

Splitting of Antineoplastic Tablets Used in Acute Leukemias Treatment in Children and Adolescents

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Partição de Comprimidos Antineoplásicos Utilizados no Tratamento de Leucemias Agudas em Crianças e Adolescentes

Partición de Comprimidos Antineoplásicos Empleados en el Tratamiento de Leucemias Agudas en Niños y Adolescentes

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Abstract

Introduction: Antineoplastic drug manipulation for dose adjustment, such as tablet splitting, is standard in acute leukemia treatment for children and adolescents. **Objective:** To identify the frequency and describe the practice of household splitting of antineoplastic tablet for oral treatment of children and adolescents with acute leukemias in the maintenance phase. **Method:** Cross-sectional descriptive study performed in a public health system hospital from Distrito Federal (Brazil) with specialized pediatric assistance. Children and teenagers between 1 and 18 years old, diagnosed with acute leukemia and in treatment maintenance phase during the study period were included. A semi-structured questionnaire was applied to the main responsible for administering oral chemotherapy drugs, which could be the caregiver or the child/adolescent themselves. **Sociodemographic variables of patients and caregivers and variables on the practice of splitting antineoplastic drugs at home were collected. Results:** All 48 interviewees in the study period reported having split antineoplastic tablets during the treatment for acute leukemias, such as mercaptopurine (n = 45 [93.75%]) and thioguanine (n = 3 [6.25%]). **Conclusion:** The splitting of antineoplastic tablets was a unanimous practice due to the reported need to adjust the individual dose for acute leukemia treatment in children and adolescents, considering the unavailability of adequate formulations. The results reinforce the need for splitting to be standardized and performed in a way that minimizes risks and ensures safety for patients and their caregivers.

Key words: Antineoplastic Agents/administration & dosage; Tablets/administration & dosage; Leukemia; Child; Adolescent.

Resumo

Introdução: A manipulação de antineoplásicos para ajuste de dose, como partição de comprimidos, é comum no tratamento de leucemias agudas de crianças e adolescentes. **Objetivo:** Identificar a frequência e descrever a prática da partição domiciliar de comprimidos antineoplásicos utilizados no tratamento oral de crianças e adolescentes com leucemias agudas na fase de manutenção. **Método:** Trata-se de um estudo transversal descritivo, realizado em um hospital pertencente à rede de saúde pública do Distrito Federal com assistência especializada em pediatria. Foram incluídos no estudo crianças e adolescentes entre 1 e 18 anos, diagnosticados com leucemias agudas e em fase de manutenção do tratamento no período de estudo. Foi aplicado um questionário semiestruturado ao responsável principal pela administração dos medicamentos quimioterápicos via oral, podendo ser o cuidador ou a própria criança/adolescente. Foram coletadas variáveis sociodemográficas dos pacientes e cuidadores e variáveis sobre a prática de partição de medicamentos antineoplásicos no domicílio. **Resultados:** Todos os 48 entrevistados no período do estudo relataram ter partido comprimidos antineoplásicos ao longo do tratamento de leucemias agudas, sendo estes mercaptopurina (n=45 [93,75%]) e tioguanina (n=3 [6,25%]). **Conclusão:** A partição de comprimidos antineoplásicos foi uma prática unânime em virtude da necessidade referida de ajuste de dose individual para o tratamento de leucemias agudas de crianças e adolescentes, considerando a indisponibilidade de formulações adequadas. Os resultados reforçam a necessidade de a partição ser uniformizada e realizada de maneira a minimizar os riscos e a garantir a segurança para as crianças e adolescentes e seus cuidadores.

Palavras-chave: Antineoplásicos/administração & dosagem; Comprimidos/administração & dosagem; Leucemia; Criança; Adolescente.

Resumen

Introducción: La manipulación de fármacos antineoplásicos para el ajuste de dosis, como las particiones de comprimidos, es frecuente en el tratamiento de las leucemias agudas en niños y jóvenes. **Objetivo:** Identificar la frecuencia y describir la práctica de la división domiciliar de medicamentos antineoplásicos utilizados en el tratamiento oral de niños y adolescentes con leucemias agudas en la fase de mantenimiento. **Método:** Se trata de un estudio transversal descriptivo realizado en un hospital de la red de salud pública del Distrito Federal (Brasil) con asistencia especializada en pediatría. El estudio incluyó a niños y jóvenes de entre 1 y 18 años de edad diagnosticados con leucemia aguda y en fase de mantenimiento del tratamiento en el período del estudio. Se aplicó un cuestionario semiestructurado a la persona principal responsable de la administración de fármacos quimioterápicos por vía oral, que puede ser el cuidador o el propio niño/joven. Fueron colectadas variables sociodemográficas de los pacientes y cuidadores y variables sobre la práctica de la división de los medicamentos antineoplásicos en domicilios. **Resultados:** Los 48 entrevistados en el período de estudio informaron haber roto las pastillas antineoplásicas durante el tratamiento de la leucemia aguda, siendo éstas mercaptopurina (n=45 [93,75%]) y tioguanina (n=3 [6,25%]). **Conclusión:** La partición de comprimidos antineoplásicos fue una práctica unánime debido a la necesidad mencionada de ajustar la dosis individual para el tratamiento de las leucemias agudas de niños y adolescentes, considerando la falta de formulaciones apropiadas. Los resultados refuerzan la necesidad de estandarizar y realizar la partición para minimizar los riesgos y garantizar la seguridad de los niños, jóvenes y sus cuidadores.

Palabras clave: Antineoplásicos/administración & dosificación; Comprimidos/administración & dosificación; Leucemia; Niño; Adolescente.

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INTRODUCTION

Cancer already represents the first cause of death (8% of the total) by disease in Brazil in children and adolescents from 1 to 19 years old¹. Leukemias¹ are the most frequent tumors of pediatric neoplasms. Leukemia is a malignant disease of hematopoietic cells and its main characteristic is the building up of abnormal cells in the bone marrow replacing normal blood cells². There are more than 12 types of leukemia, including acute primary types².

The treatment of acute leukemias is divided in stages with three main phases: induction of remission, consolidation and maintenance². The last, maintenance phase, characterizes by less strong and continuous treatment for several months², with prescriptions of oral medications at home under family oversee.

Maintenance therapy is as important as the initial phases of the treatment³ to achieve cure and prevent relapse². The correct use of chemotherapics and best support care contributed to improve the treatment and increased the survival rates throughout the years^{4,5}. The proper adjustment of individual dose is important to prevent the reappearance of the leukemic clone and to reduce the toxicity by leukopenia³, leading to better result of treatment and cure⁴.

Manipulation of pediatric drugs to adjust individual dose including tablet splitting is quite common and split tablets are frequently used in clinical practice to reach the prescribed dose⁶⁻⁸. Chemotherapics used for treatment of acute leukemias in children and adolescents are manipulated to meet pediatric demands due to unavailability of several pharmaceutical formulas^{9,10}.

This can be problematic considering that great part of the antineoplastics are cytotoxic and hazardous agents and can cause damages to individuals involved in the preparation and dispensation of drugs and in the care provided to those in chemotherapy¹¹⁻¹⁴, since tablet splitting in uncontrolled environment exposes them to cytotoxic dust¹⁰. In addition, manipulation causes concerns due to issues related to stability, bioavailability and accuracy of the drug dosage and toxic or sub-therapeutic doses might be administered to children/adolescents^{6,8}. This becomes more relevant considering that chemotherapics have narrow therapeutic index, so the correct administration is crucial for safety and efficacy purposes¹⁵.

Scarce knowledge about household antineoplastic tablet splitting exists and how it is performed. In addition, data about contamination and exposure to these hazardous drugs in off-hospital environment are also rare¹⁴. This becomes relevant because encompasses factors needing more studies about the safety of the patient and the caretaker/family, in addition to the treatment efficacy and

potential late adverse events resulting from household splitting process.

Therefore, the objective of the present study was to identify the frequency of household antineoplastic drugs splitting used in the oral treatment of children and adolescents with acute leukemias in maintenance phase attended in a pediatric hospital and describe the practice of splitting, how it is performed to understand the process better, considering the risks these drugs can cause to those using and manipulating them.

METHOD

Cross-sectional descriptive study conducted between January and March 2019, in a reference pediatric hospital in Brasilia, DF.

The flowchart (Figure 1) presents a selection of study participants based in the list of oncohematologic patients attended in the site and visits registered in electronic chart. Of the 82 children and adolescents diagnosed with acute leukemias once more or in relapse who were in treatment during the study period, children and adolescents ranging from 1 to 18 years old who reached the maintenance phase of chemotherapy were included with prescription of continuous use of oral chemotherapics at home and accompanied by the main responsible for providing care to the child or adolescent in the study period (n=49).

A semi-structured questionnaire was applied to collect data about the practice of antineoplastic splitting in an interview with the main responsible for the administration of the drug, with the caretaker or to the own child/adolescent in a secluded waiting room at the hospital's outpatient facilities.

Sociodemographic variables of all the children/adolescents and their respective caretakers were collected. The variables for children/adolescents were gender, age, skin color and access to health insurance. For

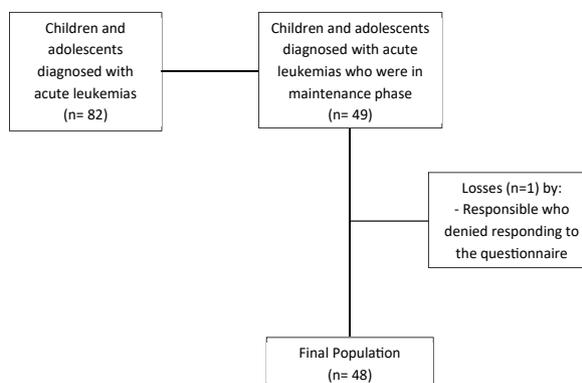


Figure 1. Flowchart of study participants selection

caretakers, gender, age, education, marital status, skin color, family income and degree of kinship with the patient. Information from electronic charts as history of pathological condition and drugs used by the patient were collected as complement.

For oral antineoplastic splitting practice at home, a questionnaire was applied to collect the following variables: whether the interviewee split or had split during the treatment and the conditions how this process was performed. Therefore, it was investigated the instrument utilized, place at the house where splitting occurred, how the other fractions of the tablets were stored, changes of split tablets reported by the interviewee, the hygiene of the manipulator and of the instrument utilized and symptoms perceived by the responsible for the splitting after antineoplastic manipulation. Considering the current practice of splitting, it was analyzed in how many fractions the tablets were split (halves, thirds or quarts), taking into account the capacity the interview had of recollecting and the importance of demonstrating the splitting at home in that moment.

Based in the data gathered, a database was prepared through the program *Epi Info* version 7.0 and performed the statistical analysis. In the descriptive analysis, the data were expressed as absolute or relative frequency, measures of central tendency and variability.

In compliance with resolution CNS (National Health Council) number 466/12, with Guidelines and Ruling Norms of Researches Involving Human Beings, the study was submitted for review and approved by the Institutional Review Board of the College of Sciences of Health of the University of Brasilia (UnB), number CAAE: 87652818.5.0000.0030, approval report 2,808,180 dated August 11, 2018 and by the Institutional Review Board of Foundation of Teaching and Research in Sciences of Health (FEPECS), number CAAE: 87652818,5,0000,0030 and approval report number 2,979,001 dated October 24, 2018. The interviews were conducted after the responsible caretakers signed the Informed Consent Form and the children older than 5 years and adolescents signed the Assent Form.

RESULTS

In total, 48 responsible for the administration of the antineoplastic drugs, 45 [93.75%] were children and adolescents caretakers, in 40 cases (85.42%), the mother was the main responsible for the treatment and in three cases (6.25%) the adolescent itself responded the questionnaire about tablets splitting. As shown in Table 1, with the sociodemographic characteristics of the caretakers (n=48), the mean age was 33.56 years (SD = 9.66), the

majority were females (n=44 [91.67%]), Brown skin (n=27 [56.25%]). The biggest percentage of caretakers was married (n=17 [35.42%]), had completed high school (n=18 [37.5%]) with mean family income ranging between one and two minimum wages (n=29 [60.43%]).

The data collected for children/adolescents (n=48) revealed the predominance of Brown color (n=20 [41.67%]), males (n=32 [66.67%]), mean age of 6.71 years (SD=3.81). It was observed hegemony of acute lymphoid leukemia (n=47 [97.92%]) over acute myeloid leukemia (n=1 [2.08%]). Another relevant data is that most part of children and adolescents had no health insurance (n=42 [87.50%]).

Based in the data collected, it was observed that the continuous use of oral antineoplastics by children and adolescents in the maintenance phase of acute leukemias were methotrexate (n=41 [85.42%]), desatinib (n=1 [2,08%]), mercaptopurine (n=45 [93.75]) and thioguanine (n=3 [6.25%]). The results demonstrated that the 48 interviewees reported they had split antineoplastic tablets during the treatment, mercaptopurine 50 mg and thioguanine 40 mg. 45 interviewees (93.75%) split mercaptopurine and three (6.25%) split thioguanine while the interviews were being conducted or previously. Of the 48 interviewees, 33 (68.75%) were splitting tablets at home in the period when the interviews were being conducted to adjust the individual dose (Table 2).

One aspect evaluated was in how many fractions the tablet was split to reach the required dose. For this, the analysis considered splitting at home while the interviews were being conducted based in the capacity the interviewees had to recollect and the importance of reenacting the splitting in that moment. The antineoplastics were split in halves, quarts or both, depending of the prescription for dose adjustment according to the day. These data are detailed in Table 2.

The analysis of the conditions of the antineoplastic tablets splitting process considered also the splitting at home conducted previously to the interviews, since all reported having split along the treatment of acute leukemias. According to Table 3, the main instrument utilized for the splitting was the tablet splitter (n=23 [47.92%]), splitting was performed mainly in the kitchen (n=37 [77.09%]). The 48 interviewees stored fractions for future use, most of them (n=38 [79.17%]) reported they stored in the own package containing split and whole tablets.

Other factors about the conditions of splitting included the perception of changes in split tablets and hygiene. In relation to changes, 16 interviewees (33.33%) reported they perceived tablets crumbling after splitting. Regarding hygiene, all reported they washed their hands

Table 1. Sociodemographic data of caretakers of children and adolescents in treatment of acute leukemias

Sociodemographic data	Caretakers (n)	Frequency (%)
Gender		
Female	44	91.67
Male	4	8.33
Age (years)		
From 18 to 27	16	33.33
From 28 to 37	16	33.33
From 38 to 47	11	22.92
From 48 to 57	5	10.42
Skin Color		
Caucasian	7	14.58
Yellow	8	16.67
Black	5	10.42
Native	1	2.08
Brown	27	56.25
Marital Status		
Single	11	22.92
Married	17	35.42
Stable union	13	27.08
Divorced	7	14.58
Education		
Illiterate	1	2.08
Complete Elementary School	3	6.25
Incomplete Elementary School	12	25.00
Complete High School	18	37.50
Incomplete High School	8	16.66
Complete University	2	4.17
Incomplete University	2	4.17
Complete post-graduation	2	4.17
Family Income		
Until 1 minimum wage	6	12.50
From 1 to less than 2 minimum wages (R\$ 788.00 to R\$1,575.99)	29	60.43
From 2 to less than 4 minimum wages (R\$ 1,576.00 to R\$3,151.99)	7	14.58
From 4 to less than 6 minimum wages (R\$ 3,152.00 to R\$ 4,727.99)	4	8.33
From 6 to less than 10 minimum wages (R\$ 4,728.00 to R\$ 7,879.99)	1	2.08
10 minimum wages or more (≥ R\$ 7,880,00)	1	2.08

before splitting the tablets, but seven (14.58%) claimed they did not wash their hands after splitting. For the hygiene of the instruments, 32 interviewees (66.67%) reported they cleaned them before and after using to split the tablets and four (8.33%) cleaned the instrument only before splitting. Some interviewees (n=12 [25%]) claimed

they neither clean before or after each splitting. There was a concern whether the responsible for splitting noticed any symptoms while splitting the tablets, two (4.17%) interviewees reported itching while splitting the tablets of mercaptopurine, while one interviewee (2.08%) had headache and nausea when this drug was split.

DISCUSSION

This study about oral antineoplastics tablets splitting utilized in the maintenance treatment of acute leukemias of children and adolescents revealed that the 48 interviewees had split to adjust individual dose in some moment. The calculation of the antineoplastic doses is

Table 2. Tablets splitting of mercaptopurine and thioguanine utilized by children and adolescents in treatment with acute leukemias during the interviewees

Tablets splitting	Interviewees (n)	Frequency (%)
Mercaptopurine		
Whole	15	31.25
Halves (1/2)	14	29.17
Quarts (1/4)	7	14.58
Halves and quarts (1/2 and 1/4)	9	18.75
Thioguanine		
Whole	0	0.0
Halves (1/2)	0	0.0
Quarts (1/4)	2	4.17
Halves and quarts (1/2 and 1/4)	1	2.08

initially performed through the body surface value (m^2), but must be adjusted according to leukometry^{3,16,17} for having relatively narrow therapeutic index and potentially fatal toxicity, mainly as myelosuppression^{18,19}, and for that reason, the prescription must be individualized.

The split antineoplastic tablets were mercaptopurine 50 mg and thioguanine 40 mg, which are analogous of purine nucleoside utilized in the treatment of acute leukemias¹⁸⁻²⁰. The practice of manipulating this chemotherapics for adjustment of individual dose is common⁹ considering the unavailability of proper formulations^{21,22}. Regulatory agencies in some countries have already approved the commercialization of oral suspension of mercaptopurine^{10,17,23}, but as it is not available in general, is far from being a Brazilian reality. The severity of acute leukemias in childhood and the problems associated to the correct dosage of antineoplastic demand proper oral pediatric formulations^{10,24}, because, despite being a severe disease, it has high rate of cure and survival if the treatment is conducted correctly^{4,5}.

The results demonstrated that when the interviews were being conducted, 33 (68.75%) of the interviewees were splitting these tablets at home to reach the therapeutic target-dose. Sometimes, it is observed, it was necessary more than one splitting to reach quarts. In the literature, it is discussed that as more tablets are split to reach quarts, higher will be the mass variation and weight loss, compromising its uniformity^{7,8,25}. Therefore, more

Table 3. Conditions of the antineoplastic tablets splitting process

Process of splitting	Interviewee (n)	Frequency (%)
Instrument utilized		
Tablets splitter	23	47.92
Knife	17	35.42
Hand	7	14.58
Stiletto	1	2.08
Place where tablets are split		
Kitchen	37	77.09
Room	7	14.58
Undefined	4	8.33
How split tablets are stored		
Vial of the antineoplastic containing split and whole tablets	38	79.17
Vial of the antineoplastic containing only split tablets	3	6.25
Other containers and tablets organizers	4	8.33
Inside tablets splitter	3	6.25

irregular fractions leads to fluctuation and inaccuracy of the dose^{7,26}. If splitting in more than one form (halves and quarts) is necessary according to the prescriptions, it may occur reduction of efficacy or increase of the toxicity because of confusion with the fractions that must be administered at every day, considering that tablets splitting can cause errors of medication²⁴.

Mercaptopurine and thioguanine tablets splitting is a concern, considering they are cytotoxic, hazardous agents and with relatively narrow safety margin^{11,12,17,27,28}. The contamination can be oral, topic and occurs through inhalation^{11,12,17,28}. Therefore, the conditions of the process of antineoplastic tablets splitting were evaluated.

In relation to the perception of changes in the antineoplastic split tablets, the results demonstrated that 16 interviewees (33.33%) reported tablets crumbling, which is potential damaging to the household environment²⁹. Crumbling interferes in the variation of weight that, according to Teixeira et al.³⁰, is one of the most important indexes to define the safety of the process of splitting because is directly related to the dose when the active substance is uniformly distributed in the tablet mass³⁰. In this study, it is still more relevant because they are cytotoxic chemotherapies^{11,12,17,27,28}, that can cause contamination and risk to the health of the individuals splitting the tablets²⁵, and for those using them. According to the experimental study of Breitzkreutz et al.²⁹ comparing methods utilized for extemporaneous preparations of mercaptopurine for children, until 0.46% of the total mass of the tablet of mercaptopurine is lost and released as cytotoxic dust at each procedure of splitting.

The instrument utilized to split the tablets is an important factor that can impact the crumbling. The results demonstrated that the main instruments utilized to split antineoplastic drugs were: tablets splitter, knife and hands. Tablets splitters are safe and easy to use³¹, but dexterity is required to place the tablet in the right spot avoiding irregular split tablets²⁶. In addition, because of its sharp blade, the splitter requires care and attention when used²⁵. An experimental study compared the use of tablets splitter and knife and demonstrated that the weight variation of the split tablets is lower with fractions cut with the splitter than with the knife³⁰. The experimental study of Habib et al.³¹ evaluated the accuracy of the splitting comparing the tablets splitter *versus* hands to cut salbutamol 4 mg pills and showed that the splitter is more accurate and better than the manual splitting because of lower variation of weight and drug content between the fractions. Fractions of tablets split by hand may deviate 20% of its ideal weight³², which is a risk for the wholeness of the tablet³¹. Therefore, it is discussed in the literature that when splitting cannot be avoided, the most indicated

form to split tablets is the splitter because of less variation and weight loss than other splitting methods³³.

The place where antineoplastics are split was also an important factor. The results demonstrated that the majority of the interviewees split in the kitchen, which is prejudicial since remains of split tablets can mingle with food and cause intoxication to whom ingest them^{17,28}. It should be avoided to eat, drink and store food where chemotherapies are administered and handled²⁸.

Another factor to be considered when splitting antineoplastic drugs is storage of fractions not administered. All the interviewees reported they stored fractions for future use. Remove tablets from the package to split can accelerate the degradation of the active principle and consequently, the administration of lower dose, further to potentializing adverse events²⁶. When many split tablets are stored in a package, risk of stability issues and inaccurate doses can increase^{25,32,34} because of the friction between fractions which can cause more drugs³⁴ crumbling. The literature reports that the best way to store fractions to be used later is to keep them in their own package to minimize environment^{34,35} exposure. For tablet organizers and other boxes, it is possible to occur exposure to environment humidity and to light^{34,35} like storing in the own tablet splitter. Storage in general brings concerns about the period the split tablets are exposed to air and light before they are used²⁶.

The hygiene of the manipulator of the antineoplastic drugs and the device used to split were also analyzed, it is important to emphasize that when dermal contact with chemotherapies cannot be avoided, strict hygiene practices must be followed¹⁴. The results demonstrated that all the interviewees washed their hands before splitting the tablets to ensure the safety of children and adolescents, but some of them did not wash their hands after splitting. Because of possible intoxication from handling these toxic drugs, as they can enter the body through inhalation, dermal absorption and mouth contact, hygiene is essential after the splitting process^{11,12,17,28,34} and can potentially cause cancer, toxicity and injuries to organs^{11,12,17,28}, representing risk for those who manipulate them. Contaminated hands can transfer residues to the mouth and other surfaces²⁸. Hands washing after handling antineoplastics is required, if possible, wear personal protective equipment as gloves^{11-14,17,28}, to avoid dermal contact and contamination by ingestion and inhalation. Protective and hygiene measures in general should be incorporated to the domestic environment to minimize the risk to everyone¹⁴.

In what concerns the hygiene of instruments utilized in antineoplastics splitting, it is important to emphasize that part of the interviewees reported not cleaning them before and after the splitting process and some of the interviewees

cleaned them only before. Crossed contamination caused by crumbling if different drugs are split with the same instrument can occur due to lack of hygiene^{25,32}.

Some interviewees reported symptoms as itching, headache and nausea. The exposure to hazardous drugs can result in acute and chronic adverse events, as rash, reproductive toxicity and even cancer^{11,12,17,27,28,36}.

Pediatric extemporaneous formulas can be advantageous over tablets splitting⁷. Therefore, as a possible strategy to avoid antineoplastic splitting at home, extemporaneous preparation in liquid suspension of mercaptopurine and thioguanine¹⁷ could be provided in chemotherapy specialized compounding pharmacies. Biosafety cabinets for manipulation need to be used as protection measures for professionals safety^{17,36}; and additional studies of stability need to be conducted to ensure the drug efficacy because this type of formulation may cause problems in this topic^{25,29}. However, the ideal would be to have antineoplastic liquid formulations available commercially.

The cross-sectional design of the study is a limitation that hampers the definition of causality. Another potential limiting factor might be the number of children/adolescents and caretakers interviewed, and the fact that the study was conducted in only one health facility. Finally, the comparison was conducted with experimental studies considering the paucity of clinical trials addressing pediatric antineoplastic tablets splitting at home.

CONCLUSION

The investigation of the frequency of antineoplastic tablets splitting showed that all the interviewees have already split to adjust the individual dose. When splitting cannot be avoided as in the case of the chemotherapies in study because of the unavailability of proper formulations, it is important to standardize this practice, reducing the risk for children, adolescents and caretakers. Health services must incorporate information about safe handling of antineoplastics. It is important to conduct more studies and more investments for proper pediatric formulations.

CONTRIBUTIONS

All the authors contributed substantially for the conception and design of the study, wording, critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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