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Evaluation of potential drug interactions in hospitalized pediatric oncology patients

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Abstract

Cancer is a disease characterized by the disordered growth of cells capable of invading adjacent tissues. In pediatric oncology, drug-drug interactions occur mainly with supportive drugs prescribed during treatment. Thus, the present study aims to identify and evaluate the potential drug-drug interactions (PDDIs) in hospitalized pediatric oncology patients. 203 prescriptions of 47 patients were analyzed. A total of 55 PDDIs were identified, with 14 different PDDIs, and 1.2 PDDI per patient. The most prevalent 47.2% (n = 26) was methotrexate and cotrimoxazole. 21 types of neoplasms were identified, the most frequent being acute lymphoblastic leukemia (ALL). The Spearman correlation was +0.71 (p<0.001), indicating a strong correlation with the occurrence of potential drug-drug interactions and the number of drugs prescribed. In the multivariate logistic regression analysis, the results showed that having ALL and polypharmacy were the main associated factors for the occurrence of PDDI. The probability of the occurrence of PDDIs increases by 9.7 times in polymedicated patients (95%CI = 4.6-21.4 (p=0.001)) and 12.1 times in ALL patients compared to those without ALL (95% CI=5.8-26.9 (p = 0.001)). In this perspective, the data obtained make it possible to provide subsidies for the implementation of strategies to monitor and provide clinical interventions that guarantee a more effective treatment, contributing to the safety of pediatric oncology patients.

Key words: Antineoplastics. Cancer. Pharmacotherapy. Oncology.

INTRODUCTION

Annually, about 20 million childhood cancers are diagnosed worldwide, with a projected increase of 30% of cases to be identified and treated by 2020. Although the treatment of childhood cancer is being optimized, the disease is still the leading cause of mortality in children and adolescents aged 1 to 19 years, generating a negative impact on the economy of health services[1]. According to the report by The Lancet Oncology Commission on Sustainable Care for Children with Cancer (2020), it estimates that between 7.6 million and 13.7 million children will be diagnosed with cancer during the period 2020-2050 and up to 11.1 million deaths can occur during this period[2]. Childhood cancer usually affects blood cells and supporting tissue cells. The most frequent types include leukemias, lymphomas, and those that affect the central nervous system[3].

In this context, pediatric patients are more vulnerable to the occurrence of drug interactions (DDI) than adults. This is due to the possibility of receiving more than

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25 drugs during hospital stay, reacting differently to medication administration, reacting to changes in the absorption, distribution, metabolism, and excretion of drugs. In addition to the prescription of off-label drugs[4,5,6].

DDI is defined as the change in pharmacological effects between two or more drugs administered concomitantly, which may result in an increase or decrease in therapeutic efficacy or in the adverse events caused by such effects, as well as causing the appearance of new effects[7]. Regarding severity, DDIs are classified as: generally mild, not requiring changes in therapy; moderate, where the interaction may result in deterioration of the patient's clinical condition and/or requires a change in therapy; and severe, the interaction can be fatal or require intervention to minimize or avoid serious adverse events[8].

In this sense, the World Health Organization (WHO) has proposed six international goals for patient safety, the third related to safety in the prescription, use and administration of medication. In 2017, the Third Global Patient Safety Challenge was launched, with the theme Medication Without Harm. It is a global initiative to reduce serious and preventable damage associated with drugs by 50% in all countries in the next five years[9].

Despite new therapeutic strategies and advances in supportive care reflected in improvements in the quality of life of pediatric oncology patients, the high number of drugs administered during treatment increases the risk of drug-drug interactions[10]. Therefore, the present study aimed to determine the frequency and characteristics of potential drug-drug interactions in a pediatric oncology unit at a public hospital in Petrolina, Pernambuco.

METHODS

This was an analytical study with a quantitative approach carried out at the Oncology Unit of a public hospital, located in Petrolina, Pernambuco during the period from June to December 2019.

The sampling was non-probabilistic, and the sample size was chosen by convenience. The sample studied covered the universe of daily medical prescriptions for pediatric oncology patients, which were deposited at the Hospital's Medical File and Statistics Service (MFSS). Thus, the following criteria were considered:

Inclusion criteria:

- Patients of both sexes and under 18 years old;
- Length of stay in the Oncology Unit equal to or greater than 24 hours.

Exclusion criteria:

- Prescriptions with changes after the delivery time.

Data were collected from patients who were admitted to the Oncology Unit of the hospital from January to December 2018 and from January to December 2019. Only prescriptions from pediatric oncology patients were selected to undergo the pharmacotherapy review process.

Regarding patient information, the following variables were considered: age, sex, diagnosis, length of stay, and polypharmacy. The total amount of drugs prescribed, and the therapeutic class were also analyzed.

During the analysis of the prescriptions, the drugs were divided into either antineoplastic drugs or drugs prescribed for support. The drugs were classified according to their therapeutic classification, using the Anatomical Therapeutical Chemical

Classification Index (ATC)[11] as a reference, and used up to the second level. The PDDIs were identified and assessed for the level of severity, scientific evidence, and mechanism of action using the Micromedex®[12] database. The use of 5 or more medications was adopted as polypharmacy. In addition, the diagnoses of pediatric oncology patients were classified according to the International Disease Code (ICD-10)[13].

Data were expressed as frequency distribution (absolute and relative), measures of central tendency (mean and median), and dispersion measures (standard deviation and interquartile range - IQR). The normality of the distributions was determined by the Kolmogorov-Smirnov test. Spearman's correlation coefficient and the Chi-squared test were calculated. The dependent variables considered were the occurrence and the number of potential drug-drug interactions. The independent variables (gender, age, length of stay, polypharmacy, and diagnosis) that obtained a p value ≤ 0.05 in the univariate analysis were included in the logistic regression model for multivariate analysis. In the final model, the variables that maintained a value of p <0.05 remained. The magnitude of the association was expressed by the odds ratio (OR) with a 95% confidence interval (CI). Data analysis was performed using R Studio software, version 3.6.1[14].

The project met all ethical requirements according to the Resolution of the National Health Council (CNS) No. 466/2012[15], which contains the guidelines and regulatory standards for research involving human beings. Data collection was initiated only after consideration by the Research Ethics Committee of the Federal University of Vale do São Francisco (CEP-UNIVASF) which was approved under opinion No. 3.245.961 and CAAE: 06669419.6.0000.5196. The Informed Consent Form (ICF) was waived because it is a study to review secondary data.

RESULTS

203 prescriptions from 47 pediatric oncology patients were analyzed, most of them male (66.0%; n=31). The mean age of the patients was 7.3±5.1 years old. The median age was 7 years old, and the interquartile range was 8.5.

In the present study, the average number of prescription drugs was 5.95 per medical prescription. In addition, 55 PDDIs were identified in total, 14 of which were of different types. 1.2 PPDIs were observed per patient.

52 types of support medication (SM) were observed, prescribed 682 times, 14.5 SM per patient and 3.3 SM per prescription (Table 1). The most frequently prescribed SM was ondansetron (26.2%; n=179).

24 types of antineoplastic medication (AM) were observed, prescribed 526 times, 11.2 AMs per patient, and 2.6 AMs per prescription (Table 1). The AM most frequently prescribed was cytarabine (19.9%; n=105).

The prescribed drugs were presented according to the ATC classification. It was observed that group L belonging to antineoplastic and immunomodulating agents was the most prevalent, corresponding to 38.7% (n=468), followed by group A that act in the food and metabolism systems with 15.8% (n=191); of this class, antiemetics and

anti-nauseating agents (A04) corresponded to 14.8% (n=179). The drugs acting on the nervous system of group N, including analgesics, antiepileptics, and psychoanalytic agents corresponded to 13.1% (n=159), of these, the analgesic drugs (N02) were the most prescribed (n=154; 12.6%). Group H referring to systemic hormones comprised 10.9% (n=132). Group J anti-infective agents for systemic use including antibiotics, antimycotics, and antiviral drugs were 9.7% (n=117), with the majority (n=113; 9.3%) being antibiotics for systemic use (J01), also representing the most prevalent in the PDDIs identified.

Detoxifying agents for antineoplastic treatment were 7.6% (n=92) of the total. The group R drugs that act on the respiratory system are those indicated for coughs and colds, as well as antihistamines for systemic use, were 1.5% (n=18).

Finally, the emollient and protective dermatological drugs (D02), corresponded to 0.6% (n=8). The agents that act on sensory organs and the anticholinergic drugs, both presented 0.5% (n=6). Medication for the cardiovascular system, including antihypertensive drugs, diuretics, and agents on the renin-angiotensin system, obtained 0.5% of the total (n=5).

Table 2 presents the results of the PDDIs classified according to their mechanism of action, severity, and scientific evidence. 50.9% (n=28) were identified with a pharmacokinetic mechanism, those with a pharmacodynamic mechanism resulted in 30.9% (n=17), and an unknown mechanism was 18.1% (n=10) of the PDDIs. Most of the observed PDDIs had a high severity in 90.9% (n=50) of the total, while moderate was 3.6% (n=2), mild was 1.8% (n=1), and contraindicated was 3.6% (n=2). As for the level of scientific evidence, great evidence resulted in 47.2% (n=26), reasonable was 36.3% (n=20), and good represented 16.3% (n=9) of the PDDIs.

The most prevalent PDDI was between methotrexate (MTX) and cotrimoxazole (47.2%; n=26) (Table 3). The support drug most identified in PDDIs was cotrimoxazole present in 40 PDDIs (72.7%). On the other hand, the drug belonging to the group of antineoplastics, MTX, demonstrated 28 PDDIs (50.9%).

The Spearman correlation coefficient calculated between the number of potential drug interactions and the number of prescription drugs was +0.71 ($p<0.001$), indicating a strong correlation between the occurrence of drug-drug interactions and the number of prescription drugs. The average length of stay was 4.1±3.3 days and the correlation between the number of drugs prescribed and the length of stay observed was +0.02 ($p=0.7$).

As for the diagnosis, the results were evaluated according to the International Classification of Diseases (ICD-10)[13]. 20 types of neoplasms were identified, including solid and hematological ones as presented in Table 4. The diagnosis of acute lymphoblastic leukemia (ALL) was more frequent (42.5%; n=20). Most patients correspond to males with a relative frequency of 73.7% (n=14) and females at 26.3% (n=5).

In the present study, of the 20 patients diagnosed with ALL, 10 patients (50.0%) had at least one potential drug-drug interaction in their prescriptions. The presence of polypharmacy was identified in 59.5% (n=117) of the medical records. As for the length of stay, 82.75% (n=168) had a period longer than 3 days in the hospital oncology unit. In the multivariate logistic regression analysis, the results showed that having ALL and polypharmacy were the main associated factors for the occurrence of PDDIs (Table 5). The probability of the occurrence of PDDIs

increases by 9.7 times in polymedicated patients (95%CI = 4.6-21.4 (p=0.001)) and 12.1 times in ALL patients compared to those without ALL (95% CI=5.8-26.9 (p = 0.001)).

Table 1 – Most prescribed supportive drugs and antineoplastic drugs. Petrolina, Pernambuco, Brazil, 2019.

	Supporting Medications	N	%	ATC
1º	Ondansetron	179	26.2	A04
2º	Dipyrone	148	21.7	N02
3º	Dexamethasone	95	13.9	H02
4º	Cotrimoxazole*	56	8.2	J01
5º	Cefepime	34	4.9	J01
6º	Calcium folinate	31	4.5	V03
7º	Hydrocortisone (sodium succinate)	23	3.4	H02
8º	Dexchlorpheniramine	12	1.7	R06
9º	Mineral oil (emulsion)	8	1.2	D02
10º	Piperacillin + Tazobactam	7	1.0	J01
	Antineoplastic Medications	N	%	ATC
1º	Cytarabine**	105	19.9	L01
2º	Methotrexate**	80	15.2	L01
3º	Mesna	58	11.0	V03
4º	Etoposide	52	9.8	L01
5º	Ifosfamide	45	8.5	L01
6º	Dexamethasone*	36	6.8	L01
7º	Vincristine	36	6.8	L01
8º	Oncaspar (Pegasparase)	25	4.7	L01
9º	Cyclophosphamide	18	3.4	L01
10º	Carboplatin	18	3.4	L01

*Cotrimoxazole (sulfamethoxazole + trimethoprim).
**Includes MADIT-associated pharmacotherapy (Methotrexate, Cytarabine, and Dexamethasone).

Table 2 – Classification of potential drug-drug interactions according to their mechanism of action, severity, and scientific evidence, respectively. Petrolina, Pernambuco, Brazil, 2019.

CLASSIFICATION	N	%
MECHANISM OF ACTION		
Pharmacokinetics	28	51.0
Pharmacodynamics	17	31.0
Unknown	10	18.0
SEVERITY		
High	50	91.0
Moderate	2	3.6
Mild	1	1.8
Contraindicated	2	3.6
SCIENTIFIC EVIDENCE		
Great	26	47.0
Good	9	16.5
Reasonable	20	36.5
TOTAL	55	100

Source: Micromedex®.

Table 3 – Most prevalent potential drug-drug interactions classified according to severity, mechanism of action, scientific evidence, and clinical effect (N=55). Petrolina, Pernambuco, Brazil, 2019.

PDDI	N	(%)	Mechanism	Severity	Evidence	Clinical effect
Methotrexate* and Cotrimoxazole**	26	47.2	Pharmacokinetic	High	Great	Increased risk of myelotoxicity, pancytopenia, megaloblastic anemia
6-Mercaptopurine and Cotrimoxazole**	7	12.7	Pharmacodynamic	High	Reasonable	Additive myelosuppressive effect
Codeine and Ondansetron	5	9.0	Pharmacodynamic	High	Reasonable	Risk of serotonin syndrome
Cotrimoxazole and Folinic acid**	4	7.2	Unknown	High	Good	Increased treatment failure rate
Paclitaxel and Cisplatin	2	3.6	Unknown	High	Good	Administration of Paclitaxel after Cisplatin may decrease the clearance of Paclitaxel and cause profound myelosuppression
Captopril and Trimethoprim**	2	3.6	Pharmacodynamic	Contraindicado	Reasonable	Increased risk of hyperkalaemia
Prednisone and Desmopressin	2	3.6	Unknown	High	Reasonable	Increased risk of severe hyponatremia
Promethazine and ondansetron	1	1.8	Pharmacodynamic	High	Reasonable	Risk of CT prolongation
Methotrexate and omeprazole	1	1.8	Pharmacokinetic	High	Good	Risk of MTX toxicity
Morphine and ondansetron	1	1.8	Pharmacodynamic		Reasonable	Risk of causing serotonin syndrome

Source: Micromedex®.
*Includes MADIT-associated pharmacotherapy (Methotrexate, Cytarabine, and Dexamethasone).
**Cotrimoxazole (Sulfamethoxazole + Trimethoprim).

Table 4 – Distribution of diagnoses of pediatric oncology patients (N=47) according to the International Classification of Diseases (ICD-10). Petrolina, Pernambuco, Brazil, 2019.

Diagnosis	ICD 10	N	(%)
Acute lymphoblastic leukemia	C91.0	20	42.6
Acute myeloid leukemia	C92.0	4	8.6
Langerhans cell histiocytosis	*	2	4.2
Malignant neoplasm of kidney, except pelvis	C64.0	2	4.2
Malignant neoplasm of pelvis bones, sacrum, and coccyx	*	2	4.2
Other neoplasms	-	17	36.2
Total		47	100

*Has no classification in the ICD-10.

Table 5 – Frequency of the analyzed variables of the prescriptions (N=203). Petrolina, Pernambuco, Brazil, 2019.

Variable	N	%	p	OR (95%CI)
Sex	**68**	**33.5**	***0.30**	
Female	135	66.5		
Male				
Length of stay			***0.43**	
1 to 3 days	37	18.2		
> 3 days	116	57.1		
Undefined	50	24.6		
Polypharmacy			***< 0.001**	
Yes	117	59.5		
No	86	40.4		
ALL			***< 0.001**	
Yes	80	39.4		
No	123	60.6		
Prescriptions for patients with ALL and polypharmacy				
Yes	52	25.6		
No	151	74.4		
**ALL			< 0.001	12.1(5.8 -26.9)
**Polypharmacy			< 0.001	9.7(4.6-21.4)

* Chi-squared test.
** Logistic regression.

DISCUSSION

In this study, it was identified that ondansetron was the most prescribed support medication (24.2%; n=179). Ondansetron is a potent selective antagonist of serotonin receptors (5-HT3) and acts to block specific peripheral receptors located in the gastrointestinal tract and in the chemoreceptor trigger zone. It is an antiemetic drug used to prevent nausea and vomiting induced by antineoplastic chemotherapy and radiation therapy. The lack of dopaminergic antagonist activity, unlike metoclopramide, makes the antiemetic not to have extrapyramidal effects and other dose-limiting effects[12].

The drug ondansetron was identified in the PDDIs among the opioid analgesic drugs codeine (9%; n=5) and morphine (1.8%; n=1); with both drugs the combination can cause serotonin syndrome[12]. Signs and symptoms, when manifested, include changes in mental status (agitation), autonomic hyperactivity (diaphoresis, mydriasis, tachycardia, or diarrhea), and neuromuscular abnormalities (clonus and hyperreflexia)[16,17]. Thus, careful observation of the patient during the start of treatment is indicated. If necessary, adjust the dose. When the syndrome is suspected, codeine should be discontinued[8]. In addition, this antiemetic drug has been found to be associated with promethazine (1.8%; n=1). This DDI can increase the risk of prolonging of the CT (chemotherapy) interval; it is considered relevant to monitor changes in the electrocardiogram during use[18].

Other studies have shown ondansetron altering the pharmacokinetics of antineoplastic drugs in adults who have undergone bone marrow transplants. The plasma concentration area under the curve (AUC) for cyclophosphamide was smaller when compared to those who received the antiemetic prochlorperazine. The AUC of cisplatin was also lower in patients treated with ondansetron vs. prochlorperazine. However, these differences in the AUC did not correlate with long-term survival[19,20].

On the other hand, among antineoplastic drugs, cytarabine was more frequent in prescriptions (22.4%; n=105). The drug cytarabine (cytosine arabinoside, ara-C) has been used for the treatment of acute myeloid leukemia for over 40 years, constituting one of the most effective drugs for the treatment of this type of cancer[21]. In addition to myelosuppression, it has severe neurological toxicity in high doses[22]. It can be used alone or in combination with other antineoplastic agents, obtaining better results in combination therapy[23]. In the treatment of ALL, it is included in the GBTLI-99 protocol (Brazilian Group for the Treatment of Leukemia in Childhood) for patients with low and high risk of relapse and is administered in different stages[24].

In the present study, no PDDI with cytarabine was identified, but care should be taken with the associations. Cytarabine when administered concomitantly with methotrexate intrathecally may increase the risk of serious neurological effects such as chemical arachnoiditis, which is an acute syndrome that occurs hours after administration, characterized by headache, back pain, vomiting, fever, meningism, and pleocytosis[25,26].

Considering the PDDIs with the prescribed drugs, cotrimoxazole as a support medicine was identified in 40 PDDIs (72.7%). MTX belonging to the antineoplastic group was present in 28 PDDIs (50.9%), with cotrimoxazole and MTX PDDIs being the most prevalent in the study (n=26; 47.6%). Cotrimoxazole

can increase the plasma concentration of MTX, produce nephrotoxicity, reduce folate metabolism, and cause reduced clearance of MTX[27]. According to Micromedex®[12], there is a risk of pancytopenia, myelotoxicity, and megaloblastic anemia. In addition, it classifies DDIs as severe and recommends avoiding the combination of MTX (unspecified dose) and cotrimoxazole. Balk *et al.*[28], proposed an intervention for high and intermediate doses of MTX. Cotrimoxazole was discontinued 48 hours prior to 7 days after the infusion of MTX (according to the Dutch Childhood Oncology Group (DOCG) - Supportive Care Guidelines). In cases where the dose of MTX was low, it did not require intervention or cotrimoxazole had already been discontinued[28]. In addition, recent research has not shown evidence of DDIs between high doses of MTX and prophylactic cotrimoxazole[29].

MTX is an antifolate agent indicated for the treatment of several types of cancer and some autoimmune diseases (including rheumatoid arthritis). In oncology it is often administered in high doses (> 1g/m2) and intravenously. However, in autoimmune diseases it is administered in low doses and orally or intramuscularly[30]. It is known that most interactions with MTX encompass a pharmacokinetic mechanism of action and involve membrane transporters whose activity and expression can be altered[31]. Studies have shown children with acute lymphoblastic leukemia presenting a genetic polymorphism with high expression of the Organic Anion Transporter Polypeptide (OATP) 1B1 in the liver and this expression significantly affected the total clearance and gastrointestinal toxicity of MTX[32,33].

Severe MTX poisoning can be managed by administering a rescue agent called glucarpidase. This enzyme hydrolyzes the antifolate in the serum. The administration of folinic acid (leucovorin) is another strategy to reduce the toxic effects of MTX, restoring the reduced folate levels[34,35].

The second most prevalent PDDI was between 6-mercaptopurine (6-MP) and cotrimoxazole. This is an interaction capable of increasing the myelosuppressive effect (anemia, leukopenia, thrombocytopenia). In case of coadministration, the complete blood count must be monitored for signs of myelosuppression, hematological, and/or renal toxicity[12]. In addition, studies have shown a reduction in the absorption of 6-MP by cotrimoxazole. This was done by measuring the level of an active 6-MP metabolite, 6-thioguanine, in children with lymphoblastic leukemia, and was compared in the presence or absence of cotrimoxazole. Thus, they suggest that cotrimoxazole may interfere with the absorption and cytotoxicity of 6-MP and, consequently, alter its anti-leukemic effect[36].

The management and prevention of problems related to cancer drugs are particularly important due to the excessive cost, high toxicity, and narrow therapeutic index of antineoplastic agents, in addition to the patients' health status. Therefore, the presence of the pharmacist as a member of the multidisciplinary team is essential for favorable clinical results, such as reducing side effects, improving patients' quality of life, and reducing health costs[37,38].

The present study has as a limitation the performance of data collection in a single oncology unit with patients in the age range ranging from 1 to 18 years. Thus, it is not possible to extrapolate the data found for the hospitalized pediatric oncology population with specific age groups.

CONCLUSION

From the analysis of the results, it was observed that pediatric oncology patients when admitted to hospital, are susceptible to be affected by PDDIs. Therefore, the relevance of the pharmacotherapeutic review in the treatment of cancer is highlighted to identify the PDDIs and, thus, contribute to the definition and development of strategies with the multiprofessional team that can positively impact the prevention and clinical management of these interactions and the negative outcomes in children with cancer. It is worth mentioning the importance of an individualized approach in the management of pharmacotherapy for pediatric oncology patients, as well as the multiple health problems, with a focus on minimizing the unnecessary use of drugs, reducing adverse events and costs.

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