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Drug-Drug Interaction Intensity Differences Depending On The Hematopoietic Stem Cell Transplantation Type And Existing Polypharmacy Prior To Transplantation

Hematopoietik Kök Hücre Nakli Türüne ve Nakil Öncesi Mevcut Polifarmasiye Bağlı Olarak İlaç-İlaç Etkileşimi Farklılıkları

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Öz

Amaç: İlaç ilaç etkileşimleri, kök hücre nakli işleminin başarısını etkileyebilmektedir. Bu nedenle, bu etkileşimlerin riskini analiz etmek sağlık profesyonelleri için gerekliliktir. Bu çalışma, allojenik ve otolog kök hücre nakli hastalarında nakil öncesi ve sonrası ilaç-ilaç etkileşimlerini belirlemek amacıyla yapılmıştır.
Material and Methods: Çalışmaya allojenik kök hücre nakli ve otolog kök hücre nakli yapılan hastalar dahil edildi. Hastaların nakil gününden on gün önce, nakil gününde ve nakil gününden on gün sonrasına ait tedavi şemaları toplandı. İlaç-ilaç etkileşimleri, dört ilaç-ilaç etkileşimi kontrol veri tabanı kullanılarak analiz edildi.
Bulgular: Her iki transplantasyon tipinden 50 hasta dahil edildi. Allojenik ve otolog nakiller için ortalama yaş sırasıyla 42.4 ve 51.8 idi. Allojenik nakillerin %52'si ve otolog nakillerin %28'i nakilden önceki onuncu günde ≥5 ilaç kullanıyordu. Allojenik ve otolog kök hücre nakli hastalarında ortalama etkileşim sayıları sırasıyla 75.42 ve 43.62 idi. Allojenik ve otolog nakil hastalarında sırasıyla %94 ve %92 oranında en az bir kontrendike etkileşimin saptandı. Allojenik nakillerin %48'inde ve otolog nakillerin %36'sında iki veya daha fazla kontrendike etkileşim tespit edildi.
Sonuç: Allojenik kök hücre nakli hastaları, otolog kök hücre nakli hastalarına göre neredeyse iki kat daha fazla ilaç-ilaç etkileşimine maruz kaldı. Transplantasyon tipi, hastanın transplantasyon öncesi ve sonrası dönemde olması ve transplantasyon sürecinin başındaki ilaç sayısı ilaç-ilaç etkileşim sayısı açısından önemlidir. Transplantasyon tipi ve hastaların mevcut ilaçları açısından etkileşimlerin belirlenmesi önem arz etmektedir.

Anahtar Kelimeler: İlaç-ilaç etkileşimleri, hematopoietik kök hücre nakli, klinik eczacılık, HKHN, KİT

Abstract

Objective: Drug drug interactions can effect the success of stem cell transplantation process. Therefore, analyzing the risk of these interactions would be helpful for practitioners. This study was conducted to identify drug-drug interactions in allogeneic and autologous stem cell transplantation patients before and after transplantation.
Materials and Methods: Patients who underwent allogeneic stem cell transplantation and autologous stem cell transplantation were included in the study. Patients' treatment sheets were collected ten days before transplantation day, on the transplantation day, and ten days after transplantation day. Drug-drug interactions were analyzed by using four drug-drug interaction checking databases.

Results: 50 patients from both transplantation types were included. The mean ages for allogeneic and autologous transplants were 42.4 and 51.8, respectively. 52% of allogeneic transplants and 28% of autologous transplants were on ≥5 drugs at tenth day before transplantation. The means of interactions in allogeneic and autologous stem cell transplantation patients were 75.42 and 43.62, respectively. The detection of at least one contraindicated interaction in allogeneic and autologous transplant patients were 94% and 92%, respectively. In 48% of allogeneic transplants and 36% of autologous transplants, two or more contraindicated interactions were detected.
Conclusion: Allogeneic stem cell transplantation patients experienced almost two times more drug-drug interactions than autologous stem cell transplantation patients. Transplantation type, being in the pre and post-transplantation period and the drug number at the beginning of the transplantation process matter in terms of the number of drug-drug interactions. Identifying interactions in terms of transplantation type and existing medications is very important.

Keywords Drug-drug interactions, hematopoietic stem cell transplantation, clinical pharmacy, HSCT, BMT

1. Introduction

Drug-drug interactions (DDIs) happen when one of the drugs alters the other drug's effect. Interaction mechanisms are mostly pharmacodynamic or pharmacokinetic [1, 2]. Patients may get prescriptions from many doctors, and they may not be aware of all of their medication lists. Therefore, combining drugs without proper supervision may cause drug-drug interactions. DDIs are a significant cause of hospital visits. It was estimated that 22.2% of adverse drug event experiencing patients were admitted to hospitals due to DDIs [2].

Cancer patients are relatively more prone to DDIs due to the intensity of their cancer treatment schemes and the drugs used for comorbidities [3]. Polypharmacy simultaneous use of five or more drugs increases drug interactions in cancer patients [4]. In a cross-sectional study conducted on hematopoietic stem cell transplantation (HSCT) patients, it was estimated that on transplantation day, the mean number of drugs per patient was 12.06 [5]. Studies estimated different DDI rates for cancer patients, and it is thought that one in three cancer patients is exposed to severe DDIs [6].

HSCT is a curative method that is used for a variety of diseases, including hematological cancers. Transplantation can be autologous or allogeneic according to the source of stem cells. Autologous HSCT is used for cancers such as multiple myeloma, lymphoma types, and autoimmune diseases. Allogeneic HSCT, autotransplantation, is used for diseases such as leukemia, lymphoma, myelodysplastic/myeloproliferative diseases, and anemias by using a histocompatible donor stem cells [7, 8].

HSCT is a complex, multi-drug involving process. Therefore, DDIs are common among these patients. In a study, 60% of BMT patients experienced at least one DDI, and one in three experienced a major DDI. In addition, organ toxicities and other adverse events may be seen in this patient group [9]. In a retrospective cohort study, DDI was detected in 69.8% of patients, while DDI-related symptoms or signs of toxicity were observed in 97.3% of these patients [10].

Our study aimed to identify and analyze cause and effect of DDIs seen in autologous HSCT and allogeneic HSCT patients. We used four different drug-drug interaction detection databases to obtain more comprehensive results. We analyzed the most common interactions for both transplant types and unique interactions among transplantation types. By analyzing the time interval in which the drug interaction was observed, we determined the period in which these interactions pose a risk.

2. Methods

This retrospective study was conducted in a bone marrow transplantation (BMT) centre accredited by The Joint Accreditation Committee (JACIE). XXX University Clinical Research Ethics Committee approved this study with Decision No. 2020/392. Patients who underwent autologous and allogeneic HSCT from January 2018 to August 2020 were included in the study. The treatment sheets from 100 eligible patients were recorded for the 10-day pre-transplant period, on transplantation day, and 10-day post-transplantation. Demographical and clinical data were collected as well. Patients who did not complete the transplantation process or under the age of 18 were excluded. Of patients who underwent multiple transplantations, only the records from their first transplantations were included in the study.

Drug-Drug Interactions

Every patient's treatment sheets for 21-days were checked by using four drug-drug interactions in two subscription-based and two open-access databases. Ointments, mouthwashes, electrolyte-containing solutions, and nutritional products were excluded. If a drug was used only once, it was included for a period according to its half-life. The most commonly used drugs and common interactions were defined in terms of frequency, severity level, evidence level, clinical effect, and general mechanism. Also, DDIs were analyzed according to the transplantation type and process. Drug-Drug Interaction Databases

In order to detect DDIs comprehensively, four popular drug-drug interaction checkers were used. Uptodate and Micromedex are subscription-based databases, and they provide extra features such as evidence-level categories and the timing of the interactions. Drugs.com and Epocrates were

included in our study because they are popular open-access databases among clinicians and clinical pharmacists. Severity and evidence levels assigned by databases are shown in Table 1 [11-14]

Table 1. Severity and evidence level categories according to databases

Database/Severity	**Contraindicated**	**Major**	**Moderate**	**Minor**	**No Int. Observed**
Micromedex	Contraindicated	Major	Moderate	Minor	-
Uptodate	Avoid (X)	Major (D)	Moderate (C)	Minor (B)	No Known Int. (A)
Drugs.com	Major-Contraind.	Major	Moderate	Minor	-
Epocrates	Contraindicated	Avoid or Use Alt.	Monitor/modify	Caution Advised	-
Database/Evidence	**Excellent**	**Good**	**Moderate**	**Poor**	**Unknown**
Micromedex	Clearly demonstrated with control studies.	Strong indication, but lacking control studies.	The available documentation is poor, but suspection due to pharmacological considerations/ good documentation for a similar drug.	-	Unknown.
Uptodate	Multiple randomized control studies/ two additional case reports from one randomized control study	A randomized control study+ <2 case reports.	At least 2 case reports; theoretically based on <2 case reports/ the pharmacological nature of the agents with other supporting data.	In <2 case reports	Unknown.

Abbreviations: Contraind.: contraindicated, int: interaction, alt: alternatives

Statistical analysis

Summary statistics were used to determine patient clinical and demographical characteristics, the frequent drugs, the most common DDIs according to transplantation type and process, and polypOKharmacy related information. Results were presented as proportion, mean ± standard deviation (SD) or range.

3. Results

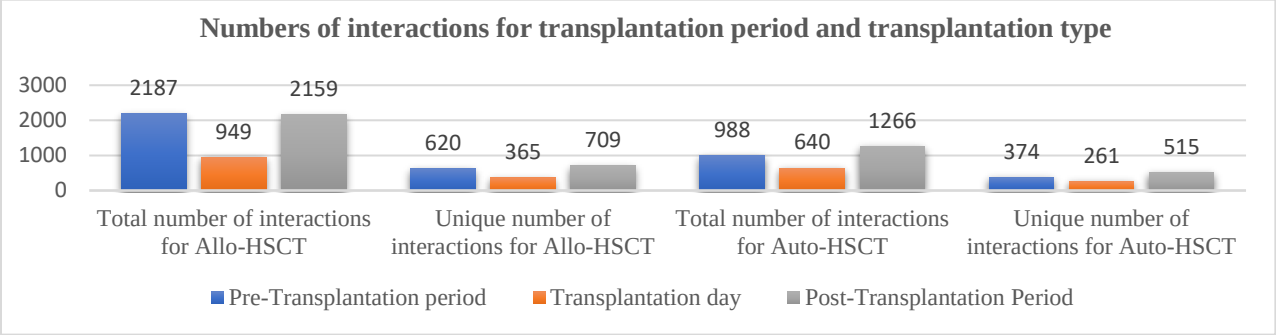
Patient characteristics

Fifty patients from each transplantation type were included in the study; the majority were males in both transplantation types, 60%, and 62%, respectively. The most frequent diseases were leukemia and multiple myeloma. The median ages for allogeneic and autologous HSCT patients were 42.4 and 51.8, respectively. Twenty-seven autologous HSCT patients had melphalan protocol for conditioning regimens. The cyclophosphamide-busulfan combination was the most commonly used chemotherapy regimen in allogeneic HSCT, and it was used to treat 21 patients. Patients from both transplantation types had comorbidities at different rates (Table 2).

Drug-drug interactions

A total of 3771 interactions were identified during the transplantation process in patients who underwent allogeneic HSCT, and a total of 1006 types of DDIs were identified among the total of 3771. DDIs observed in autologous HSCT patients were lower than in allogeneic HSCT patients. A total of 2181 interactions were detected during the 21-day process. A total of 716 types of DDIs were identified among 2181 interactions (Figure 1). Major interactions were common in both transplantation types. In 50 allogeneic HSCT patients, a total of 1204 major interactions have been identified, resulting from 343 different major interactions.. The mean number of major level interactions was 24.08 (7-70, SR: 12.37). In 50 patients with autologous HSCT, 657 major interactions consisting of 195 different major interaction types were detected. The mean number of major level interactions was 13.14 (3-37, SR: 7.88). Ninety-four major level interactions were common in both transplantation types. 47 (94%) allogeneic HSCT patients and 46 (92%) autologous HSCT patients had at least one contraindicated DDI.

Figure 1. Distribution of the number of interactions for the transplantation period and transplantation type.



Abbreviations: Allo-HSCT: Allogeneic stem cell transplantation patients, Auto-HSCT: Autologous stem cell transplantation patients.

A total of 164 different drugs were identified from patients' drug-drug interaction lists [15]. The most frequent drugs involved in interactions among allogeneic HSCT patients were cyclosporine and fluconazole, with 682 and 478 interactions, respectively. The drugs used in the transplant process differ before and after the transplant, so the drug-drug interactions also vary. The drugs most commonly involved in DDIs of autologous HSCT patients were dexamethasone and fluconazole, with 365 and 338 interactions, respectively. Drugs such as cyclosporine and methotrexate were specific to allogeneic HSCT. Etoposide, cytarabine, and loperamide were only detected in autologous HSCT patients (Table 3).

Table 3. The frequently detected drugs in interactions in terms of transplantation types.

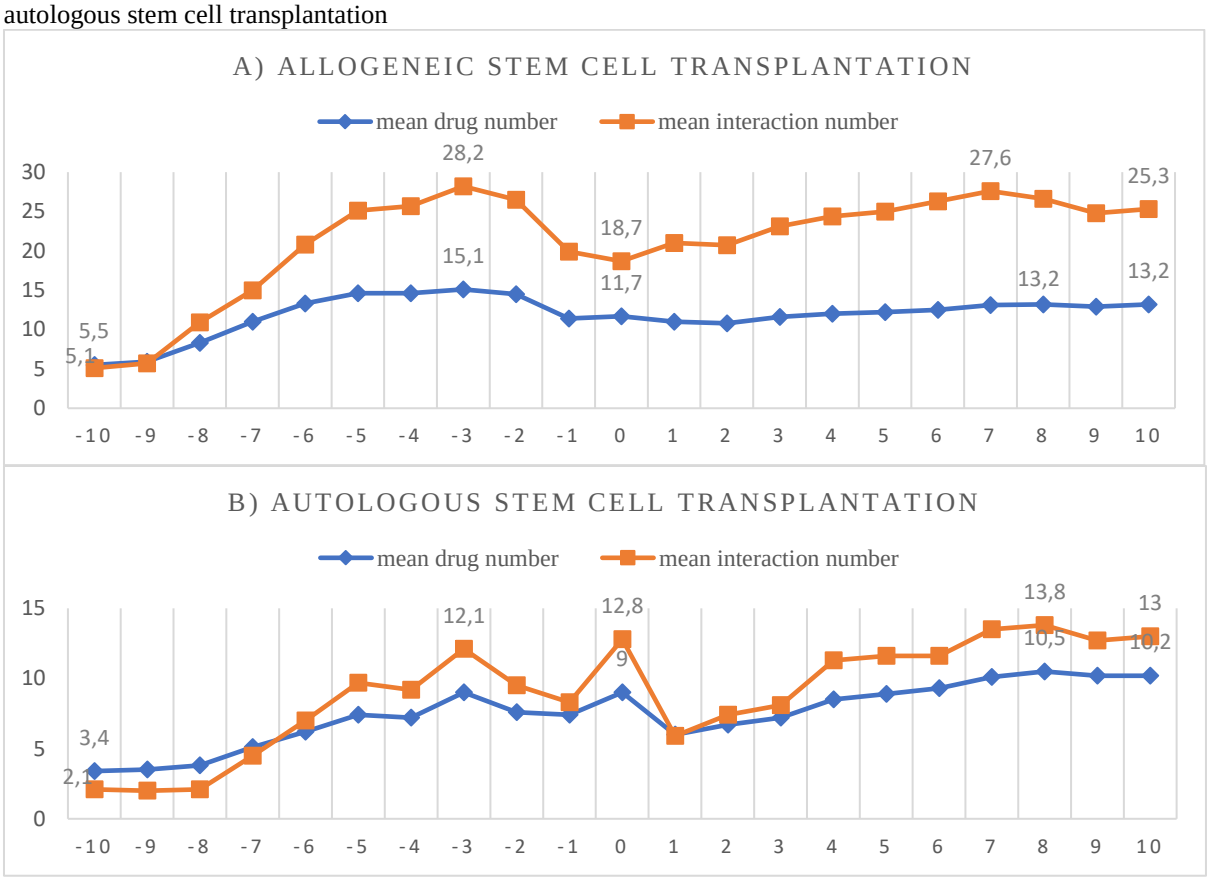
Drug Class	**Drug Name**	**Allo-HSCT**	**Auto-HSCT**
J02 Antimycotics for Systemic Use	Fluconazole	478	338
H02 Corticosteroids for Systemic Use	Dexamethasone	415	365
J05 Antivirals for Systemic Use	Valacyclovir	340	111
S01 Ophthalmologicals	Acetazolamide	294	191
C03 Diuretics	Furosemide	284	201
J01 Antibacterials for Systemic Use	Levofloxacin	151	274
A04 Antiemetics and Antinauseants	Granisetron	261	241
A02 Drugs for Acid Related Disorders	Lansoprazole	244	157
J01 Antibacterials for Systemic Use	Metronidazole	152	156
J01 Antibacterials for Systemic Use	Amikacin	180	103
Drug Class	**Drug Name**	**Allo-HSCT**	
L04 Immunosuppressants	Cyclosporine	682	
L01 Antineoplastic Agents	Methotrexate	313	
N03 Antiepileptics	Phenytoin	249	
L01 Antineoplastic Agents	Cyclophosphamide	205	
J01 Antibacterials for Systemic Use	Sulfamethoxazole	186	
Drug Class	**Drug Name**		**Auto-HSCT**
L01 Antineoplastic Agents	Etoposide		79
L01 Antineoplastic Agents	Cytarabine		51
A07 Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	Loperamide		32
L01 Antineoplastic Agents	Carmustine		20
N03 Antiepileptics	Valproate		18

Abbreviations: Allo-HSCT: allogeneic stem cell transplantation patients, Auto-HSCT: autologous stem cell transplantation patients

Since HSCT is a progressive process in which certain protocols are applied gradually, the drugs used in our study and therefore the interactions detected differed on a day-by-day basis, specific to the type of transplantation. Allogeneic HSCT patients were prescribed the highest number of medications during the 21-day period on the three days before transplantation. The mean number of prescribed drugs on day -3 was 15.14 (SD=2.8). The lowest mean number of prescribed drugs was recorded on day -10, and it was 5.52 (SD=3.92). The third day before transplantation was also the day with the highest mean number of interactions, which was 28.2 (SD=14.63). Ten days before the transplantation was the one with the lowest mean number of interactions. Drugs and DDIs were low at

the beginning of the process. Then, the curves reached a peak three days before transplantation. After transplantation, the mean number of interactions rose dramatically, but the mean number of drugs did not rise with that ratio (Figure 2).
The highest mean number of medications and detected interactions of autologous stem cell transplants were on the eighth day after transplantation, 10.46 (SD=3.38) and 13.8 (SD=12.0), respectively. The lowest mean number of medications was recorded on the 10th day before transplantation. The lowest mean number of interactions was detected nine days before transplantation. In the beginning, the mean number of drugs was higher than the mean number of interactions. However, after the sixth day before transplantation, the mean number of interactions started to be higher than the prescribed drugs (Figure 2).

Fig. 2 Mean number of prescribed drugs and detected interactions per day in patients with allogeneic and autologous stem cell transplantation



The most detected interactions in both transplantation types are defined in Table 4. The acetazolamide-dexamethasone interaction was the most common interaction in allogeneic and autologous HSCT patients, with 47 and 48 interactions, respectively. It was specific to the pre-transplantation process. However, some interactions were detected in every transplantation period, such as fluconazole-granisetron interaction, dexamethasone-fluconazole interaction, and fluconazole-granisetron interaction. Amikacin-valacyclovir interaction was specific to the post-transplantation process, and it was detected in 30 allogeneic HSCT patients and 24 autologous HSCT patients. Some interactions were specific to the transplantation type. Granisetron-sulfamethoxazole was observed in 48 allogeneic HSCT patients. Cyclosporine-involving interactions were prevalent among allogeneic HSCT patients, and they were specific to this transplantation type. All of the databases detected the methotrexate-cyclosporine interaction, and the databases assigned different levels of severity to this interaction. The most common types of autologous HSCT -specific interactions were chemotherapeutic-related interactions (Table 5). In order to examine the effect of the number of drugs used at the beginning of the treatment on the number and severity of interactions later in the transplantation process, we classified the patients by the medication numbers on the tenth day before the transplantation. While the rate of the polypharmacy, simultaneous use of five or more drugs, was 52% in the patients who underwent allogeneic HSCT, at the beginning of the study period, this rate was determined as 28% in the patients with autologous HSCT.

Table 4. The most detected common interactions for both transplant types according to transplant type and transplant process, and definition of interactions by databases

Interaction Pair	Allo-HSCT	Auto-HSCT	Severity	Mechanism	Clinical effect
Acetazolamide+ Dexamethasone	**Total*: 47** Pre-T: 47 T: 0 Post-T: 0	**Total*: 48** Pre-T: 48 T: 0 Post-T::0	**D**: Moderate **E**: Monitor/modify	Electrolyte loss Additive and antagonistic effects related seizure treshold decrease	Hypokalemia Seizure treshold decrease
Acetazolamide+ Valacyclovir	**Total*: 42** Pre-T: 42 T: 0 Post-T: 0	**Total*:18** Pre-T: 18 T: 0 Post-T: 0	**E:** Caution adv.	Antagonistic effects	Seizure treshold decrease
Fluconazole+ Granisetron	**Total*: 41** Pre-T: 40 T: 37 Post-T: 31	**Total*: 46** Pre-T: 18 T: 19 Post-T: 43	**U:** Minor (B) (RR: Fair) **M:** Conraindicated (RR: Fair) **D:** Moderate	Additive QT prolongation Additive QT prolongation and CYP3A4 inh. CYP3A4 inh.	QT prolongation QT prolongation and granisetron level elevation Granisetron level elevation
Dexamethasone+ Fluconazole	**Total*: 39** Pre-T: 39 T: 36 Post-T: 21	**Tota*l: 26** Pre-T: 18 T: 19 Post-T: 9	**U:** Moderate (C) (RR: Good) **M:** Moderate (RR: Fair) **D:** Moderate **E:** Caution adv.	CYP3A4 inh. CYP3A4 inh. CYP3A4 inh. Hepatic met. İnh.	(Consensus) Dexamethasone level elevation
Dexamethasone+ Furosemide	**Total*: 33** Pre-T: 31 T: 2 Post-T: 5	**Total*: 49** Pre-T: 2 T: 49 Post-T::0	**U:** Moderate (C) (RR:Fair) **D:** Moderate **E:** Monitor/modify	Electrolyte loss Electrolyte loss Additive and antagonistic effects	(Consensus) Hypokalemia
Fluconazole+ Lansoprazole	**Total*: 30** Pre-T: 29 T: 1 Post-T: 29	**Total*: 32** Pre-T: 16 T: 15 Post-T: 32	**U:** Moderate (C) (RR:Good) **M:** Moderate (RR:Fair) **D:** Moderate **E:** Caution adv.	CYP2C9 inh. CYP2C9 inh. CYP2C9 inh. Hepatic met. İnh.	(Consensus) Lansoprazole level elevation
Amikacin+ Valacyclovir	**Total*: 30** Pre-T: 0 T: 0 Post-T: 30	**Total*: 24** Pre-T: 0 T: 0 Post-T: 24	**D:** Moderate **E:** Avoid or use alt.	Additive nephrotoxicity Additive effects	Nephrotoxicity Nephrotoxicity and drug level elevation
Granisetron+ Metronidazole	**Total*: 28** Pre-T: 1 T: 23 Post-T: 22	**Total*: 32** Pre-T: 2 T: 2 Post-T: 31	**M:** Major (RR:Fair) **D:** Moderate	Additive QT prolongation Additive QT prolongation	(Consensus) QT prolongation
Fluconazole+ Metronidazole	**Total*: 27** Pre-T: 1 T: 19 Post-T: 24	**Total*: 34** Pre-T: 1 T: 2 Post-T: 34	**U:** Minor (B) (RR:Fair) **M:** Major (RR:Fair) **D:** Moderate	Additive QT prolongation Additive QT prolongation	(Consensus) QT prolongation
Dexamethasone+ Melphalan	**Total*: 2** Pre-T: 2 T: 0 Post-T: 0	**Total*: 46** Pre-T: 46 T: 0 Post-T: 0	**E:** Caution adv.	Additive effects	Infection

Abbreviations: Allo-HSCT: Allogeneic stem cell transplantation, Auto-HSCT: Autologous stem cell transplantation, Pre-T: Pre transplantation period, T: Transplantation day, Post-T: Post transplantation period, U:Uptodate, M:Micromedex, D:Drugs.com, E:Epocrates, RR: reliability rating, caution adv.: caution advised, avoid or use alt.:avoid or use alternative, met.:metabolism, inh.:inhibition.
*Describes the total number of different patients in whom the interaction was detected.

Table 5. Transplant type spesific most common interactions in terms of transplantation process, and their definitions by databases

Interaction Pair	Allo-HSCT	Severity	Mechanism	Clinical effect
Granisetron+ Sulfamethoxazole	**Total*: 48** Pre-T: 48 T: 3 Post-T: 1	**D**:Minor	Additive QT prolongation	QT prolongation
Cyclosporine+ Ursodeoxycholic Acid	**Total*: 47** Pre-T: 36 T: 41 Post-T: 47	**D**: Minor	Absorption increasing effect	Drug level elevation
Cyclosporine+ Valacyclovir	**Total*: 45** Pre-T: 37 T: 41 Post-T: 44	**D**: Moderate **E**: Monitor /modify	Additive nephrotoxic effect Additive effects	Nephrotoxiciy Nephrotoxicity and drug level elevation
Methotrexate+ Cyclosporine	**Total*: 42** Pre-T: 0 T: 0 Post-T: 42	**U:** Moderate (C) (RR**:**Good) **M:** Moderate (RR: Excellent) **D**: Moderate **E**: Avoid or use alt.	Unknown Drug metabolism blockage Drug metabolism blockage Drug metabolism blockage	Drug level increase of both drugs and toxicity Drug level increase of both drugs and toxicity Methotrexate level elevation and toxicity Methotrexate level elevation and toxicity
Dexamethasone+ Cyclosporine	**Total*: 42** Pre-T: 16 T: 39 Post-T: 22	**U:** Minor (B) (RR:Fair) **D**: Moderate **E**: Monitor /modify	CYP3A4 ind. CYP3A4 inh. And ind. Additive effects and hepatic met. İnh.	Cyclosporine level decrease and lowered seizure treshold Drug level changes of both drugs Drug level changes of both drugs and increased adverse drug event
Interaction Pair	**Auto-HSCT**	**Severity**	**Mechanism**	**Clinical effect**
Dexamethasone+ Etoposide	**Total*: 22** Pre-T: 22 T: 0 Post-T: 0	**E**: Caution adv	Additive effects	Increased infection risk
Dexamethasone+ Cytarabine	**Total*: 22** Pre-T: 22 T: 0 Post-T: 0	**E**: Caution adv	Additive effects	Increased infection risk
Etoposide+ Cytarabine	**Total*: 21** Pre-T: 21 T: 0 Post-T: 0	**D**:Moderate	Additive toxicity	Increased toxicity
Levofloxacin+ Melphalan	**Total*: 15** Pre-T: 15 T: 0 Post-T: 0	**D**:Minor	Decrease in absorbtion	Decrease in drug level
Dexamethasone+ Carmustine	**Total*: 15** Pre-T: 15 T: 0 Post-T: 0	**E**: Caution adv	Additive effects	Increased infection risk

Abbreviations: Allo-HSCT: Allogeneic stem cell transplantation, Auto-HSCT: Autologous stem cell transplantation, Pre-T: Pre transplantation period, T: Transplantation day ,Post-T: Post transplantation period, U:Uptodate, M:Micromedex, D:Drugs.com, E:Epocrates, RR: reliability rating, caution adv.: caution advised, avoid or use alt.:avoid or use alternative, met.:metabolism, inh.:inhibition.
*Describes the total number of different patients in whom the interaction was detected.

The average numbers of drugs and interactions before the transplant, on the day of the transplant, and in the post-transplant period were found to be high in both types of transplants in patients who started the transplant process with polypharmacy. The mean highest number of drugs and interactions among the patient groups in the study were observed in allogeneic transplant patients with polypharmacy in the post-transplant period and were found to be 13.35 (SD=2.99) and 29.96 (SD=13.23), respectively.

The mean of detected unique interactions in patients who underwent allogeneic HSCT with or without polypharmacy at the tenth day before transplantation were 89.85 (SD=35.76) and 61.21 (SD=15.50), respectively. During the process, the mean of different major and contraindicated drug-drug interactions were found to be 28.85 (SD=14.67) and 18.93 (SD=12.29) in allogeneic and autologous HSCT patients with polypharmacy, respectively (Table 6).

Table 6. Information about patients in terms of polypharmacy ten days before transplantation

	Allo-HSCT		**Auto-HSCT**	
	Drug number at the -10th day of transplantation		Drug number at the -10th day of transplantation	
	<5	≥5	<5	≥5
	24 (48%)	26 (52%)	36 (72%)	14 (28%)
Demographic features				
Age (mean (SD))	37.5 ±11.75	46.88 ±12.36	49.31 ±15.35	58.29 ±7.56
Sex (male)	14	16	21	10
Additional diseases (mean (SD))	0.33±0.92	0.65±1.13	0.58±0.60	1.93±0.73
Information of number of drugs				
Drug number per day before transplantation (mean (SD))	9.62±1.49	13.07 ±2.54	5.07±2.06	8.56±3.14
Drug number at the transplantation day (mean (SD))	10.79±1.56	12.5 ±2.79	8.08±1.66	11.5±2.71
Drug number per day after transplantation (mean (SD))	11.08±1.89	13.35±2.99	7.74±1.93	11.3±2.97
Information of detected interactions				
Interaction number per day before transplantation (mean (SD))	13.16±4.42	23.46±10.06	8.16±4.69	18.11±14.11
Interaction number at the transplantation day (mean (SD))	14.38±5.27	23.62±16.55	9.58±4.74	21.29±13.78
Interaction number per day after transplantation (mean (SD))	18.76±6.77	29.96±13.23	5.01±4.09	10.93±8.96
Unique interaction numbers for the 21-day period (mean (SD))	61.21±15.50	89.85±35.76	36.61±15.91	62.29±35.05

Information of the severity of interactions				
Number of major and contraindicated interactions (mean (SD))	22.42±9.89	28.85±14.67	13.03±6.38	18.93±12.29

Abbreviations: Allo-HSCT: Allogeneic stem cell transplantation, Auto-HSCT: Autologous stem cell transplantation, SD: Standard deviation

4. Discussion

This study showed that HSCT recipients are at high risk for DDIs. While all of the patients had DDIs during their transplantation period, in allogeneic HSCT patients we detected more DDIs during their transplantation process than autologous HSCT patients. The mean number of detected interactions per allogeneic HSCT patients were 75,42 for the 21-day period. Detected interactions for that period were in the range of 37-177. All of the allogeneic HSCT patients were at risk for major level interactions, and the range for major level interactions was 8-68. Contraindicated interactions were detected in 94% of the allogeneic HSCT patients.

The mean number of detected interactions in autologous HSCT patients were 43,62. Every autologous HSCT patient experienced interactions, and the interaction number was in the range of 10-129. Major interactions were common in this transplantation type, and the range for major level interactions was 2-36. 92% of autologous HSCT patients experienced at least one contraindicated level interaction. A study found that 82.5% of HSCT patients were at risk of at least one major or contraindicated drug-drug interaction [5]. Our results were compatible with the literature, but the rates of interactions were higher than other studies. This difference is the result of using multiple drug-drug interaction checking databases. None of the databases in the study detected all of the interactions, and using the combined data derived from these databases helped create a comprehensive DDI list. During the study period, clinical pharmacists worked at the center and gave recommendations about DDIs and other drug-related problems.

The most common drugs in the interactions of allogeneic HSCT patients were immunosuppressants, antimycotics, corticosteroids, and antivirals. Autologous HSCT patients did not receive immunosuppressant therapy after transplantation; therefore, this patient group did not have an immunosuppressant-related DDI burden. Instead, the most common ones were antimycotics, corticosteroids, antibacterials, and antiemetics.

The distribution of prescribed drug numbers during the 21-day period was different between the two transplantation types. In patients who underwent allogeneic HSCT, the highest number of drugs and detected interactions were on the -3rd day. On the other hand, in autologous HSCT patients, the highest mean number of prescribed medicines were after the transplantation.

Some interactions were common among the study sample. For example, acetazolamide-dexamethasone interactions were detected in 95% of the patients. Drugs.com defined its mechanism as electrolyte loss and informed the user to check potassium levels to avoid hypokalemia [13]. On the other hand, Epocrates warned the user that this interaction might cause seizures [14]. In the literature, acetazolamide and dexamethasone have been linked to hypokalemia [16-18].

Fluconazole-granisetron interaction was common in both transplantation patients and was detected by Uptodate, Micromedex, and Drugs.com (11-13). Micromedex categorized this interaction at a contraindicated level (12). Fluconazole and granisetron are drugs that are known to prolong the QT interval (19, 20). Fluconazole inhibits the cytochrome P450 3A4 (CYP3A4) moderately (20). Another common interaction that attracted attention was the dexamethasone-fluconazole interaction. Drug level elevations that are caused by enzyme inhibition are flagged to the user (11-14).

Some interactions were detected only in one transplantation group. Cyclosporine and methotrexate are used for Graft versus Host Disease prophylaxis in allogeneic HSCT patients (21). In a study on rheumatoid arthritis patients, cyclosporine increased methotrexate levels (22). At the BMT center, cyclosporine levels were analyzed routinely three times a week, and clinical pharmacists addressed DDIs related to cyclosporine levels.

93% of all patients had at least one contraindicated DDI. Fluconazole-granisetron interaction was the most common contraindicated interaction in both transplantation types. Case reports describing fluconazole-related QTc prolongation and Torsade de Pointes are present in the literature (23, 24). Tramadol, escitalopram, domperidone, dasatinib, and quetiapine were also listed as drugs with QTc prolongation effects [25-29]. Clinical pharmacists identified drugs with potential QTc prolongation effects and interactions with these drugs, and patients were observed in terms of arrhythmias.

The dasatinib-lansoprazole interaction has an X-level warning by Uptodate, with a high level of literature support [11]. In a study on leukemia patients, using dasatinib with lansoprazole resulted in low dasatinib levels due to impaired absorption from the gastrointestinal tract [30]. After the warning given by the

clinical pharmacist, the combination of dasatinib with acid suppressant drugs was avoided.

Polypharmacy has been shown to be the cause of important drug-related problems such as drug-drug interactions and adverse drug reactions [4]. In our study, it was observed that allogeneic HSCT patients started the transplantation process with polypharmacy at a higher rate than autologous HSCT patients, 52% and 28%, respectively. The averages of additional diseases, age, number of drugs, detected interactions, and serious interactions were found to be higher in patients who started the process with ≥5 drugs in both transplant types.

5. Conclusion

We recommend checking for potential DDIs in this patient group to prevent adverse drug events. With this initiative, higher therapy outcomes can be achieved, and the cost of the HSCT treatments can be minimized. Drug-drug interaction checking databases show potential drug-drug interactions and explain how clinically severe those interactions are. There is a need for more studies in this patient group to understand the clinical significance of these interactions and show their clinical relevance. We believe that physicians and clinical pharmacists should work together to detect, prevent, and manage drug-drug interactions without causing adverse drug events. With this perspective, complicated treatment schemes can be managed more safely.

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Author contribution: This paper is based on the clinical pharmacy speciality thesis of Ayse Gunay. All authors contributed to the study conception and design. Data collection and analysis were performed by Ayse Gunay. The first draft of the manuscript was written by Ayse Gunay, and all authors reviewed and amended the manuscript. All authors read and approved the final manuscript.

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