Evaluation of Potential Drug-drug Interactions in Patients with Hematologic Malignancies at a Referral Hematology–oncology Hospital: A Single-center Experience

Abstract

Background: Drug-drug interaction (DDI) is a complication that results from the combined use of two or more drugs. DDIs can create problems and increase drug toxicity. In some DDIs, a drug can reduce the effectiveness of other drugs. The treatment regimen of hematologic malignancies includes various medicines. Patients may have another disease and receive other medicines in their treatment regimen, resulting in an elevation of DDI rate. This study was aimed to study the rate, pattern, and probable risk factors for moderate and major interactions. **Subjects and Methods:** In this cross-sectional study, data including type of administrated drugs, type of malignancies, and patients' demographic data were obtained from medical records of patients referred to Tohid Hospital, Sanandaj, Iran, between 2011 and 2015. Major or moderate interactions were considered eligible for further analysis and minor interactions were excluded. DDIs were identified by Lexicomp software and *Drug Interaction Facts* book. Data analysis was carried out by descriptive statistics. **Results:** A total of 441 DDIs (moderate to major) were identified in 76 patients. DDIs in men were higher compared to women. In addition, most of the interactions in terms of intensity were moderate (62% of total interactions) and in terms of mechanism were pharmacodynamic (60% of total interactions). Interaction between acetaminophen and granisetron had the highest frequency. Among cancer drugs, cyclophosphamide (7% of total interactions) and among non-cancer drugs, granisetron (10% of total interactions) had the highest frequencies. **Conclusion:** Moderate or major DDIs occurred frequently in patients with blood cancer or related diseases. Most of the found DDIs were categorized as moderate with regard to severity. DDIs identification by the treatment team and replacement of treatment regimen will impose fewer complications on patients and increase patients' survival.

Keywords: *Chemotherapy, drug interactions, hematology, oncology*

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Introduction

Drug-drug interaction (DDI) is defined as a pharmacological or clinical response to the administration of drugs combination in which a second drug modifies the patient's response to an initial one.[1] DDIs are classified into three categories: pharmacodynamic, pharmacokinetic, and pharmaceutical ones. Pharmacodynamic interaction is defined as the interaction where the first drug affects the second one either by increasing or decreasing effect. In pharmacokinetic interaction, the first drug affects the absorption, distribution, metabolism, discharge, and bioavailability of the second one. In pharmaceutical interaction, physiochemical properties of the second drug are changed, which may affect the drug effects and side effects as a result.[1,2] DDIs severity is classified into three levels: minor, moderate, and major. No medical intervention is needed

for minor interaction, which is considered tolerable in most cases. Moderate interaction may need medical interventions. Therapeutic failure, hospitalization, permanent injury, and death are the results of major interaction. This type of interaction imposes irrecoverable side effects on the patient.[1,2] It has been estimated that 20%–30% of all drug side effects are because of DDIs, of which clinical attention is needed for 70%,[3,4] raised by 80% in old people.[5] Some of these interactions can cause irretrievable side effects.[6-8] In a study in Norway, it was revealed that approximately 18% deaths were associated with DDIs directly or indirectly.[9]

Various treatment regimens can be used in hematologic malignancies.[1] It should be noticed that patients with cancer are particularly vulnerable to DDIs because normally various medications are taken concurrently to manage

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malignancy, cancer-associated syndromes, chemotherapy-induced toxicities, and other comorbid illnesses such as nausea, vomiting, pain, and depression.[1,2] As more than one drug is used in their treatment regimen, drug interactions and related complications become probable. Treatment team should identify and evaluate such interactions and prescribe an effective treatment regimen with least side effects and interactions. Well establishing of this process can reduce unwanted DDIs and side effects.[3]

Chemotherapy drugs have a narrow treatment window with many side effects. To reduce these side effects, a series of drugs should be added to drug regimen. In addition, patients with cancer may have chronic diseases such as hypertension, liver and kidney failure, and gastrointestinal diseases, which may increase DDI risk.[10-13]

Pharmacist plays an effective role in increasing the efficacy of drugs as well as reducing their side effects by giving information on drug consumption time and drug interactions. Unfortunately, accessible clinical data about the rate and pattern of interactions in patients obtaining anticancer therapy are less. A study by Hadjibabaie *et al.*[1] was carried out at hematology–oncology ward of Dr. Shariati Hospital, Iran, but more studies are needed in this area. This study was designed to investigate the rate, pattern, and probable risk factors for moderate and major DDIs at referral hematology–oncology ward in Tohid hospital, Sanandaj, Iran.

Subjects and Methods

All admitted patients to 340-bed Tohid Hospital of Sanandaj, Iran, during four years from 2011 to 2015, were recruited into this cross-sectional study. By referring to the hospital pathology lab and checking reports book, the number of medical records of patients with cancer has been determined.

Demographic data (age and sex) and all prescribed and administered drugs (anticancer and non-anticancer drugs),

during hematology–oncology ward stay, were collected from patients' medical records by a pharmacist. Any patient who received at least two anticancer or non-anticancer medications concurrently during ward stay was considered eligible. Study was approved by the medical ethics committee of the hospital (317IR.UMSHA.REC.1394).

The screening of DDIs was performed using the Lexi-Interact online (Lexi-Interact™ Online, Hudson, Ohio) and *Drug Interaction Facts* book.[14,15] In *Drug Interaction Facts* book, drug interactions are classified based on their severity as major, moderate, and minor. Drug interactions are classified into five groups: A, B, C, D, and X in Lexicomp software. Group X means that prescription of two drugs must be prohibited. D means that treatment method must be modified in terms of dose or even drug type; in group C, monitoring is needed; group B does not need any intervention in treatment regimen; and group A means that no information on drug interaction is available. Because severity of interactions is common in both screening programs, interactions are analyzed based on severity. Definitions for severity and reliability rating of DDIs as per Lexi-Interact software are shown in Table 1.[14] Only interactions of major or moderate severity were considered eligible for further analysis, and interactions of minor severity due to lack of clinical significance were excluded.

On the basis of results of investigations to weigh the accuracy of DDIs' screening programs, Lexi-Interact software has both suitable sensitivity (87%–100%) and specificity (80%–90%).[1]

The recorded data were analyzed by descriptive statistics (Statistical Package for the Social Sciences [SPSS] version 24 and Excel version 2016, IBM® SPSS® Version 24.0). To determine the association between the occurrence and nonoccurrence of DDIs and sex, age, and number of prescribed medications, multiple logistic regression model was used to calculate confidence intervals (CIs) and odds ratios (OR). The P values less than 0.05 were considered statically meaningful.

Table 1: Lexi-Interact software definitions for severity and reliability rating of DDIs[14]

Classification	Definition
Severity	
A	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
C	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients
D	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, or choosing alternative agents
X	Data demonstrate that the specified agents may interact with each other in a clinically significant matter. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated

Results

Demographic and clinical characteristics of 76 patients during a 4-year period were registered in checklist paper, which are summarized in Table 2. More than half of the patients (59.2%) were male in this study. Total number of interactions were 514. The severity of 122 (24% of total interactions) DDIs was considered as major and 319 (62% of total interactions) as moderate. It should be noticed that 197 (38.3% of total interactions) DDIs were classified as pharmacokinetic, 311 (60.5% of total interactions) DDIs as pharmacodynamic, and 6 (1.2% of total interactions) DDIs had both pharmacokinetic and pharmacodynamic effects.

The number of administered medications during hematology–oncology ward stay was considered as an independent risk factor for developing DDIs according to the multivariate logistic regression analysis (OR = 2.25, 95% CI = 1.35–3.74, P value = 0.002) [Table 3]. Characteristics of the 10 most frequent detected DDIs are shown in Table 4. The most common DDI was interaction of granisetron with acetaminophen. Interaction of doxorubicin with cyclophosphamide had the highest frequency among interaction of anticancer drugs. Granisetron (52 times repetition) had the highest repetition among non-anticancer drugs, and cyclophosphamide had the highest repetition among anticancer drugs (37 times repetition).

Acute myeloid leukemia (AML) was the most frequent disease. Average of drugs prescribed in acute lymphoblastic leukemia (ALL) treatment regimen was the most (20.14 ± 7.40), but average of drug interactions in multiple myeloma (MM) treatment regimen was the most (11.36 ± 9.43). In addition, the mean age of patients with MM was more than others (65.8 ± 10.39 years).

Discussion

According to the results of this cross-sectional study, more than half (86.84%) of our patients showed at least one DDI, which is higher than previous reports.[1,16] This DDI frequency can be explained by the differences in methodology and study design, method of DDI screening and detection, and population and study setting.

The highest severity of interactions in our study was moderate and the most DDI frequency was associated with the interaction between granisetron and other drugs. Granisetron was the most frequently offending medication in this study, which could be attributed to the fact that it was prescribed in most of our patients. The most common DDI in this study was interaction between acetaminophen and granisetron (2% of total DDIs). Severity of this interaction was moderate. Anti-nausea and anti-vomiting drugs (5HT3 antagonists) reduce pain relief effects of acetaminophen for which intervention by treatment team is not required.

In a research by Hadjibabaie *et al.*,[1] 183 potential drug interactions were identified of which the highest was pharmacokinetic (69.73% of all interactions). Fluconazole was a drug with the highest interaction (25.95%), whereas sulfamethoxazole and fluconazole interaction had the highest repetitions (27.27). The only interaction in cancer drugs was realized between vincristine and imatinib. More than three-fifths of DDIs were determined as major. The results of this study were not consistent with our research It should be noted that different drug interaction software used in various studies

Table 2: Demographic and clinical characteristics of the study population (*n* = 76, male: 45, female: 31)

Disease	Number of patients	Average prescription drugs (mean ± SD)	Average drug interactions (mean ± SD)	Average patients age
CLL	10 (13.15%)	12.4 ± 5.01	9.2 ± 9.88	62.9 ± 14.04
CML	11 (14.48%)	4.9 ± 2.94	0.6 ± 1.56	46.4 ± 21.57
ALL	14 (18.42%)	20.14 ± 7.40	9.6 ± 6.84	26.6 ± 15.38
NHL	4 (5.26%)	20 ± 5.09	11 ± 4.83	43.5 ± 17.25
Hodgkin	3 (3.95%)	11.6 ± 3.78	5.3 ± 4.93	39 ± 5.56
MM	11 (14.48%)	14.09 ± 5.18	11.36 ± 9.43	65.8 ± 10.39
AML	23 (30.26%)	17.56 ± 6.91	4.13 ± 2.58	37.2 ± 13.9

SD = standard deviation, NHL = non-hodgkin lymphoma

Table 3: Results according to multivariate logistic regression analysis

Variable	Patients with DDIs (*n* = 66)	Patients without DDIs (*n* = 10)	Odds ratio (95% CI)	*P* value
Sex			0.316 (0.014–7.25)	0.471
Male	40 (61%)	5 (50%)		
Female	26 (39%)	5 (50%)		
Age (year) (mean ± SD)	43.36 ± 19.47	52.2 ± 22.76	1.000 (0.917–1.09)	0.999
Number of prescription drugs (mean ± SD)	16.59 ± 6.65	3.9 ± 1.66	2.25 (1.35–3.74)	0.002

SD = standard deviation

Table 4: The characteristics of the 10 most frequent drug-drug interaction detected in the study population (*n* = 76)

Drug-drug interactions	Mechanism of interaction	Interaction frequency	Type of interaction	Severity
Acetaminophen + granisetron	Antiemetic may diminish the analgesic effect of acetaminophen	12	Pharmacodynamic	Minor
Doxorubicin + cyclophosphamide	Cyclophosphamide may enhance cardiac toxic effect of doxorubicin	11	Pharmacodynamic	Major
Cyclophosphamide + filgrastim	Filgrastim may enhance the adverse effect of cyclophosphamide	11	Pharmacodynamic	Major
Pethidine + granisetron	Granisetron may enhance the probability of serotonin syndrome induced by pethidine	9	Pharmacodynamic	Major
Pantoprazole + fluconazole	Fluconazole may increase serum concentration of PPIs	8	Pharmacokinetic	Moderate
Cyclophosphamide + allopurinol	Allopurinol may enhance the adverse effect of cyclophosphamide	8	Pharmacodynamic	Moderate
Granisetron + ciprofloxacin	QTc-prolonging effect may be enhanced	7	Pharmacodynamic	Major
Vincristine + fluconazole	Fluconazole may decrease the metabolism of vincristine	6	Pharmacokinetic	Moderate
Allopurinol + magnesium hydroxide	Antacids may decrease the absorption of allopurinol	6	Pharmacokinetic	Moderate
Dexamethasone + magnesium hydroxide	Antacids may decrease the bioavailability of corticosteroids	6	Pharmacokinetic	Moderate

PPIs = proton pump inhibitors

can describe differences in the reported severity of DDIs.[1] Different criteria for classification of severity of DDIs by various drug interaction software, diversity of underlying diseases, and prescription drugs could explain this discrepancy.

In a research by Tavakoli *et al.*,[7] among 224 patients, 228 cases of potential DDIs were identified. Moderate severity drug interaction was 60% of all interactions.[7] Men were outnumbered compared to women in this study. In a research by Riechelmann *et al.*,[16] 180 potential interactions were identified among 63 patients, of which the highest was related to moderate category (56.7% of all interactions). Results of these studies were consistent with our research.[16] In a research by van Leeuwen *et al.*,[4] 1359 cases of drug interactions were identified among 426 patients with the highest frequency for moderate severity of drug interaction. In another research in 2011, among 278 patients, 348 potential drug interactions were identified.[2] Most of the patients were men (55% of all patients). Pharmacodynamic interaction was the highest (64%).[2,8] Results were consistent with our research.

In chronic myelogenous leukemia (CML), AML, ALL, and chronic lymphocytic leukemia (CLL), male patients were more than female patients. Drug interactions were present in 298 cases in men and 216 cases in women. Drug interactions were more registered in men because more than half of the patients were men; drug interactions in people older than 50 years were higher due to potential of underlying diseases such as cardiovascular, gastrointestinal, brain, and nerve diseases. Thus, treatment team must provide a complete and exact description of the patient's condition and consider drugs prescribed in case they may cause interactions.

Use of broad spectrum of pharmacological classes is associated with QT interval prolongation. On the basis of the possibly serious and even fatal consequences of drug combinations, which are resulted in QT interval prolongation, it has been recommended to avoid the prescription of many drug combinations. Owing to the widespread use of drugs that induced QT interval prolongation, such as doxorubicin, quinolones, and ondansetron, and high prevalence of electrolyte abnormalities in patients with cancer, a significant problem may result from QT interactions.[2,17]

It should be noticed that increasing the number of administered medications during hematology–oncology ward stay is significantly associated with the development of a DDI. It is in agreement with other studies for the occurrence of DDIs.[18-20] On the contrary, the age of the patients is not associated with the development of a DDI. This finding is not in agreement with previous studies.[1,8]

The strength of this study is that it obtained efficient and less expensive results, which were effective in improving patients' treatment regimen. The best approach to prevent drug interactions is unidentified. Electronic alert, kind of alert guidelines, which is designed to remind drugs with potential interactions to pharmacists or physicians after entering patients' medication orders into the electronic medical record could be appropriate approach to help identify potentially hazardous interactions. Increasing recognition of such interactions by computerized programs can provide an applicable tool for screening them.[14]

Limitations of our study can be enumerated as follows: First, because the study was conducted in a single hospital, the

results could not be generalized to other related setting. Second, because of the research methodology used, the real clinical consequences of most of these DDIs potential were not determined. Third, because of detecting and screening DDIs by a single software, some of the detected DDIs might be clinically worthless. In this way, it was better to search related literature and databases. In addition, opinions of a multispecialty team including oncologists, hematologists, and clinical pharmacists can be helpful in clinical judgment of DDIs. Fourth, because of various types of hematologic malignancies, the number of patients in some types was very low.

To minimize the risk of DDIs, numerous direct and indirect preventive approaches can be adopted. Direct strategies include medication databases development and physician order entry computerization linked to screening electronic programs that help health-care professionals in detecting possibly life-threatening and lethal drug combinations. Moreover, direct approaches involve contribution of clinical pharmacists in prescription, dispensing, and administration of medications, along with patients' close monitoring for serious DDIs, avoiding polypharmacy, regular level monitoring of medications, especially with narrow therapeutic index, and switching from high-risk medications to safer replacements. Indirect preventive strategies include enhancing awareness and knowledge of health-care professionals about common and clinically significant DDIs by teaching medical students, residents, as well as nursing staff, beside holding workshops and journal clubs.[1]

Drug interaction identification by pharmacist is required for providing an efficient treatment regimen with the least interaction and the highest effect. Sometimes it should be replaced by another drug by treatment team, if needed.

Conclusion

In conclusion, moderate or major DDIs occur frequently in patients with hematological malignancies or related diseases. Most of the found DDIs had pharmacodynamic mechanism and were classified as moderate with regard to severity. Interaction of granisetron with acetaminophen was the most common DDIs, and granisetron was recognized as the most repeated offending medication in DDIs. Most of the found DDIs were among the non-anticancer medications.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hadjibabaie M, Badri S, Ataei S, Moslehi AH, Karimzadeh I, Ghavamzadeh A. Potential drug-drug interactions at a referral hematology-oncology ward in Iran: A cross-sectional study. Cancer Chemother Pharmacol 2013;71:1619-27.

2. van Leeuwen RW, Brundel DH, Neef C, van Gelder T, Mathijssen RH, Burger DM, *et al*. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer 2013;108:1071-8.

3. Nabovati E, Vakili-Arki H, Taherzadeh Z, Hasibian MR, Abu-Hanna A, Eslami S. Drug-drug interactions in inpatient and outpatient settings in Iran: A systematic review of the literature. Daru J Pharm Sci 2014;22:52.

4. van Leeuwen RW, Swart EL, Boom FA, Schuitenmaker MS, Hugtenburg JG. Potential drug interactions and duplicate prescriptions among ambulatory cancer patients: A prevalence study using an advanced screening method. BMC Cancer 2010;10:679.

5. Girre V, Arkoub H, Puts MT, Vantelon C, Blanchard F, Droz JP, *et al*. Potential drug interactions in elderly cancer patients. Crit Rev Oncol Hematol 2011;78:220-6.

6. Fuhr U. Improvement in the handling of drug-drug interactions. Eur J Clin Pharmacol 2008;64:167-71.

7. Tavakoli-Ardakani M, Kazemian K, Salamzadeh J, Mehdizadeh M. Potential of drug interactions among hospitalized cancer patients in a developing country. Iran J Pharm Res 2013;12:175-82.

8. Tavousi F, Sadeghi A, Darakhshandeh A, Moghaddas A. Potential drug-drug interactions at a referral pediatric oncology ward in Iran: A cross-sectional study. J Pediatr Hematol Oncol 2019;41:e146-51.

9. Buajordet I, Ebbesen J, Erikssen J, Brørs O, Hilberg T. Fatal adverse drug events: The paradox of drug treatment. J Intern Med 2001;250:327-41.

10. van Leeuwen RW, Jansman FG, van den Bemt PM, de Man F, Piran F, Vincenten I, *et al*. Drug-drug interactions in patients treated for cancer: A prospective study on clinical interventions. Ann Oncol 2015;26:992-7.

11. Del Re M, Fogli S, Derosa L, Massari F, De Souza P, Crucitta S, *et al*. The role of drug-drug interactions in prostate cancer treatment: Focus on abiraterone acetate/prednisone and enzalutamide. Cancer Treat Rev 2017;55:71-82.

12. Umar A, Steele VE, Menter DG, Hawk ET. Mechanisms of nonsteroidal anti-inflammatory drugs in cancer prevention. Semin Oncol 2016;43:65-77.

13. Douketis JD. Patient self-monitoring of oral anticoagulant therapy: Potential benefits and implications for clinical practice. Am J Cardiovasc Drugs 2001;1:245-51.

14. Lexi-interact. Available from: http://webstore.lexi.com/Lexi-Interact. [Last accessed 2012 June 1].

15. David, S. Tatro. Drug Interaction Facts: The Authority on Drug Interactions. 2014. Alphen aan den Rijn: Wolters Kluwer Health/ Facts & Comparisons, 2014.

16. Riechelmann RP, Del Giglio A. Drug interactions in oncology: How common are they? Ann Oncol 2009;20:1907-12.

17. Bagnes C, Panchuk PN, Recondo G. Antineoplastic chemotherapy induced QTc prolongation. Curr Drug Saf 2010;5:93-6.

18. Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst 2007;99:592-600.

19. Kannan G, Anitha R, Rani VN, Thennarasu P, Alosh J, Vasantha J, *et al*. A study of drug-drug interactions in cancer patients of a south Indian tertiary care teaching hospital. J Postgrad Med 2011;57:206-10.

20. Riechelmann RP, Zimmermann C, Chin SN, Wang L, O'Carroll A, Zarinehbaf S, *et al*. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage 2008;35:535-43.