Potential drug–drug interactions in children with acute lymphoblastic leukaemia: a cohort study

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KEYWORDS

drug interaction; polypharmacy; precursor cell lymphoblastic leukaemia-lymphoma; neoplasms; paediatrics.

ABSTRACT

Objective
To evaluate the potential drug interactions in patients with acute lymphoblastic leukaemia in the remission induction period of treatment.

Design
A prospective cohort study.

Setting
A tertiary referral centre.

Subjects
Twenty-two children undergoing treatment for acute lymphoblastic leukaemia. The median age was 4.5 years (minimum of 1 and maximum of 18 years) with male predominance (54.4%).

Main outcome measure
Presence of potential drug interactions in patients undergoing treatment for precursor cell lymphoblastic leukaemia-lymphoma. The potential drug interactions term refers to the ability of a drug to affect the pharmacologic intensity as well as the therapeutic effect of another and cause adverse reactions, as well as the possibility of clinical manifestations.

Results
All participants were exposed to at least one potential drug interaction. About 60% of interactions classified as more severe. Every new drug included in the treatment increased the chance of potential drug-drug interactions by 0.4 times.

Conclusion
These results demonstrated the patients under chemotherapeutic care for lymphoblastic leukaemia-lymphoma have high potential for drug interactions of greater severity.

INTRODUCTION

After accidents, paediatric cancer is the second leading cause of infant mortality. About 1,250 children younger than 15 years old are expected to die from cancer in 2016. The acute lymphoblastic leukaemia accounts for 30% of all malignant neoplasms in children and 75% of all childhood acute leukaemia's (de Lima et al 2016; Jiménez de Samudio et al 2016; Cazé et al 2010).

The treatment period of acute lymphoblastic leukaemia is at least two years and is characterised by long periods of hospitalisation. In the first stage of treatment, named remission induction, patients undergo high-dose chemotherapy aiming for complete clinical remission of the cancer. Due to this treatment regimen, myelosuppression and other related clinical complications occur (Loghavi et al 2015; Pui et al 2015; You et al 2015).

The concomitant use of numerous medications is essential, making the incidence of polypharmacy inevitable. This is characterised by the use of five or more drugs generally used for the purpose of avoiding or reducing undesired effects and complications of treatment (Gillette et al 2015; Secoli 2010). The need to use polypharmacy makes it essential to assess potential drug–drug interactions (PDDI) related to its administration, as most drugs have interactive potential; this subject is not often discussed in the practice of health professionals (de Lima et al 2016; Sharifi et al 2014).

Drug interaction occurs when there is interference with the effect of a drug due to prior or concomitant administration of other drugs or food. Healthcare providers rarely consider potential drug interactions as a factor that may be responsible for ineffective therapy (Dai et al 2016; Miller et al 2015; Payne et al 2015).

Therefore, it is essential for the healthcare team to reflect on PDDI as they are responsible for the prescription and administration of medications, thus playing an important role in identifying potential drug interactions or reducing adverse reactions of these interactions (Dai et al 2016; Miller et al 2015; Payne et al 2015). Therefore, this study aimed to evaluate the potential drug interactions in children with acute lymphoblastic leukaemia in the remission induction period of treatment.

METHOD

This is a prospective cohort study conducted in the cancer centre at the University Hospital of the Federal University of Santa Maria, Santa Maria, Brazil, from April 2013 to April 2014. This is a reference centre in paediatric hemato-oncology for the southern region of Brazil. The study was approved by the Ethics Committee of the Federal University of Santa Maria.

A consecutive sample was composed of all patients with first hospitalisation during the data collection period, with confirmed diagnosis of acute lymphoblastic leukaemia. The choice of patients at first admission is justified by the fact that these patients are hospitalised for at least 30 days.

Data were collected daily by the researcher, using a questionnaire composed by demographics data, patient identification (name, age, and gender), data on hospitalisation (date of admission and length of stay), and information on prescription drugs (name, dose, route, administration times, and drug use time).

The dependent variable is the presence of PDDI. The PDDI term refers to the ability of a drug to affect the pharmacologic intensity as well as the therapeutic effect of another and cause adverse reactions, as well as the possibility of clinical manifestations (Secoli 2001).

Drugs were initially classified according to the Anatomical Therapeutic Chemical (ATC) of the World Health Organization, which allows active substances to be divided into different groups according to the organ or

system in which they operate and their therapeutic properties, both pharmacological and chemical. For the identification of PDDI, level 5 of the ATC, which corresponds to the chemical, was used (WHO 2013).

All drugs have been included for analysis of potential drug interactions, using the electronic database (Micromedex® Healthcare Series). This database allows the user to sort the potential drug interactions by second gravity, evidence, and onset of effect. Additionally, no description of the clinical impact of drug interactions is given (Hutchison et al 2003).

Descriptive statistics were used to present potential drug interactions. Linear logistic regression was used to obtain estimates of odds ratios (OR) and confidence intervals, with a significance level of α = 0.05. Data analysis was performed using SPSS software (Version 21.0).
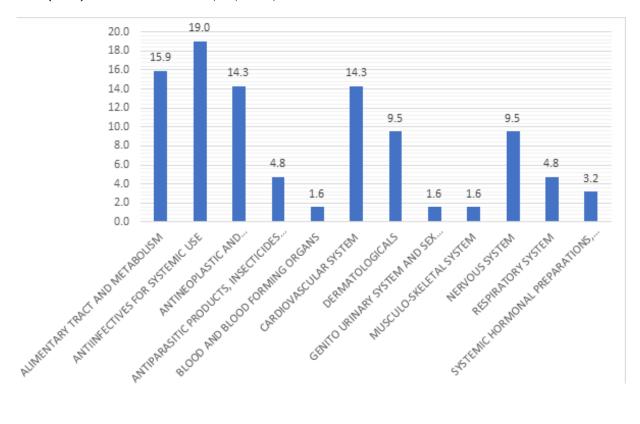
FINDINGS

The study included 22 children undergoing treatment for acute lymphoblastic leukaemia with the median age was 4.5 years (minimum of 1 and maximum of 18 years) with male predominance (54.4%). They were exposed to a median of 19.5 PDDI (minimum of 8 and maximum of 101 PDDI).

The median time of hospitalisation was 36 days (minimum of 30 and maximum of 63 days), during which 869 prescriptions were given and a total of 4,481 doses of medication were administered. The median days of treatment with potential drug interactions was 11 days (minimum of 4 and maximum of 41 days), resulting in a 39.7% prevalence of days with potential drug interactions.

Sixty-six different drugs were identified. According to the ATC, the majority of these (19%) belonged to the class of anti-infective drugs for systemic use (Group J), followed by drugs with action on the digestive system and metabolism (Group A), representing 15.9% and drugs with action on the cardiovascular system (Group C), with 14.3%, as shown in figure 1.

Figure 1: Distribution of the prescription drugs according to the classification Anatomical Therapeutic Chemical Code (ATCC) as level 1. Santa Maria, RS, Brazil, 2014

Medications that had a higher frequency of administration were sulfamethoxazole/trimethoprim (634 administrations), Omeprazole (495 administrations), prednisolone (405 administrations), and Dexamethasone (283 administrations).
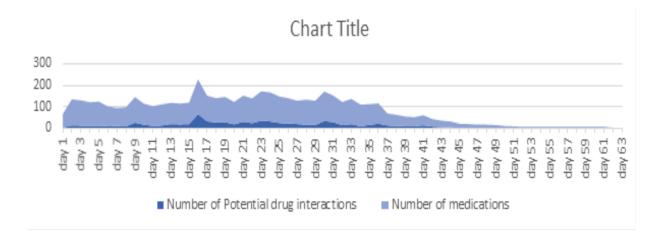
They identified 758 PDDI in the study period. The most frequent potentially interactive combination was asparaginase x Prednisolone (more severe), followed by Fluconazole x sulfamethoxazole/trimethoprim (more severe) and Fluconazole x Omeprazole (moderate severity). Approximately 60% of potential drug interactions were more severe. The main potential drug interactions are described and listed in table 1.

Table 1: Potential drug–drug interactions in children with precursor cell lymphoblastic leukemia-lymphoma. Santa Maria, RS, Brazil, 2014.

Drug 1	Drug 2	Effects *	%
Asparaginase Erwiniachry Santhemi	prednisoLONE	Increased risk of asparaginase toxicity	10,0
Fluconazole	Sulfamethoxazole / Trimethoprim	Increased risk of cardiotoxicity	8,4
Fluconazole	Omeprazole	Increased plasma concentrations of omeprazole	8,4
Fluconazole	predniSONE	Decrease in the metabolic degradation of predniSONE and an increase in predniSONE efficacy	6,5
Dexamethasone	vinCRIStine Sulfate	Decreased vinCRIStine plasma concentrations	6,3
Enalapril Maleate	Sulfamethoxazole / Trimethoprim	Increased risk of hyperkalemia	5,5
Sulfamethoxazole Trimethoprim	Methotrexate Sodium	Increased risk of methotrexate toxicity	4,9
Hydrochlorothiazide	predniSONE	Hypokalemia and subsequent cardiac arrhythmias	4,5
Asparaginase Erwiniachry Santhemi	vinCRIStine Sulfate	Increased risk of toxicity	4,4
Omeprazole	Methotrexate Sodium	Increased concentration of methotrexate and its metabolite and an increased risk of methotrexate toxicity	4,1

A children data receive at least 5 drugs have 2 times more risk of occurrence of PDDI, because each new prescription medication added to the course of treatment grow 0.413 times (OR = 0.402, CI = 0.186 to 0.617) the risk of occurrence of PDDI. It can be verified by figure 2.

Figure 2: Association observed between drug administration and PDDI. Santa Maria, RS, Brazil, 2014

DISCUSSION

Despite evidence of international guidelines that guide the chemotherapy combinations for the treatment of acute lymphoblastic leukemia, addressing the PDDI and adverse events associated with them (Alvarnas et al 2015; Yeoh et al 2013; Cazé et al 2010), all study participants were exposed to at least one PDDI.

In line with other research, the association between polypharmacy and PDDI was confirmed (Sharifi et al 2014; Secoli 2010). Polypharmacy is a risk factor in patients undergoing different types of treatment and is especially related to those individuals who have in their therapeutic regimen, at least one chemotherapeutic drug (Sasaki et al 2013; Hohl et al 2001; Sheppardet al 1974). This may be exacerbated by the administration of more than one drug dose in which the study demonstrated 0.4 times greater risk of presenting PDDI per drug administered.

The addition of each drug increases the risk of adverse events by 10% (LeBlanc et al 2015). However, polypharmacy is a key strategy for the treatment of precursor cell lymphoblastic leukaemia-lymphoma. Initial treatment consists of the use of methotrexate, vincristine, Daunorubicin Hydrochloride, ELSPAR, Etoposide, and Cytarabine. In addition, in cases of opportunistic infections, comorbidity, or palliative character, polypharmacy is mandatory (Dai et al 2016; Alvarnas et al 2015; Wu and Li 2014).

Febrile neutropenia already presents with hemodynamic repercussions and signs of infection and is characterised by an urgent risk of dissemination and septic shock. The infection time frame, sepsis, septic shock, and organ and organ system dysfunction resulting from neutropenia are the main causes of mortality in children with cancer and the main reasons for indicating intensive care (Caniza et al 2015; Alexander 2014; Sasse et al 2005).

In this initial phase of treatment, a dose of chemotherapy will be reduced or delayed as a result of myelosuppression and/or presence of infection, necessitating the use of other medicines to control symptoms and other complications to continue the treatment (Irving 2016; Wu and Li 2014; Cazé et al 2010).

Independent of the time of treatment, 57.3% of PDDI were classified as moderate. As patients in treatment for precursor cell lymphoblastic leukaemia-lymphoma present vulnerability in terms of disease characteristics and also because most are children, this reaction can interfere in important ways in quality of life, leading to negative outcomes. In these cases, one has to consider modifying the therapy, as PDDI may result in increased toxicity, changes in plasma concentration, and changes in the metabolic degradation of drugs, as well as so many other systemic effects that can affect the outcome of therapy and interfere with the prognosis of the patient.

The daily prescriptions included an average of 4.9 medications per day, appearing to be in accordance with the clinical demands that the patients presented in the period due to the proposed therapy. Neutropenia caused by a strong chemotherapy regimen administered in the remission induction phase justifies the class of anti-infective drugs that has been the most frequently prescribed (Buie et al 2015; Schroder et al 2001). Similarly, drugs that act on the digestive system (second-most prescribed drugs) are fundamental in relieving nausea, vomiting, epigastric pain, and other common symptoms of post-chemotherapy.

Sulfamethoxazole/trimethoprim, which is provided in the treatment plan for all patients, was the most used drug and its management is maintained even after hospital discharge, since it is the first option for antimicrobial prophylaxis of infections in immunocompromised patients (Davis et al 2014; Schroder et al 2001). As to the administration of omeprazole, prednisolone, and dexamethasone, they are prescribed regardless of treatment response and potential complications.

Considering that the prescription is the point of origin for the use of the drug, a careful evaluation of the antineoplastic therapy regimen should be carried out to identify and predict potential drug interactions and adverse effects (LeBlanc et al 2015; Payne et al 2015; Sharifi et al 2014). Therefore, prescribers should consider the aspects related to patients to assess the risk-benefit of maintaining or not maintaining the drug combination. Furthermore, conducting biochemical and clinical examinations before and after the introduction of other drugs will certainly help to reduce PDDI.

Although there are contributions and a pioneering study in Brazil, it is important to note the limitations of the research. The evaluation of potential drug interactions was taken from a convenience sample of patients in hospital, an aspect that limits the applicability of the results. Some combinations of drugs identified as potential drug interactions were necessary due to the treatment regimen or unavailability of alternatives with less interactive potential.

Real outcomes of drug interactions have not been evaluated in this quite difficult aspect because the establishment of cause and effect is complex, especially due to the presence of polypharmacy and potentially interactive features of many antineoplastic agents.

Although the study has not evaluated the adverse drug reactions, the findings although limited, are relevant to patients with precursor cell lymphoblastic leukaemia-lymphoma, especially to present the clinical findings of potential drug interactions. In addition, the therapeutic regimens used in the induction of remission treatment step are similar throughout the world.

CONCLUSION

It was found that every new drug inserted in the treatment of precursor cell lymphoblastic leukaemia-lymphoma increases the chance of risk for the occurrence of potential drug interactions by 0.4 times.

The potential drug interactions identified in this study of moderate and higher severity are events that, in addition to influencing the therapeutic response causing changes in plasma concentrations of drugs, systemic toxicity, cardiotoxicity, and can interfere with the treatment provided in the period induction of remission of precursor cell lymphoblastic leukaemia-lymphoma.

RECOMMENDATIONS

Nursing should interfere in the occurrence of PDDI, since the time of administration and planning drug application ranges are medicated effective in eliminating or reducing the adverse effects of these interactions. The findings of this research can be applied in clinical practice, permitting the identification of potential drug interactions and adverse effects of medication.

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