitors are the main component of postgrafting immunosuppressive prophylaxis regimen against GVHD in allogeneic HSCT recipients [16], any DDI that can decrease their level may potentially increase the risk of GVHD and adversely affect clinical outcome in these patients. In this regards, a number of case reports and pharmacokinetics studies have demonstrated that co-administration of phenytoin can decrease tacrolimus

concentration, cyclosporine minimum concentration, as well as area under the curve (AUC) [22–25]. Therefore, close therapeutic monitoring and modifying the dose of calcineurin inhibitors are strongly recommended in these conditions.

Interaction between cyclophosphamide and phenytoin was considered as the only PDDI between an anticancer and non-anticancer medications among the 10 most frequent detected DDIs in the current study. In the conditioning course, phenytoin is given as a prophylactic anticonvulsant therapy before the first dose of busulfan. It is usually continued for 24 to 48 h after the last dose of busulfan [26]. Cyclophosphamide is an inactive prodrug that requires bioactivation by hepatic enzymes, specifically CYP 2B6, to form its activated metabolite, 4-hydroxycyclophosphamide [27]. For the first time in clinical practice, Slattery et al. showed that individuals receiving phenytoin and busulfan in combination with cyclophosphamide in the conditioning regimen had cyclophosphamide clearance and 4-hydroxycyclophosphamide AUC 112 and 48 % higher than those given cyclophosphamide with radiotherapy, respectively [28]. De Jonge et al. also reported a case of relapsing germ cell cancer patient that demonstrated a 51 % increase in exposure to 4-hydroxycyclophosphamide following receiving 5 days phenytoin before starting a chemotherapy regimen that contained high dose of cyclophosphamide [29]. In line with these findings, a more recent study by McCune et al. demonstrated that in comparison to patients receiving cyclophosphamide and total body irradiation, those who received phenytoin and busulfan preceding cyclophosphamide had the AUC of cyclophosphamide and 4-hydroxycyclophosphamide significantly lower and higher (about 100 %), respectively. However, there was no statistically significant association between the AUC of cyclophosphamide as well as its measured metabolites and studied clinical outcomes like veno-occlusive disease (VOD) [30]. Regarding its clinical importance and unpredictability among individuals, it is preferable to avoid concomitant administration of phenytoin and cyclophosphamide whenever possible. If anticonvulsant prophylaxis or treatment is inevitable, other approaches such as replacing phenytoin by agents with no significant hepatic enzyme induction activity (e.g., valproic acid, gabapentin, levetiracetam, and benzodiazepines) or regular monitoring of 4-hydroxycyclophosphamide and adjusting cyclophosphamide dose should be considered [29]. Eberly et al. did not recommend valproic acid as a viable and practical alternative to phenytoin for busulfan-induced seizure prophylaxis due to lack of clinical effectiveness and also concerns about hematologic and hepatic toxicities. In contrast, they suggested benzodiazepines, most notably clonazepam and lorazepam, or levetiracetam as acceptable options for this purpose [31]. In this regards, many HSCT centers throughout the world have switched from phenytoin to levetiracetam for the prophylaxis of busulfan-induced seizure [26].

The PDDI between busulfan and metronidazole was the second most common detected interaction of an anticancer and non-anticancer medication in our cohort. Busulfan has narrow therapeutic index and the pharmacokinetics of its either oral or intravenous dosage form may vary extensively among individuals [32–34]. Furthermore, busulfan pharmacodynamics and its toxicities like VOD also depend on the conditioning regimen and the underlying diagnosis (e.g., CML versus other diseases) [30]. Co-administration of busulfan with metronidazole prior to HSCT to prevent Clostridium difficile infection and continuing at the postgraft course to prevent GVHD was associated with 79–87 % increase in the trough serum concentrations of busulfan along with its relevant signs and symptoms of toxicity (e.g., VOD, hemorrhagic cystitis) [35]. Similarly, Gulbis et al. described a case of acute myeloid leukemia that demonstrated busulfan AUC about 86 % greater than expected as well as a 46 % decrease in its clearance following concurrent administration of intravenous busulfan and oral metronidazole within the conditioning regimen [36]. The precise mechanism for this DDI remains unknown. Metronidazole is an inhibitor of some cytochrome P-450 subfamilies such as CYP3A4 and CYP2C9 [37]. Furthermore, metronidazole-reactive metabolites can interact with and deplete hepatic glutathione content [38]. On the other hand, busulfan metabolism is suggested to be mediated mainly via hepatic conjugation to glutathione by glutathione S-transferase A1 [39]. Altogether, it seems that metronidazole can decrease the clearance and increase exposure to busulfan through depleting hepatic glutathione content [35]. Therefore, simultaneous administration of busulfan and metronidazole should be avoided whenever possible. Otherwise, close and regular monitoring of busulfan AUC and its relevant toxicities is mandatory [36]. Glotzbecker et al. recommended that a time interval of at least 72 h should be elapsed between completion of busulfan therapy and initiating metronidazole in cases that administration of metronidazole is inevitable (e.g., documented severe anaerobic infections) [40].

The present study appears to suffer from three major drawbacks. First, real clinical consequences of detected PDDIs are unclear. This is predominantly due to the retrospective design of our survey. Moreover, as the serum levels of 4-hydroxycyclophosphamide and busulfan are not currently measured in our center, the clinical relevance and significance of PDDIs including phenytoin with cyclophosphamide, busulfan with metronidazole, and busulfan with clarithromycin are unknown in our cohort. Nevertheless, it is worthwhile mentioning that very limited studies have investigated real DDIs and their outcomes in the oncology and HSCT settings so far [41–43]. Second, the onset of detected PDDIs was undetermined because Lexi-Interact software generally does not support this feature. In contrast, Drug Interaction Facts and Micromedex Drug-Reax software offer the onset of detected DDIs. Finally, despite Lexi-Interact software has acceptable sensitivity and specificity, some potentially important DDIs in the HSCT setting such as cyclophosphamide with

cyclosporine is not provided by this program compared to other software such as Drug Interaction Facts and Micromedex Drug-Reax. It was among the five most frequent major PDDIs in the Guastaldi et al. survey [8]. According to results of a retrospective study, the administration of cyclophosphamide as a part of conditioning regimen, significantly decreased serum concentration of cyclosporine by an unknown mechanism within 2 weeks after HSCT [44].

In conclusion, our entire cohort was exposed to at least one PDDI during the conditioning and early post-HSCT periods. The predominant mechanism of detected PDDIs was pharmacokinetics and their majority of severity was moderate. Sulfamethoxazole-trimethoprim with fluconazole was the most frequent identified PDDIs and fluconazole was considered as the most common causative medication in DDIs. No PDDI was identified between two anticancer agents. Interactions of cyclophosphamide with phenytoin, and busulfan with metronidazole, dexamethasone or clarithromycin were the only detected PDDIs between anticancer and non-anticancer medications. Type of HSCT and the numbers of administered medications were the independent associated factors of PDDIs. The epidemiology, real clinical consequence, and economic burden of DDIs on patients undergone HSCT particularly around the transplantation period should be assessed further by prospective, multicenter studies. Findings of such investigations can be used as a guide for developing preventive strategies such as identifying risk factors of common DDIs with potentially life-threatening or lethal consequences in the HSCT setting. We can also stratify patients in this respect and improve the alertness as well as knowledge of healthcare professionals regarding these DDIs.

Acknowledgments The authors would like to thank all the staff of the adult HSCT wards at the Hematology-Oncology and Stem Cell Transplantation Research Center of the Dr Shariati Hospital for their kind cooperation.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Fuhr U (2008) Improvement in the handling of drug-drug interactions. Eur J Clin Pharmacol 64:167–171
2. Riechelmann RP, Del Giglio A (2009) Drug interactions in oncology: how common are they? Ann Oncol 20:1907–1912
3. Köhler GI, Bode-Böger SM, Busse R, Hoopmann M, Welte T, Böger RH (2000) Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. Int J Clin Pharmacol Ther 38:504–513
4. Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354:1813–1826
5. Appelbaum FR (2007) Hematopoietic-cell transplantation at 50. N Engl J Med 357:1472–1475
6. Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A et al (2010) Hematopoietic stem cell transplantation: a global perspective. JAMA 303:1617–1624
7. Ghavamzadeh A, Alimoghaddam K, Ghaffari F, Derakhshandeh R, Jalali A, Jahani M (2013) Twenty years of experience on stem cell transplantation in Iran. Iran Red Crescent Med J 15:93–100
8. Guastaldi RB, Reis AM, Figueras A, Secoli SR (2011) Prevalence of potential drug-drug interactions in bone marrow transplant patients. Int J Clin Pharm 33:1002–1009
9. Jaklič A, Collins CJ, Mrhar A, Sorror ML, Sandmaier BM, Bemer MJ, Locatelli I, McCune JS (2013) High prevalence of potential drug interactions affecting mycophenolic acid pharmacokinetics in nonmyeloablative hematopoietic stem cell transplant recipients. Int J Clin Pharmacol Ther 51:711–717
10. Barrons R (2004) Evaluation of personal digital assistant software for drug interactions. Am J Health Syst Pharm 61:380–385
11. Vonbach P, Dubied A, Krähenbühl S, Beer JH (2008) Evaluation of frequently used drug interaction screening programs. Pharm World Sci 30:367–374
12. Reis AM, Cassiani SH (2010) Evaluation of three brands of drug interaction software for use in intensive care units. Pharm World Sci 32:822–828
13. Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK (2007) Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst 99:592–600
14. World Health Organization. Collaborating Center for Drug Statistics Methodology. ATC/DDD Index 2013. http://www.whocc.no/atc_ddd_index/. Accessed 17 October 2013
15. Hadjibabaie M, Badri S, Ataei S, Moslehi AH, Karimzadeh I, Ghavamzadeh A (2013) Potential drug-drug interactions at a referral hematology-oncology ward in Iran: a cross-sectional study. Cancer Chemother Pharmacol 71:1619–1627
16. Kannan G, Anitha R, Rani VN, Thennarasu P, Alosh J, Vasantha J, Martin JR, Uma MR (2011) A study of drug-drug interactions in cancer patients of a south Indian tertiary care teaching hospital. J Postgrad Med 57:206–210
17. de Jonge ME, Huitema AD, van Dam SM, Beijnen JH, Rodenhuis S (2005) Significant induction of cyclophosphamide and thiotepa metabolism by phenytoin. Cancer Chemother Pharmacol 55:507–510
18. Choi SW, Levine JE, Ferrara JL (2010) Pathogenesis and management of graft-versus-host disease. Immunol Allergy Clin North Am 30:75–101
19. Guastaldi RB, Secoli SR (2011) Drug interactions of anti-microbial agents used in hematopoietic stem cell transplantation. Rev Lat Am Enfermagem 19:960–967
20. Cronin S, Chandrasekar PH (2010) Safety of triazole antifungal drugs in patients with cancer. J Antimicrob Chemother 65:410–416
21. van der Ven AJ, Schoondermark-van de Ven EM, Camps W, Melchers WJ, Koopmans PP, van der Meer JW, Galama JM (1996) Anti-toxoplasma effect of pyrimethamine, trimethoprim and sulphonamides alone and in combination: implications for therapy. J Antimicrob Chemother 38:75–80
22. Kowalsky SF, Dixon DM (1991) Fluconazole: a new antifungal agent. Clin Pharm 10:179–194
23. Schmidt H, Naumann R, Jaschonek K, Einsele H, Dopfer R, Ehninger G (1989) Drug interaction between cyclosporin and phenytoin in allogeneic bone marrow transplantation. Bone Marrow Transplant 4:212–213
24. Keown PA, Laupacis A, Carruthers G, Stawecki M, Koegler J, McKenzie FN, Wall W, Stiller CR (1984) Interaction between phenytoin and cyclosporine following organ transplantation. Transplantation 38:304–306
25. Freeman DJ, Laupacis A, Keown PA, Stiller CR, Carruthers SG (1984) Evaluation of cyclosporin-phenytoin interaction with observations on cyclosporin metabolites. Br J Clin Pharmacol 18:887–893

26. Thompson PA, Mosley CA (1996) Tacrolimus-phenytoin interaction. Ann Pharmacother 30:544
27. Green KGE, Rogosheske JR (2012) Hematopoietic cell transplantation. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR (eds) Koda-Kimble and Young's applied therapeutics: The clinical use of drugs. Lippincott Williams & Wilkins, Philadelphia, p 2248
28. Boddy AV, Yule SM (2000) Metabolism and pharmacokinetics of oxazaphosphorines. Clin Pharmacokinet 38:291–304
29. Slattery JT, Kalhorn TF, McDonald GB, Lambert K, Buckner CD, Bensinger WI, Anasetti C, Appelbaum FR (1996) Conditioning regimen-dependent disposition of cyclophosphamide and hydroxycyclophosphamide in human marrow transplantation patients. J Clin Oncol 14:1484–1494
30. McCune JS, Batchelder A, Deeg HJ, Gooley T, Cole S, Phillips B, Schoch HG, McDonald GB (2007) Cyclophosphamide following targeted oral busulfan as conditioning for hematopoietic cell transplantation: pharmacokinetics, liver toxicity, and mortality. Biol Blood Marrow Transplant 13:853–862
31. Eberly AL, Anderson GD, Bubalo JS, McCune JS (2008) Optimal prevention of seizures induced by high-dose busulfan. Pharmacotherapy 28:1502–1510
32. Krivoy N, Hoffer E, Lurie Y, Bentur Y, Rowe JM (2008) Busulfan use in hematopoietic stem cell transplantation: pharmacology, dose adjustment, safety and efficacy in adults and children. Curr Drug Saf 3:60–66
33. McCune JS, Holmberg LA (2009) Busulfan in hematopoietic stem cell transplant setting. Expert Opin Drug Metab Toxicol 5:957–969
34. Kebriaei P, Basset R, Ledesma C, Ciurea S, Parmar S, Shpall EJ, Hosing C, Khouri I, Qazilbash M, Popat U, Alousi A, Nieto Y, Jones RB, de Lima M, Champlin RE, Andersson BS (2012) Clofarabine combined with busulfan provides excellent disease control in adult patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 18:1819–1826
35. Nilsson C, Aschan J, Hentschke P, Ringdén O, Ljungman P, Hassan M (2003) The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation. Bone Marrow Transplant 31:429–435
36. Gulbis AM, Culotta KS, Jones RB, Andersson BS (2011) Busulfan and metronidazole: an often forgotten but significant drug interaction. Ann Pharmacother 45:e39
37. Levy RH (1995) Cytochrome P450isozymes and antiepileptic drug interactions. Epilepsia 36:S8–S13
38. Larsson P, Cybulski W, Tjalve H (1997) Binding of 3H-metronidazole in olfactory, respiratory and alimentary epithelia in rats. Pharmacol Toxicol 81:65–73
39. Gibbs JP, Yang JS, Slattery JT (1998) Comparison of human liver and small intestinal glutathione S-transferase-catalyzed busulfan conjugation in vitro. Drug Metab Dispos 26:52–55
40. Glotzbecker B, Duncan C, Alyea E 3rd, Campbell B, Soiffer R (2012) Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. Biol Blood Marrow Transplant 18:989–1006
41. Buajordet I, Ebbesen J, Erikssen J, Brørs O, Hilberg T (2001) Fatal adverse drug events: the paradox of drug treatment. J Intern Med 250: 327–341
42. Egger SS, Meier S, Leu C, Christen S, Gratwohl A, Krähenbühl S, Haschke M (2010) Drug interactions and adverse events associated with antimycotic drugs used for invasive aspergillosis in hematopoietic SCT. Bone Marrow Transplant 45:1197–1203
43. Miranda V, Fede A, Nobuo M, Ayres V, Giglio A, Miranda M, Riechelmann RP (2011) Adverse drug reactions and drug interactions as causes of hospital admission in oncology. J Pain Symptom Manag 42:342–353
44. Nagamura F, Takahashi T, Takeuchi M, Iseki T, Ooi J, Tomonari A, Uchimaru K, Takahashi S, Tojo A, Tani K, Asano S (2003) Effect of cyclophosphamide on serum cyclosporine levels at the conditioning of hematopoietic stem cell transplantation. Bone Marrow Transplant 32:1051–1058