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Potential drug–drug interactions in hospitalised haematological patients

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Abstract

Background: Frequently, haematological patients undergo highly complex and intensive treatment protocols, so a high risk of drug–drug interactions could be expected.

Objectives: To determine prevalence of clinically relevant drug–drug interactions, to identify the most frequent drug–drug interactions and associated risk factors.

Methods: A prospective, observational and descriptive study was carried out from November 2012 to February 2013. Twice a week, every patient's treatment sheet was collected. Each medication list was screened through two databases: Thomson MicromedexTM and Drug Interaction FactsTM. All identified potential drug–drug interactions with a moderate or higher severity rating were recorded. Summary statistics were used to describe patient and disease characteristics, most often prescribed drugs, and frequency, types and classification of drug–drug interactions. Multiple logistic regression models were used to identify risk factors associated with drug–drug interactions.

Results: A total of 2061 drug–drug interactions were detected in 317 treatment sheets from 58 patients. The prevalence of treatment sheets with drug–drug interactions by Micromedex and Drug Interaction Facts databases were 74.1% and 56.8%, respectively. Azole antifungals, immunosuppressive drugs, antiemetics, antidepressants, acid suppressants and corticosteroids were the most frequent involved drugs. In multivariate analysis, the main risk factor associated with increased odds for drug–drug interactions was a higher number of non-antineoplastic drugs.

Conclusions: The prevalence of drug–drug interactions was common, with immunosuppressant and azole antifungal agents being the most commonly involved drugs. The factor having the greatest influence on drug–drug interactions was a higher number of non-antineoplastic drugs.

Keywords

Drug–drug interaction, chemotherapy, inpatient, haematological

Introduction

A drug–drug interaction (DDI) is defined as an alteration in the clinical effect of an initial drug due to interference by a second drug, which might contribute to therapeutic failure and, occasionally, lead to serious adverse clinical events, being an important issue in medication safety. Drug interactions can be the result of pharmacokinetic, pharmacodynamic, pharmaceutical or a combination of mechanisms. Knowledge of the mechanism by which a given DDI occurs is often clinically useful, as the mechanism could help us to elucidate an alternative to minimise or even avoid its negative effects.[1,2]

Some studies about DDIs in cancer patients have been published. They have been performed both in ambulatory and hospitalised settings and included

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patients undergoing and not undergoing systemic anticancer therapy.[3–6] Most of them included oncological patients. The incidence of potential DDIs ranged from 27% to 63% of patients[3,7] and most potential DDIs were caused by non-anticancer agents. Two studies performed in onco-haematological wards have shown a positive correlation between DDIs and the number of drugs administered to the patient,[5,8] but the pharmacokinetic and pharmacodynamic characteristics of these medications are also significant factors.[9,10]

There are a wide range of clinical conditions among haematological patients: patients with non-malignant disease, patients with malignant disease and those who, independent of the type of disease they suffer, require hematopoietic stem cell transplantation (HSCT). Given the highly complex and intensive treatment protocols used in many of these conditions, the risk of DDIs is increased. Drugs received by these patients can be classified into three types: antineoplastic agents, supportive care agents and many different drugs to treat comorbid conditions.[3,9,11] In general, supportive care measures may include the use of antiemetics, blood products or transfusion support for severe cytopenias, nutritional support, gastroenterology support, pain management, tumour lysis prophylaxis, anti-infective prophylaxis or management of infectious complications, immunosuppressive agents or the use of growth factors.[12]

Furthermore, some drugs' pharmacokinetics may be distorted because of hampered drug absorption by mucositis, malnutrition and infection; variation in drugs' volume of distribution because of reduced levels of serum binding proteins and generalised oedema; drug interaction with CYP liver enzymes; and impaired drug excretion in patients with renal and/or hepatic dysfunction.[2]

After these considerations, a high risk of DDIs could be expected. However, little information about the frequency and pattern of drug interactions in these patients exists, with only two previous publications focusing on haematological patients.[8,9]

The primary objective of this study was to determine the prevalence of clinically relevant potential DDIs in hospitalised patients at a haematological ward, comparing two commonly used drug interaction databases. The secondary objectives were to describe the most frequent DDIs and to investigate the possible risk factors associated with the presence or absence of potential DDIs.

Methods

A prospective, observational and descriptive study was carried out during a 12-week period (from November 2012 to February 2013). All inpatients, undergoing treatment with two or more drugs, at the Haematology Department of a reference hospital were included. The study did not focus on the clinical consequences of drug interactions, but rather on their potential for occurrence.

Every patient's treatment sheet was collected twice a week and analysed afterwards. Demographical, clinical and analytical data were recorded on the date of admission. Every drug was tabulated, distinguishing the route of administration. When a medication contained two or more pharmacologic compounds, each drug was considered as separate in the analysis. Drugs were divided into antineoplastic agents (defined as medications to treat malignant diseases or drugs included in HSCT's conditioning stage) and non-antineoplastic agents (defined as medications to treat symptoms and any other clinical condition present at admission).

Each medication list was screened through two databases: Micromedex™ software[13] and Drug Interaction Facts™.[14] All identified potential DDIs with a *moderate* or higher severity rating were recorded and graded by their level of severity and scientific evidence (Table 1). DDIs classified as minor were excluded since they were not considered as clinically relevant interactions.

Prevalence of DDIs was defined as the number of treatment sheets with any DDI divided by the number of treatment sheets collected in the study period, multiplied by 100.

This study was approved by the local Ethical Committee of Clinical Investigation on October 2012.

Statistical analyses

Summary statistics were used to describe patient and disease characteristics, most often used drugs, and frequency, types and classification of DDIs. Results were presented in terms of the median and range, mean ± standard deviation or as a proportion. The dependent variables were presence or absence of DDIs for each database. The independent variables were age, sex, type of admission (urgent or scheduled), type of disease (malignant/non-malignant), antineoplastic treatment administration in the current hospitalisation (yes/no), performance status, comorbidities number, serum creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, total drugs number and antineoplastic and non-antineoplastic agents number.

Multiple logistic regression models were used to identify risk factors associated with DDIs. In univariate analysis, t-tests and chi-squared tests were applied to assess differences among groups, where appropriate. Only independent variables which were found to be

Table 1. Micromedex and Drug Interactions Facts classification scheme of levels of severity and scientific evidence of drug interactions.[13,14]

Micromedex database	
Level of severity	Description
Contraindicated	The drugs are contraindicated for concurrent use.
Major	The interaction may be life-threatening and/or require medical intervention to minimise or prevent serious adverse effects.
Moderate	The interaction may result in exacerbation of the patient's condition and/or require an alteration therapy.
Minor	The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration therapy.
Unknown	Unknown.
Level of scientific evidence	Description
Excellent (3)	Controlled studies have clearly established the existence of the interaction.
Good (2)	Documentation strongly suggests the interaction exists, but well-controlled studies are lacking.
Fair (1)	Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or, documentation is good for pharmacologically similar drug.
Unknown (0)	Unknown.
Drug Interactions Facts database	
Level of severity	Description
Major	An adverse effect can cause permanent damage or life risk.
Moderate	An adverse effect can harm and treatment is required.
Minor	Small or no clinical effect, with no treatment required.
Level of scientific evidence	Type of scientific data
Established (1)	Adverse effect confirmed by large clinical trials.
Probable (2)	Adverse effect with high likelihood of occurrence but without definitive randomised clinical trials.
Suspect (3)	Adverse effect likely to occur; data derived from case reports.
Possible (4)	Adverse effect may occur but data are scarce.
Unlikely (5)	Adverse effect may theoretically occur.

significant predictors ($p < 0.05$) were included in the logistic regression model. All statistical analyses were performed using SPSS® software v.20.0.

Results

During the study period, a total of 317 treatment sheets were collected, belonging to 58 patients. The main patient characteristics are summarised in Table 2. The admission and treatment characteristics are shown in Table 3. A median of 3 (1–21) treatment sheets were analysed per patient, with a median of 13 (2–32) drugs per treatment sheet. A total of 4450 drugs were prescribed, of which only 95 were antineoplastic agents. The first 20 drugs most frequently prescribed are listed in Table 4.

The prevalence of treatment sheets with clinically relevant potential DDIs was 74.1% and 56.8% by Micromedex and Drug Interaction Facts, respectively.

Regarding DDIs, the summary for each database is as follows:

Micromedex: In 236 treatment sheets (74.4%), a total of 1321 DDIs were detected, counting 172 different pairs of drugs and obtaining a median of 3 (0–26) DDIs per treatment sheet. From all identified DDIs, 64 were classified as contraindicated, 539 as major and 718 as moderate. Most DDIs (97.8%) occurred between non-antineoplastic drugs. In respect of the mechanisms, 46.3% DDIs were classified as pharmacokinetic, followed by 35.1% as pharmacodynamic.

Drug Interaction Facts: In 220 treatment sheets (69.4%), a total of 740 DDIs were found, counting 96 different pairs of drugs and obtaining a median

Table 2. Patient characteristics.

Variables	By patients $n = 58$	By treatment sheets $n = 317$
Age (years)		
Median (range)	64 (11–89)	64 (11–89)
Sex		
Male	27 (46.6%)	141 (44.5%)
Female	31 (53.4%)	176 (55.5%)
Type of disease		
Malignant	43 (74.1%)	248 (78.2%)
Non-malignant	15 (25.9%)	69 (21.8%)
Hematopoietic stem cell transplantation	10 (17.2%)	73 (23.0%)
Main diagnosis		
Multiple myeloma	13 (22.4%)	69 (21.7%)
ALL	4 (6.9%)	44 (13.9%)
AML	4 (6.9%)	30 (9.5%)
HL	4 (6.9%)	23 (7.2%)
NHL	16 (27.6%)	77 (24.3%)
Myelodysplastic syndromes	2 (3.4%)	5 (1.5%)
Sézary syndrome	1 (1.7%)	15 (4.7%)
Severe aplastic anemia	1 (1.7%)	15 (4.7%)
Thrombocytopenic purpura	3 (5.1%)	10 (3.1%)
POEMS syndrome	1 (1.7%)	8 (2.5%)
Haemophilia A	1 (1.7%)	8 (2.5%)
Other nonmalignant diseases	8 (13.8%)	13 (4.1%)
Performance status		
ECOG = 0	N/A	59 (18.6%)
ECOG = 1	N/A	184 (58.1%)
ECOG = 2	N/A	39 (12.3%)
ECOG = 3	N/A	22 (6.9%)
ECOG = 4	N/A	13 (4.1%)
Comorbidities number		
0	9 (15.5%)	71 (22.4%)
1	14 (24.1%)	84 (26.5%)
2	12 (20.7%)	46 (14.5%)
3	10 (17.2%)	58 (18.3%)
≥4	13 (22.5%)	58 (18.3%)

ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; ECOG: Eastern Cooperative Oncology Group; N/A: non-applicable, because the same patient could have more than one admission; POEMS: Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin.

Table 3. Admission and treatments characteristics.

Variables	By treatment sheets $n = 317$
Admission type	
Urgent	152 (47.9%)
Scheduled	165 (52.1%)
Admission cause	
Admission for treatment	
Stem cell transplantation	73 (23.0%)
Pharmacological	52 (16.4%)
Antineoplastic treatment adverse effects	
Infectious disease	28 (8.8%)
Non-infectious disease	8 (2.5%)
Others	
Infectious complications	45 (14.2%)
Clinical deterioration	29 (9.1%)
Graft versus host disease	16 (5.0%)
Intestinal obstruction	11 (3.5%)
Others	55 (17.4%)
Analytical values at admission (n; mean ± sd)	
Serum creatinine (mg/dL)	317; 1.14 ± 1.32
Total bilirubin (mg/dL)	314; 0.64 ± 0.59
Aspartate aminotransaminase (U/L)	308; 29.45 ± 35.17
Alanine aminotransaminase (U/L)	217; 35.82 ± 39.23
Alkaline phosphatase (U/L)	185; 146.48 ± 188.26
Administration of antineoplastic treatment	
Yes	187 (59.0%)
No	130 (41.0%)
Antineoplastic treatment type ($n = 187$)	
Chemotherapy[a]	183 (97.9%)
Radiotherapy	4 (2.1%)

[a]Including classic chemotherapy, monoclonal antibodies and new mechanisms.

of 1 (0–17) DDI per treatment sheet. From all identified DDIs, 203 were classified as major and 537 as moderate. Most DDIs (96.5%) occurred between non-antineoplastic drugs. In respect of the mechanisms, 74.1% DDIs were classified as pharmacokinetic, followed by 12.4% as pharmacodynamic.

The 20 most commonly found DDIs for each database are shown in Table 5; they involve 44% and 60% of total DDIs detected by Micromedex and Drug Interaction Facts, respectively.

Data collected from all treatment sheets were included in the logistic regression to determine risk factors associated with DDIs. In multivariate analysis, a higher number of non-antineoplastic drugs appears to be related to the presence of DDIs in both databases ($p = 0.001$ by Micromedex and $p = 0.0001$ by Drug Interaction Facts). In addition, a higher number of comorbidities was associated with the presence of DDIs detected by Micromedex ($p = 0.0001$); and an older age and a higher bilirubin, with the presence of DDIs detected by Drug Interactions Facts ($p = 0.026$ and $p = 0.002$, respectively).

Table 4. Twenty most common prescribed drugs.

Drugs and route of administration	Frequency, *n* (%)	Therapeutic Group[a]
Acetaminophen iv	266 (6.0%)	N02BE
Omeprazole po	227 (5.1%)	A02BC
Dextrose-sodium chloride iv	169 (3.8%)	B05BB
Lorazepam po	168 (3.8%)	N05BA
Potassium chloride iv	163 (3.7%)	B05XA
Dexchlorpheniramine iv	151 (3.4%)	R06AB
Meropenem iv	142 (3.2%)	J01DH
Metoclopramide iv	118 (2.6%)	A03FA
Enoxaparin sc	112 (2.5%)	B01AB
Furosemide iv	100 (2.2%)	C03CA
Aciclovir po	95 (2.1%)	J05AB
Ondansetron iv	83 (1.9%)	A04AA
Lactulose po	80 (1.8%)	A06AD
Allopurinol po	79 (1.8%)	M04AA
Ursodeoxycholic acid po	71 (1.6%)	A05AA
Folic acid po	69 (1.5%)	B03BB
Filgrastim sc	67 (1.5%)	L03AA
Saline (Sodium chloride) iv	57 (1.3%)	B05BB
Fluconazole po	56 (1.3%)	J02AC
Atorvastatin po	52 (1.2%)	C10AA

[a]Therapeutic Group by Anatomical Therapeutic Chemical (ATC) Classification System.
iv: intravenous route; po: per oral; sc: subcutaneous.

Discussion

The present study investigates the epidemiology, risk factors and potential severity of drug interactions exclusively among haematological patients, about which little information exists. In addition, an inpatient setting was selected because these patients are often treated with complex regimens according to their severe clinical condition, which include very different types of drugs, increasing the risk for drug interaction occurrence. In fact, a high risk of potential DDIs was observed in this group, where more than a half (56–74%) of all treatment sheets contained at least one DDI.

The incidence of potential DDIs ranged from 27% to 63% in oncological patients.[3,7] Some studies have reported a higher frequency of DDIs in haematological patients than in oncological patients: Tavakoli-Ardakani et al.[5] determined a prevalence of a total of 37.5% of DDIs in 224 hospitalised onco-haematological patients receiving antineoplastic treatment (72.8% oncological and 27.2% haematological patients). Of them, 54.1% of haematological patients (33/61) suffered any DDI at all, regardless of the severity rating. In that study, Drug Interaction Facts database was used in the analysis. Hadjibabaie et al.[8] reported a frequency of 62.9% of DDIs (major and moderate) in a group of 132 haematological patients, and DDI screening was performed by the Lexi-Interact On-Desktop software. In 70 adult patients undergoing HSCT, the prevalence of DDIs was determined on day-1, using Micromedex database. In respect of the total percentage of DDIs, a prevalence of 60% was obtained, while 21.4% of patients presented at least one major DDI.[9] Nevertheless, regarding methodologies used in this topic there are multiple differences with respect to databases, study designs and definitions, so it is difficult to establish a comparison.

Applying the same methodology to the present study, the prevalence of treatment sheets with relevant DDIs in the onco-haematological paediatric population was lower (44.7% and 51.3% by Micromedex and Drug Interaction Facts respectively).[15] This fact may be explained because in children less or even no comorbid conditions are present and, therefore, a lower number of drugs can reduce the likelihood of DDIs.

In this study, most DDIs occurred between non-antineoplastic drugs, so these results are consistent with those reported in both oncological patients (about 13% involving antineoplastic, compared with 87% in the rest of the treatment)[3,4] and haematological patients (93.5% of the detected IF occurred among non-chemotherapy drugs).[8] Most frequently, these non-antineoplastic drugs include azole antifungals, immunosuppressive drugs, antiemetics, diuretics, analgesics, antidepressants (selective serotonin re-uptake inhibitors, SSRI), acid suppressants (proton pump inhibitors, PPI), benzodiazepines, statins and corticosteroids. It is noteworthy that azole antifungals and immunosuppressive drugs were the most frequent pharmacological classes involved in DDIs, as previously described in other studies.[8,9] Finally, the predominant recorded mechanism of interaction was pharmacokinetic by both databases (46.3% and 74.1% respectively), similar to other studies (52.3% in bone marrow transplantation patients[9] or 69.7% in haematological patients[8]).

Some of the most significant interactions found in this study group share their effect or mechanism, or involve a small group of drugs.

QT interval prolongation is a serious side effect that may occur and/or be enhanced by the combination of certain groups of drugs. Patients with malignant disease or who undergo HSCT are at particularly increased risk of these cardiac arrhythmias, as they receive numerous medications, and a high prevalence of electrolyte abnormalities exists (hypokalaemia, hypomagnesaemia).[8] If concomitant use of drugs with this effect cannot be avoided, it is recommended that the electrocardiogram be monitored and plasma levels

Table 5. Twenty most common clinically relevant DDIs identified by each database.

Clinically relevant DDIs detected by Micromedex database

Pairs of drugs	*N*	Description	Mechanism	Severity	Level of scientific evidence[a]
Cyclosporine–omeprazole	64	Concurrent use of both drugs may result in altered cyclosporine concentrations.	PK	Moderate	1
Fluconazole–omeprazole	63	This combination may result in increased plasma concentrations of omeprazole.	PK	Moderate	3
Omeprazole–voriconazole	45	This combination may result in increased plasma concentrations of omeprazole.	PK	Moderate	3
Cyclosporine–furosemide	44	Concurrent use of both drugs may result in increased risk of gouty arthritis.	PD	Moderate	2
Cyclosporine–methylprednisolone	36	Concurrent use of cyclosporine and methylprednisolone may result in cyclosporine toxicity and steroid excess.	PK	Moderate	2
Fluconazole–ondansetron	32	The risk of QT interval prolongation may be increased.	PK	Contraindicated	1
Lorazepam–morphine	30	Concurrent use of opioid analgesics and benzodiazepines may result in additive respiratory depression.	PD	Major	2
Cyclosporine–voriconazole	25	Concurrent use of both drugs may result in increased cyclosporine blood concentrations.	PK	Major	3
Atorvastatin–fluconazole	23	The risk of myopathy or rhabdomyolysis may be increased.	U	Major	1
Fentanyl–sertraline	23	The risk of serotonin syndrome may be increased.	PD	Major	1
Atorvastatine–cyclosporine	22	The risk of myopathy or rhabdomyolysis may be increased.	PK	Major	2
Cyclosporine–morphine	22	Concurrent use of both drugs may result in an increased morphine exposure.	U	Moderate	2
Cyclosporine–mycophenolate mofetil	21	Concurrent use of cyclosporine and mycophenolate mofetil may result in decreased mycophenolate plasma exposure.	PK	Moderate	3
Mycophenolate mofetil–omeprazol	21	Concurrent use of mycophenolate mofetil and omeprazole may result in reduced exposure to mycophenolic acid, the active metabolite of mycophenolate mofetil.	PK	Major	3
Irbesartan–KCl	20	Concurrent use of ARB-II and potassium may result in hyperkalemia.	PD	Moderate	1
Diazepam–morphine	19	Concurrent use of opioid analgesics and benzodiazepines may result in additive respiratory depression.	PD	Major	2

(continued)

Table 5. Continued.

Clinically relevant DDIs detected by Micromedex database

Pairs of drugs	*N*	Description	Mechanism	Severity	Level of scientific evidence[a]
Enoxaparin–sertraline	19	Concurrent use of sertraline and anticoagulants may result in an increased risk of bleeding.	U	Major	2
Alprazolam–sertraline	18	The risk of psychomotor impairment and sedation may be increased.	PK	Moderate	2
Ondansetron–voriconazole	17	The risk of QT interval prolongation may be increased.	PD	Major	1
Fentanyl–fluconazole	16	Concurrent use of fentanyl and CYP3A4 inhibitors may result in increased risk of fentanyl toxicity.	PK	Moderate	3

Clinically relevant DDIs detected by Drug Interaction Facts database

Pairs of drugs	*N*	Description	Mechanism	Severity	Level of scientific evidence
Cyclosporine–omeprazole	64	Increased, decreased and unchanged cyclosporine levels have been reported.	PK	Moderate	4
Cyclosporine–methylprednisolone	36	Toxicity of both drugs may be enhanced.	PK	Moderate	4
Omeprazole–sertraline	36	Serum concentrations and the pharmacologic effects of sertraline may be increased.	PK	Moderate	4
Dexamethasone–fluconazole	33	Corticosteroids effects and toxicity may be increased.	PK	Moderate	3
Cyclosporine–voriconazole	25	Cyclosporine levels and toxicity may increase 1 to 3 days after starting and persist more than 1 week after stopping antifungal therapy.	PK	Major	1
Atorvastatin–fluconazole	23	Increased plasma levels and adverse reactions of HMG-CoA reductase inhibitors may occur.	PK	Major	2
Atorvastatin–cyclosporine	22	Increased plasma levels and adverse reactions of HMG-CoA reductase inhibitors may occur.	PK	Major	2
Cyclosporine–mycophenolate mofetil	21	Cyclosporine reduces mycophenolic acid enterohepatic recirculation and its trough levels.	PK	Moderate	2
Mycophenolate mofetil–omeprazole	21	Mycophenolic acid concentrations may be reduced, decreasing the efficacy.	U	Moderate	3
Enoxaparin–sertraline	19	The risk of severe bleeding may be increased. Sertraline enhances enoxaparin anticoagulant effects.	PD	Moderate	4
Methylprednisolone–voriconazole	17	Corticosteroids effects and toxicity may be increased.	PK	Moderate	3
Fentanyl–voriconazole	16	Pharmacologic and toxic effects of fentanyl may be increased.	PK	Moderate	3

(continued)

Table 5. Continued.

Clinically relevant DDIs detected by Drug Interaction Facts database					
Pairs of drugs	*N*	Description	Mechanism	Severity	Level of scientific evidence
Alprazolam–voriconazole	15	Increased and prolonged depressant effects persisting after the azole antifungal is stopped.	PK	Moderate	1
Dexamethasone–voriconazole	15	Corticosteroids effects and toxicity may be increased.	PK	Moderate	3
Bisoprolol–nifedipine	14	Pharmacologic effects of both drugs may be potentiated.	PD	Moderate	4
Cyclosporine–fluconazole	14	Cyclosporine levels and toxicity may increase 1 to 3 days after starting and persist more than 1 week after stopping antifungal therapy.	PK	Major	1
Cyclosporine–nifedipine	14	Pharmacologic and toxic effects of nifedipine may be increased.	U	Moderate	4
Fluconazole–levofloxacin	14	Concurrent use of both drugs may result in an increased risk of QT interval prolongation.	PK	Major	4
Amitriptyline–sertraline	13	The risk of serotonin syndrome may be increased.	PK	Moderate	3
Cyclosporine–metoclopramide	13	Metoclopramide allow an increase in cyclosporine absorption, enhancing the immunosuppressive and toxic effects.	PK	Moderate	3

[a]See Table 1.
ARB-II: angiotensin II receptor blocker; PD: pharmacodynamic; PK: pharmacokinetic; U: unknown.

of potassium and magnesium be adjusted.[13] Micromedex database detects a broader spectrum of combinations that produce this effect than Drug Interaction Facts, and all are classified as *major* or *contraindicated*, while Drug Interaction Facts considers some as *moderate* (results not shown). However, the level of evidence is poor. The most frequent combination associated with this potential effect was azole antifungal-anti-5-HT_3. Azole antifungals were used as prophylaxis or treatment of invasive mycoses in immunosuppressed patients and anti-5-HT_3 as antiemetics in patients receiving antineoplastic agents. On the other hand, as in other studies carried out in haematological patients, fluconazole–levofloxacin and fluconazole–trimethoprim/sulfamethoxazole were detected.[8,9] In spite of the risk, no clinical consequences were expected on a frequent basis as previously reported by Armahizer et al.[16] in the intensive care unit setting.

Other potential interactions involving azole antifungals, mainly mediated by the CYP3A4 inhibition, have been described in this study. When fluconazole or voriconazole are associated with benzodiazepines metabolised by oxidation (alprazolam, clonazepam, diazepam), PPI (omeprazole), statins (atorvastatin), certain opioids (fentanyl), dihydropyridine calcium channel antagonists (nifedipine) or corticosteroids, an increase in both plasma concentration and toxic effects of these drugs may occur. Different alternatives could be proposed: benzodiazepines metabolised by glucuronidation (lorazepam, temazepam, oxazepam), anti-H_2 instead of PPI, or a dose reduction of statin, opioids, nifedipine or corticosteroids.[17–22] It is noteworthy that corticosteroids are included as antineoplastic agents in leukaemia chemotherapy regimens and some *moderate* DDIs have been detected by Drug Interaction Facts.

Cyclosporine and mycophenolate mofetil were the only two immunosuppressive agents prescribed in this study. They are commonly used in allogeneic HSCT patients for graft versus host disease prophylaxis or treatment, and were involved in clinically significant DDIs, because minor changes in their blood levels may have major effects on efficacy and safety.

One of the most significant potential DDIs in allogeneic HSCT patients was cyclosporine-azole antifungals, as has been identified in other studies.[8,9] The use of cyclosporine (CYP3A4 substrate) concomitantly

with azole antifungals (CYP3A4 inhibitors) can increase the risk of cyclosporine toxicity and impaired renal function, especially during post-transplant period, when nephrotoxic antibiotics and antivirals are often added to the drug regimen.[9] In clinical practice, and to avoid toxic effects, the dose of cyclosporine can be pre-emptively decreased on the day the azole antifungal is given, as recommended by the antifungals' product information. The dose of the calcineurin inhibitor should be subsequently adjusted, dependent on its blood concentration.

Cyclosporine–omeprazole has been the most frequent interaction involving cyclosporine and is classified as *moderate* by both databases. In a bone marrow transplant patient, a decrease in cyclosporine levels was obtained (from 254 ng/mL to 81 ng/mL) when intravenous omeprazole 40 mg/day was added. Cyclosporine levels were increased to 270 ng/mL within 4 days of ceasing administration of omeprazole.[23] In solid organ transplant patients, cyclosporine levels were enhanced to 510 ng/mL or maintained after omeprazole addition.[24,25] On the other hand, omeprazole reduces mycophenolic acid concentrations. The increase in gastric pH results in an incomplete dissolution of mycophenolate mofetil. As an alternative, mycophenolate sodium formulated in gastro-resistant tablets may be considered.[26] This interaction was classified as *major* by Micromedex and as *moderate* by Drug Interaction Facts. In the same way, cyclosporine may also decrease mycophenolic acid trough levels, but the mechanism is an alteration in its enterohepatic recirculation.[27] Monitoring mycophenolic acid levels and adjusting the dose as needed is recommended. This interaction has been classified as *moderate* by both databases.

The interaction between cyclosporine and corticosteroids could be clinically important. Corticosteroids have an initial time-dependent inhibitor effect on CYP3A4, which increases along time, and a significant rise on cyclosporine blood levels (about 50%) have been described after administration of high-dose methylprednisolone in children and adults with bone marrow transplantation.[28] However, in renal transplant patients the induction of both p-glycoprotein-mediated cyclosporine efflux and cyclosporine metabolism via CYP3A4, primarily in the intestine, has been reported.[29,30]

Different potential interactions have had repercussions on the central nervous system, mainly by a pharmacodynamic mechanism. First, the combination of opioid (morphine, fentanyl and codeine) and benzodiazepine is detected by Micromedex and classified as a *major* interaction, with a *good* level of evidence. This DDI does not appear in Drug Interaction Facts. The interaction occurs by adding the central depressant effects possessed by both drugs (hypotension, respiratory depression, deep sedation or even coma). The effect is well known and the expected clinical benefit (mainly pain relieve) outweighs the potential risks in the context of patients with malignancies.[31] Therefore, monitoring for symptoms of respiratory depression is recommended when these drugs are concomitantly administered. A decrease in the dosage of one or both drugs may be necessary. Moreover, in an HSCT setting, this DDI has been reported by Guastaldi et al.[9]

Secondly, the concomitant use of two serotonergic agents may lead to serotonin syndrome. In this group the use of antidepressants modulating serotonergic pathways, such as tricyclics (amitriptyline) or SSRIs (fluoxetine, sertraline), and opioid analgesics (fentanyl, tramadol) for depression and pain management was frequent. This effect has been reviewed by Rastogi et al.,[32] and it has a favourable prognosis with symptoms resolving in the majority of cases within 24 h of ceasing administration of the serotonergic agent.

In respect of risk factors associated with the presence of DDIs, a higher number of non-antineoplastic drugs were associated with a higher number of DDIs by both databases, as most of them were caused by these drugs. Similar results have been reported in other studies.[3–7] Moreover, a higher comorbidities number was reported to be associated with the presence of DDIs by Micromedex, sharing this finding with other authors.[6] An older age and a higher bilirubin value were related to DDIs by Drug Interaction Facts. Although an increased patient age has been reported as risk factor in some studies,[6,33,34] different results have been obtained, so it is difficult to establish a clear association.[3,7,8]

This study has several strengths. Two databases widely known in clinical practice have been used in the analysis, so this fact allows making our results generalisable to other institutions. Both of them provide a consistent and objective assessment of the presence and significance of potential DDIs. We also discuss the most important detected DDIs in this patient group, adding some alternatives or strategies to avoid them or minimise their adverse effects.

The main limitation of this study is that the results are based upon treatment evaluations and no patient outcomes have been followed over time to detect clinical consequences of interactions. The lack of agreement in DDI listing and severity ratings among databases, as was previously described with the same and different databases[35–40] hinders the assessment and makes necessary to look up more than one reference when identifying DDIs.

Conclusion

The prevalence of clinically relevant drug interactions disposed in this study was non-negligible, being higher

by Micromedex than by Drug Interaction Facts. The most commonly involved drugs were immunosuppressant and antifungals. In spite of their clinical relevance, any interactions could be avoided or minimised with other alternative drugs or easy strategies used in common clinical practice. The factor having the greatest influence on drug interactions was a higher number of non-antineoplastic drugs.

Declaration of Conflicting Interests

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