Drug-drug interactions in pediatric oncology patients

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Drug-drug interactions, Cancer Pharmacology, Pediatric hematology/oncology, Chemotherapy, Support care

Abbreviations

DDI	Drug-drug interaction

OTC	Over-the-counter
MTX	Methotrexate
ALL	Acute lymphoblastic leukemia

Abstract

Background

Drug-drug interactions (DDIs) can negatively affect pharmacotherapy. However pediatric DDI-studies are scarce. We undertook an exploratory study to investigate prevalence and clinical relevance of DDIs between cytostatic and non-cytostatic drugs in outpatient pediatric oncology patients.

Procedure

After informed consent and inclusion, the following information was collected: currently prescribed non-cytostatic and cytostatic drugs, comorbidities and use of over-the-counter (OTC) drugs, complementary and alternative medicines (CAM) and dietary supplements. All medication was screened for DDIs according to two databases: Micromedex® Solutions and the Dutch drug database G-Standard. The researcher presented DDIs with an associated potential for adverse outcome and a proposal for intervention to three independent experts. If the experts considered a DDI to be potentially clinically relevant and requiring intervention, the physician was notified.

Results

Seventy-three patients were included (median age 8.9 years). A total of 67 different DDIs were counted (66 in Micromedex® Solutions, 14 in G-standard and 13 DDIs in both databases). The medication reviews resulted in 35 interventions related to 11 different DDIs. The majority of DDIs concerned non-cytostatic drugs (25/35) and one third occurred between cytostatic and non-cytostatic drugs (10/35). The use of QTc-interval prolonging drugs

resulted in one intervention. The use of OTC drugs, CAM or dietary supplements did not lead to DDIs.

Conclusions

This study resulted in a selection of 11 potentially clinically relevant DDIs for 73 outpatients in our pediatric oncology department. Interventions were formulated in close collaboration between physicians and clinical pharmacists. Future research should focus on assessing DDIs concerning QTc-interval prolongation.

Introduction

The pharmacotherapeutic treatment of cancer patients is often associated with multiple side-effects. In addition, a combination of drugs may result in drug-drug interactions (DDIs) which can adversely impact drug/treatment efficacy, lead to (serious) side-effects or even life-threatening events [1]. Of all adverse reactions related to pharmacotherapy in adults, it is estimated that 20-30% are DDIs [1]. Moreover, the risk of a DDI due to the concomitant use of two drugs is approximately 6% and this risk increases exponentially with the number of prescribed drugs [2].

In our hospital, cytostatic drugs are electronically prescribed in a prescribing system different from, and not linked to the prescribing system used for non-cytostatic drugs. As a result, there is no automatic check for DDIs between these drugs and consequently no DDI alert for the prescriber. The majority of research on DDIs has been conducted in adult oncology patients [3-8] and pediatric DDI research in this area is scarce [9]. It is possible that pediatric patients react differently from adults to drugs or to drug combinations which (in part) could be explained for by age-related developmental differences in body composition and organ function thus affecting drug pharmacokinetics, pharmacodynamics, or both [10]. We therefore undertook an exploratory, prospective study to investigate the prevalence and clinical relevance of DDIs between cytostatic and non-cytostatic drugs (including over-the-counter (OTC) drugs, complementary and alternative medicines (CAM) and dietary supplements) in outpatient pediatric oncology patients.

Methods

A prospective, observational and descriptive a study was performed during a 4 month period (November 2014 – February 2015) at the Department of Pediatric Hematology-Oncology of

Erasmus MC-Sophia. Patients were randomly approached without regard to diagnosis, planned treatment schedule or responsible physician. After informed consent and inclusion, the following information was collected: list of currently prescribed non-cytostatic drugs (from community pharmacy & hospital prescribing system) and prescribed cytostatic drugs for the next 3 months (from hospital oncology prescribing system). Via a structured oral interview, the medication overviews were verified and specific patient related information, such as comorbidities and use of OTC drugs, CAM and dietary supplements was obtained.

The study population consisted of outpatients younger than 18 years treated with cytostatic drugs at the pediatric oncology ward of an academic children's hospital, Erasmus MC-Sophia in Rotterdam. The outpatient setting was selected because this is a population at risk for incomplete medication overviews [4], thus limiting a complete medication review by the pharmacy. Patients were included after obtaining written informed consent from both parents or guardians and also from the patient himself older than 12 years. Patients were excluded in case of insufficient knowledge of the Dutch or English language and if it was not possible to obtain a list of currently prescribed drugs or to conduct a structured oral interview.

Micromedex® Solutions and the Dutch drug database G-standard [11,12] were used to screen and assess DDIs as such, making use of both an international and national database. Additional information required to optimally assess potential DDIs was extracted from the hospital information system. Per patient the DDIs, and when applicable proposed interventions, were presented to a committee of 3 independent experts (hospital pharmacist, internist-clinical pharmacologist, resident in internal medicine) by the researcher. Feedback from each expert was independently submitted back to the researcher. If there was inconsistency in the feedback the independent experts were asked to reach a consensus, upon

which the identified DDI requiring an intervention was considered to be clinically relevant. The (hemato)oncologist in charge of the patient was advised how to manage this DDI.

Results

During the study period a total of 83 patients were randomly approached of which 73 were included (88%). Ten patients declined participation, mostly because they already participated in other studies. All patients included were treated with a curative intent. The main patient characteristics are summarized in Table 1.

Potential drug-drug interactions

Based on Micromedex® Solutions and the G-standard database a total of 67 different DDIs were identified; 66 DDIs were documented in Micromedex® Solutions, 14 DDIs in the G-Standard database and 13 DDIs were found in both databases. The DDIs of all patients summed up to a total of 432 (359 in Micromedex® Solutions, 73 in the G-standard database; Table 2), with a median of 5 DDIs per patient (range 0 – 28). Our patients used a median of 5 drugs (range 2 - 16) concomitant to the (standard) drugs prescribed in the cytostatic treatment course and concomitant to any OTC drugs, CAM or dietary supplements. In our study 83.5% of the patients were exposed to at least one DDI. The majority of DDIs were classified in the category 'major severity' which we could attribute to the interaction between co-trimoxazole and MTX, dose unspecified. However, as discussed further on only high and intermediate dose MTX required an intervention. Of note, 84 QTc-interval prolonging interactions were counted by Micromedex® Solutions whereas the G-standard database counted none. An overview of the QTc-interval prolonging drugs prescribed in our population is shown in Table 3.

Interventions

The medication reviews resulted in 35 interventions on 11 different DDIs (Table 4). Most interventions concerned interactions between non-cytostatic drugs (25 out of 35) and 10 interventions were related to an interaction between a cytostatic and a non-cytostatic drug. DDIs needing interventions mainly concerned the following (number of interventions in parenthesis): prophylactic oral ciprofloxacin in combination with magnesium gluconate (1), levothyroxin (1), dexamethasone (10) or prednisolone (13); MTX (high/intermediate dose) in combination with pneumocystis pneumonia prophylactic co-trimoxazole (2); vincristine in combination with itraconazole (2), voriconazole (1), aprepitant (3) or filgrastim (1) and a combination of 3 QTc-interval prolonging drugs: azithromycin, granisetron and crizotinib (1).

Over-the-counter (OTC) drugs - CAM - Dietary supplements

In our study, patients used a median of 1.9 OTC drugs (range 0 – 8). The following OTC drugs, CAM and dietary supplements were found (number of patients in parenthesis): acetaminophen (68), multivitamins (13), vitamin D (9), melatonin (5), fishoil (2), magnesium (1), other (45). In the Netherlands the use of vitamin D supplements is advised for children under 4 years old [14], which explains the majority of the users in the study population (7 out of 9 patients). No DDIs were found with OTC medication, CAM or with dietary supplements.

One patient used cannabidiol oil for pain relief and for anti-emetic reasons, However, this was not dispensed upon a prescription complying with the Dutch Opium Act, but purchased through an illegal distributor. Since 2001 the Office of Medicinal Cannabis (OMC) is the Dutch government agency responsible for the production and distribution of legal cannabis for medical purposes. There is currently one pharmacy in the Netherlands which prepares and

dispenses medicinal cannabis oil from the medicinal cannabis of the OMC. All other cannabis, in whatever form is illegal in the Netherlands.

Discussion

To our knowledge this study is the first to assess the prevalence of clinically relevant DDIs among outpatient pediatric cancer patients in combination with specific interventions and advice on how to manage the determined DDI. The majority of DDIs concerned non-cytostatic drugs (25/35) and one third occurred between cytostatic and non-cytostatic drugs (10/35). The use of OTC medication, CAM or dietary supplements was low and did not lead to DDIs. Close collaboration between physicians, clinical pharmacologists and pharmacists resulted in a well-defined selection of 11 clinically relevant DDIs. There are several reasons why we strongly advise this collaboration to be continued, also outside the setting of a clinical trial; in many hospitals there is (still) no automatic / electronic drug interaction alert between cytostatic and non-cytostatic drugs and as such prescribers must rely on DDI references and their proposed interventions which are often inconsistent. In addition, close interdisciplinary collaboration also increases the awareness for potentially clinically relevant DDIs and may help to reduce alert fatigue, an important issue in DDI clinical decision support [15]. We anticipate several issues which can impact on the occurrence of DDIs in pediatric oncology such as an increase in the use of tyrosine-kinase inhibitors, known to result in clinically relevant DDIs [16] and more use of complementary and alternative medications (CAM), also known to be involved in PK/PD interactions with chemotherapeutics [17], yet freely available via the internet and often of inferior pharmaceutical quality. The approach of our study has several strengths. There were no restrictions based on tumor type regarding inclusion of patients, which resulted in a varied, yet representative population. Furthermore, we used a national (G-standard) and an international (Micromedex®

Solutions) DDI database, both widely used in clinical practice. A limitation of this study is that patients were not followed over time to monitor the outcome of the proposed interventions.

Several of the DDIs we found require a short discussion here. The combination of co-trimoxazole and MTX results in increased MTX toxicity involving reduced folate metabolism, synergistic nephrotoxicity and reduced MTX clearance [18]. Indeed, Micromedex® Solutions and G-standard both classify this DDI as 'major' and advise to avoid the combination of MTX (dose unspecified) and co-trimoxazole. This explains the high rate of major DDIs found in our study (Table 2). However, we only proposed an intervention for high dose MTX (defined as ≥ 500 mg/m^2) and intermediate dose MTX (defined as 200-500 mg/m^2); co-trimoxazole was discontinued from 48 hours prior to 7 days after MTX infusion, according to the Dutch Childhood Oncology Group (DCOG) supportive care guidelines [19]. The majority of cases classified as 'major' DDI required no intervention as the MTX dose was low or the co-trimoxazole already discontinued. Interestingly, recent research found no evidence for an interaction between high dose MTX (2,5 g/m^2 or 5 g/m^2) and prophylactic co-trimoxazole [20]. Notably, Brandalise *et al* implemented the same precautions (leucovorin, hydratation, alkalization) for 3-weekly MTX 200 mg/m^2 MTX as for HD-MTX [21]. Given the most recent data from Watts *et al* [20] our current advice may require a revision.

Ciprofloxacin is used for prophylaxis of bacterial infections during neutropenia [19,22], sometimes referred to as selective decontamination of the digestive tract, SDD (although ciprofloxacin is also absorbed into the systemic circulation). Magnesium salts cause a decrease in ciprofloxacin absorption by 20% to 80% due to chelation in the gut lumen and the same occurs with calcium salts, although to a lesser extent [23]. An intake schedule in which ciprofloxacin is administered at least 4 hours before a magnesium salt is routinely advised [11,23]. Interestingly, the DCOG guidelines do not advise an interval for co-administration with

milk products or tube feeds stating that ciprofloxacin is used prophylactically and that tube feeds are often already stopped for other, more compelling reasons making it difficult to achieve the target intake per day [19]. However, the most important reason is that clinical experience has demonstrated that rectal SDD swabs are negative, implying that the amount of ciprofloxacin available in the gut lumen is still sufficient despite the chelation interaction.

In adults, the use of ciprofloxacin can cause pain around an affected tendon or lead to a complete tendon rupture. Corticosteroids may potentiate this side-effect [24]. In our study approximately one third of the patients (23/73) were prescribed a combination of ciprofloxacin with either prednisolone or dexamethasone. Although no pediatric research has been performed and tendinopathy is mostly reported in middle-aged individuals, the DDI was reported to the responsible hemato-oncologist given the severity of the outcome [25].

In the case of the DDI between vincristine and azole antifungals it is advised to avoid concomitant use by stopping the azole temporarily to prevent peripheral neuropathy [26,27], although there is no consensus about the length of this azole-free period [19,28]. This is an issue which requires further research.

The interaction between vincristine and aprepitant is based on moderate CYP3A4 inhibition by aprepitant [29]. Since this DDI could have severe implications the review committee advised to monitor neurotoxicity. Vincristine is associated with minimal emetic risk [30] and therefore aprepitant is always initiated to mitigate the emetogenic potential of another cytostatic drug in the treatment schedule. In children already experiencing vincristine-induced neurotoxicity one could consider administering vincristine 48 hours later, thereby preventing the DDI. We anticipate an increase in pediatric aprepitant use now that the suspension has become and physicians should be aware of this DDI [31].

In our study two patients who used several QTc-interval prolonging drugs [32] required a more detailed review. The G-standard database advises to avoid administration of two or more

drugs from the list 'Drugs with known Torsade de Pointes (TdP) risk' by CredibleMeds® [33] and if concomitant use is unavoidable the physician should monitor the ECG [33].

Micromedex® Solutions gives a similar advice but does not classify QTc-interval prolonging drugs in risk categories, which explains the difference in found DDIs (84 QTc-interval prolonging DDIs in Micromedex® Solutions vs 0 in G-standard database). In the first patient 5 different QTc-interval prolonging drugs were prescribed: 2 drugs with 'Known risk of TdP', 2 with 'Possible risk of TdP' and 1 with 'Conditional risk of TdP' (Table 4). As one of the 2 'Known risk of TdP' drugs was prescribed as 'on demand', this DDI was assessed to be not clinically relevant and no intervention was proposed [33]. The second patient was prescribed 3 QTc-interval prolonging drugs of which 1 on the list 'Known risk of TdP' and 2 on the list 'Possible risk of TdP'. There are currently no guidelines that propose interventions upon administration of a combination of QTc-interval prolonging drugs from different lists of CredibleMeds®. However, given the severity of the possible side-effect we advised to monitor the ECG in the case of 1 'Known risk of TdP' and 2 'Possible risk of TdP' drugs (excluding 'as needed' drugs). It is important to note that this intervention has not been validated and requires further research.

One intervention describes the concurrent use of vincristine and filgrastim, which has been associated with an increase in peripheral neuropathy [34]. A higher cumulative vincristine dose could increase the chance of neurotoxicity. Since the consequences can be serious, physicians were informed.

Research on the use of OTC drugs in the pediatric oncology population is scarce [35]. However, research in adults showed that 80% of the patients use OTC drugs, which in 10% of the cases results in a DDI [4]. In our study the use of OTC drugs, CAM and dietary supplements did not result in DDIs, possibly due to the proactive policy the physicians pursue concerning those

drugs: patients are strongly advised not to use any medication other than the anti-cancer treatment without first consulting their physician.

In conclusion, this study gives insight in the prevalence and clinical relevance of DDIs in this specific population. Research on DDIs in the pediatric population is limited and most studies have small study populations. We strongly advise hemato-oncologists, clinical pharmacologists and pharmacists to collaborate in identifying and managing the discussed DDIs. Currently there is no clear guideline on assessing DDIs concerning multiple QTc-interval prolonging drugs. This subject should be a focus for future research.

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Conflict of Interest statement

The authors declare no conflict of interest.

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Table 1: Patient characteristics

Variable	Patients (n = 73)	
Age (years)		
Median (range)	8,9	(0,5 - 17,5)
Sex		
Male	42	58%
Female	31	
Type of malignancy		
Solid tumors	*27*	*37%*
Brain tumors		
- Low-grade glioma	3	4%
- High-grade glioma	1	1%
- Medulloblastoma	7	10%
Other		
- Neuroblastoma	4	5%
- Hepatoblastoma	1	1%
- Nephroblastoma	2	3%
- Rhabdomyosarcoma	7	10%
- Ewing sarcoma	2	3%
Hematological tumors	*46*	*63%*
ALL	39	53%

Table 2: Classification of levels of severity in Micromedex Solutions® and G-standard database

Micromedex® Solutions			
Level of severity	*DDIs (n)*	*DDIs (%)*	*Description*
Minor	11	3.1	The DDI 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
Moderate	96	26.7	The DDI may result in exacerbation of the patient's condition and/or require an alteration therapy
Major	252	70.2	The DDI may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects
Contraindicated	0	0	The drugs are contraindicated for concurrent use.
Unknown	0	0	Unknown
Total	**359**	100%	

G-standard database			
Level of severity	*DDIs (n)*	*DDIs (%)*	*Description*
A	2	3.0	Clinically insignificant or no effect
B	0	0	Short-term discomfort (<24-48 h) without sequelae
C	6	9.1	Long-term discomfort (48-168 h) without sequelae

Table 3: QTc-interval prolonging drugs in the studied population

Known risk	Possible risk	Conditional risk
Azithromycin	Crizotinib	Amitryptiline
Ciprofloxacin	Dasatinib	Itraconazole
Fluconazole	Granisetron	Voriconazole
Ondansetron		

Classification according to CredibleMeds® Database [33]

Table 4: Interventions on DDIs

Drug (victim)	Route	Drug (perpetrator)	Route	N[a]	PK/ PD[b]	Effect DDI	Intervention	Interventi according Hansten & Horn's [13]
Ciprofloxacin	p.o.	Magnesium gluconate	p.o.	1	PK	20-80% decreased ciprofloxacin	Interval schedule; administer ciprofloxacin at least 4 hours before magnesium	Interval schedule, monitor response
Levothyroxin	p.o.	Ciprofloxacin	p.o.	1	PK	39% decreased AUC of levothyroxine	Interval schedule; administer ciprofloxacin 2 hours after levothyroxine	Interval schedule (hours) and monitor
MTX (HD)	i.v.	Co-trimoxazole	All	1	PK	Increased risk of MTX toxicity	Stop co-trimoxazole 48 hours before and 7 days after the MTX infusion	Choose otl antibiotic treatment
MTX (intermediate)	i.v.	Co-trimoxazole	All	1	PK			
Vincristine	i.v.	Itraconazole	All	2	PK	Increased vincristine plasma levels due to	Vincristine q3wk: stop azole 3 days in advance till	Consider other antifungal treatment