ORIGINAL ARTICLE

Chemotherapy in Pediatric Oncology Patients and the Occurrence of Oral Mucositis

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Abstract

Background: It is known that chemotherapeutic agents are not equally stomatotoxic and oral cavity lesions are the most frequent complications encountered in antineoplastic chemotherapy.

Aims: The objective of this study was to evaluate the occurrence of severe oral mucositis during a chemotherapy treatment and to identify its relationship with the chemotherapeutic class used.

Materials and methods: This is a longitudinal, prospective, and observational study that used an intensive direct observation technique for assessing the oral clinical conditions and the chemotherapy treatment administered to 105 patients (both children and adolescents).

Results: Severe oral mucositis occurred in all the 10 weeks of evaluation (ranging from 16.2 to 31.4%) and the association between the type of chemotherapy and the occurrence of severe oral mucositis is recorded only in the 6th week, with the chance to develop severe oral mucositis being 3.07 (3.85–2.29) times higher in patients underwent chemotherapy with antimetabolites than in those who have not used chemotherapy ($p = 0.012$).

Conclusion: It was concluded that the chemotherapeutic agents most related to severe oral mucositis and to the interruption in chemotherapy are those of the class of antimetabolites, especially the methotrexate and the Ara C.

Keywords: Chemotherapy, Dentistry, Oncology, Pediatric, Severe oral mucositis.

International Journal of Clinical Pediatric Dentistry (2019): 10.5005/jp-journals-10005-1633

Introduction

The antineoplastic chemotherapy used either alone or in combination with surgery and/or radiotherapy is the main mode of treatment for cancerous children. The chemotherapy involves the use of injectable pharmaceuticals, which cause a reduction of immunity, leading to the appearance of a series of oral amendments. Thus, it is necessary to follow the dental treatment along with the antineoplastic treatment, enabling the prevention and control of these amendments.[1,2]

Chemotherapy is used in order to rapidly destroy the proliferative malignant cells; however, it leads to side effects, affecting normal tissues with high mitotic rates, such as the oral mucosa, the gastrointestinal tract, and the hematopoietic tissue. Depending on the type, dosage, and frequency of administration of chemotherapeutic agents, severe or serious complications in the oral mucosa may arise.[3,4]

It is known that chemotherapeutic agents are not equally stomatotoxic, and the most commonly used medications for treating neoplasms are vincristine, taxol, citarabin (Ara C), adriamycin, 5-fluorouracil, cyclophosphamide, cisplatin, and methotrexate. Of these medications, the last four were mostly found to be involved with the emergence of changes in the oral mucosa.[2,4–6]

Oral cavity lesions comprise the most frequent complications of antineoplastic chemotherapy owing to the high sensitivity of oral tissues to the toxic effects of chemotherapeutic agents. The most common oral problems in children and adolescents in chemotherapeutic treatment are: mucositis; xerostomia; rampant caries; periodontal diseases; bacterial infections, virus apparitions, or fungal; and changes in the formation of dental germs in cases of treatment during the phases of the odontogenesis stages.[4,5]

Studies have shown that the younger the patients, the higher the chances of a chemotherapy resulting in oral health adverse effects.[7–9] Such oral manifestations can lead to major systemic complications, interfering in medical therapeutics.[4]

Approximately 15 days after the chemotherapy session, patients usually show immunosuppression.[6] Therefore, any alteration in the integrity of the oral mucosa, carious processes, and outbreaks of odontogenic infection becomes a major risk for the development of another oral and systemic infections.[10–12]

Thus, the objective of this study was to evaluate the occurrence of severe oral mucositis during chemotherapy treatment and to identify the relationship with the chemotherapeutic type used.

Material and Methods

Ethical Approval

This study was approved by the Ethics Committee in research with human beings, under CAAE of number—12922113.8.0000.5188 of April 23, 2013.

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How to cite this article: Ribeiro ILA, de Andrade Lima Neto E, *et al.* Chemotherapy in Pediatric Oncology Patients and the Occurrence of Oral Mucositis. Int J Clin Pediatr Dent 2019;12(4):261–267.

Source of support: Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior (CAPES)

Conflict of interest: None

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Study Design

This is a longitudinal, prospective, observational study that used an intensive direct observation technique for assessing the oral clinical conditions and the chemotherapy treatment administered to patients.

Spatial Location of the Study

This study was conducted at the pediatric sector of the Napoleão Laureano Hospital, in the city of João Pessoa-PB, Brazil, which is a reference center dealing with the prevention, diagnosis, and treatment of cancer for the whole state of Paraíba, performing about 7,000 monthly attendances between consultations, examinations, and surgeries, offering treatment to about 3,300 patients per month.

Sample

The study sample was of convenience type, in which all patients were included from 0 to 19 years attended by the Health Unic System in the Napoleão Laureano Hospital, who were diagnosed and treated for some kind of malignant neoplasia in the period of April 2013 to July of 2015. A total of 115 patients were included in the study throughout the evaluation period, which corresponded to all patients who entered the hospital for diagnosis and treatment in the said period, selected by examination of hospital census, weekly; however, for having been counted 10 losses throughout the segments, the final sample on which the analyses and inferences of this study were conducted was of 105 patients. The losses corresponded to: 1 death in the 3rd week; 2 deaths in the 6th week and 2 transfers to another hospital unit; 1 patient who initiated the radiotherapy in the head and neck and 2 deaths in the 8th week; and 2 deaths in the 9th week of accompaniment.

Data Collection

The data collection was performed weekly, with each patient evaluated for 10 consecutive weeks, immediately after the onset of chemotherapy treatment. The choice of this evaluation period was based on the fact that an average time of 2 months and a half was sufficient to identify changes in the oral mucosa arising from the chemotherapy imposed.[7,8,13]

The variables of interest were: gender, age, type of base disease (hematologic or not), time since the last chemotherapy, chemotherapy class, frequency of chemotherapy, and the number of interruptions in chemotherapy, either by the severe oral mucositis, for other reasons.

For the weekly evaluation of the oral mucosa, the modified oral evaluation guide was used (Oral Assessment Guide OAG),[7,14] which is easy to apply and specially constructed to evaluate the oral mucositis in children. It is primarily used for simplicity (limited to a total of 8 items) and applicability, requiring only 3–4 minutes for complete the evaluation. This instrument allows to evaluate eight items, according to the oral health compromise scales, with the values awarded being 1–3 for each item: 1—for conditions where normality is verified; 2—for the verification of mild-to-moderate changes in relation to epithelial integrity or function; 3—for a severe compromise. In the end, the total verified mucositis varies from 8 to 24; there is no cutting point between these values for the estimation of mucositis.

Calibration for identification of the oral mucositis, using the Oral Assessment Guide modified, was conducted among a researcher considered the gold standard (doctor in stomatology) and the researcher who conducted evaluations during all periods of evaluation. The calibration was performed in the dental office environment of the Napoleão Laureano Hospital, where 20 patients were evaluated between 0 year and 19 years, which were already under the treatment regimen only with the use of chemotherapy. The value of kappa obtained for the evaluator was 0.87, indicating that it obtained an excellent evaluation when compared to the gold standard, and is therefore calibrated for the realization of the evaluations.

The information on the chemotherapy regimen to which patients were subjected were collected in the medical records of each of the patients, with all the information of interest collected only at the end of the evaluation segment, in order not to influence the analyses of the degrees of oral mucositis, with priority given to the following information: the type of chemotherapeutics administered; chemotherapy administration frequency (number of times the patient received medication since the last evaluation).

For the survey of the chemotherapeutics, we used the classification of the National Sanitary Surveillance Agency,[15] which classifies the different antineoplastic compounds into 4 classes: agents alkylating, antimetabolites, natural products, and miscellaneous.

The evaluations of the presence of oral mucositis were performed in the dental office of the Pediatrics Department of the Napoleão Laureano Hospital, in the room where patients were subjected to chemotherapy or in beds in which patients found themselves admitted. In the impossibility of performing the evaluations under the ideal lighting, which is the dental office, the patients were evaluated in the beds under adapted conditions of lighting, with the use of flashlights.

The patients followed in this study received the necessary dental treatment, according to the needs perceived in the initial oral examination, and in some cases the realization of an initial oral adequacy was requested by doctor, when checking that the compromise of oral mucosa or dental elements could result in interruption of antineoplastic treatment, which would imply losses in the course of the treatment. Furthermore, since the cancer diagnosis and in all the antineoplastic treatment period, the patient instructions oral hygiene, in order to ensure that this factor is maintained, the oral problems arising from the chemotherapy treatment can be evaluated with greater ownership.

Data Analysis

The data collected were organized in a Microsoft Excel database and analysed by descriptive statistics in the R Software (version 3.1.2).

In the analysis of the data, the outcome was determined, taking into consideration that, in the OAG, the condition receiving the value "3" is the condition that can result for the patient in the main limitations as to speech, swallowing, and exposure to local and systemic infections, modifying the quality-of-life, and still compromising the ongoing antineoplastic therapy, with the interruption of the same for the establishment of an antibiotic treatment to contain a probable infection installed. In view of these aspects, we have opted to combine the values for the OAG "1" and "2" in a nominal category called "without severe oral mucositis", which received in the database the code "0" and the value "3" in another nominal category called "with severe oral mucositis", which received in the database the code" "1", the latter being the end of interest and, thereby becoming the dichotomized outcome. When was adopting this criterion, in the verification of the value

"3" in one or more of the oral cavity sites evaluated in the OAG, the patient's condition for mucositis orally became characterized as with the presence of oral mucositis, since it indicated the presence of ulceration in one or more sites, which makes the clinical picture, in the face of this condition, more worrying, comparison of the other conditions evaluated in the OAG.

Results

Of 105 patients included in this present study, 57 (54.3%) were males. The average age of patients was 7.30 years (±5.17), with the median of 7.30, minimum of 0 and maximum of 18 years, having a greater concentration of malignant neoplasm of the ages of 2 (n = 18; 17.0%), 3 (n = 10; 9.5%) and 4 years (n = 16; 15.2%). A total of 51 (48.6%) of neoplasms were solid tumors.

As you can observe in the distribution of Table 1, the severe oral mucositis, in this present study ranged from 16.2% to 31.4% in relation to the involvement in the different evaluation periods, presenting a 18.1% involvement of the sample already in the 1st week after the onset of chemotherapy and the highest values in the 2nd (14 days) and 8th (56 days) weeks, affecting these last two periods, 31.4% of children and adolescents in chemotherapy treatment.

Among the patients who had severe oral mucositis, compared to those who did not have it, in the different periods, the drugs most consumed were: in the 1st week [methotrexate (21.0%) and Ara C (15.8%)]; in the 2nd week [methotrexate (24.3%), vincristine (24.2%), and Ara C (21.2%)]; in the 3rd week [methotrexate (20.0%) and vincristine (27.5%)]; in the 4th week [vincristine (25.9%)]; in the 5th week [methotrexate (47.7%)]; in the 6th period [Ara C (38.7%)]; in the 7th week [Ara C (31.8%)]; in the 8th period [methotrexate (24.3%) and vincristine (24.3%)]; in the 9th week [Ara C (23.5%)] and, in the 10th week [vincristine (41.1%)] (Table 2).

The association between the type of chemotherapy and the occurrence of severe oral mucositis was recorded only in the 6th week, with the chance to develop severe oral mucositis being 3.07 (3.85–2.29) times higher in patients who underwent chemotherapy with antimetabolites, compared to those who have not used chemotherapeutic of this group (p = 0.012).

Table 3 shows the distribution of the median and medium (±standard deviation) for the time since the last chemotherapy and the administration frequency of the chemotherapeutic in each evaluation week. It is observed that with the advancement of antineoplastic treatment time, the time interval between the last chemotherapy and the occurrence of severe oral mucositis.

Interruptions in chemotherapy due to the occurrence of severe oral mucositis (n = 10; 66.6%) occurred in a greater number than those related to other causes (n = 5; 20.7%), and took place especially in the 2nd; 3rd; 5th; 6th and 7th weeks, affecting 3.0%; 10.3%; 9.5%; 6.5%; and 9.1% of patients with severe oral mucositis, respectively (Table 4).

Table 1: Distribution of severe oral mucositis and type of chemotherapy administered during the different evaluation weeks (n = 105)

Week	*Frequency of patients with severe oral mucositis*	*Chemotherapy class*	
1	19 (18.1%)	Alkylating agents	21 (20.0%)
		Antimetabolites	42 (40.0%)
		Natural products	58 (55.2%)
		Miscellaneous	15 (14.3%)
2	33 (31.4%)	Alkylating agents	14 (13.3%)
		Antimetabolites	47 (44.8%)
		Natural products	57 (54.3%)
		Miscellaneous	17 (16.2%)
3	29 (27.6%)	Alkylating agents	15 (14.3%)
		Antimetabolites	45 (42.9%)
		Natural products	60 (57.1%)
		Miscellaneous	15 (14.3%)
4		Alkylating agents	11 (10.5%)
	27 (25.7%)	Antimetabolites	50 (47.6%)
		Natural products	54 (51.4%)
		Miscellaneous	15 (14.3%)
5	21 (20.0%)	Alkylating agents	12 (11.4%)
		Antimetabolites	56 (53.3%)
		Natural products	47 (44.8%)
		Miscellaneous	16 (15.2%)
6	31 (29.5%)	Alkylating agents	13 (12.4%)
		Antimetabolites	51 (48.6%)
		Natural products	54 (51.4%)
		Miscellaneous	17 (16.2%)
7	22 (21.0%)	Alkylating agents	12 (11.4%)
		Antimetabolites	56 (53.3%)
		Natural products	49 (46.7%)
		Miscellaneous	17 (16.2%)
8	33 (31.4%)	Alkylating agents	11 (10.5%)
		Antimetabolites	57 (54.3%)
		Natural products	49 (46.7%)
		Miscellaneous	17 (16.2%)
9	17 (16.2%)	Alkylating agents	14 (13.3%)
		Antimetabolites	53 (50.5%)
		Natural products	49 (46.7%)
		Miscellaneous	18 (17.1%)
10	17 (16.2%)	Alkylating agents	13 (12.4%)
		Antimetabolites	55 (52.4%)
		Natural products	49 (46.7%)
		Miscellaneous	17 (16.2%)

Discussion

In this study, the age groups corresponding to children (0–12 years) and adolescents (12–18 years),[16] since treating the age group of 0–19 years is the responsibility of a pediatric oncologist, especially the band of 15–19 years, which has long been left aside, both in epidemiological studies and in the focus of the attendances in oncology because of not having the definition of who should take care of them. Moreover, in reason of the similarity in histology and the behavior of tumors in children and adolescents, the latter has been incorporated into the treatment programs and protocols before only applied to children; mainly by observations that concluded that the tumors affecting teenagers were more responsive to the therapeutic agents administered to children than those applied to adults.[17]

The largest male involvement has also been verified in other studies[18–20] and the average age of involvement corroborates the

Table 2: Main drugs used for patients with and without severe oral mucositis in the different weeks

Severe oral mucositis		*Type of chemotherapeutic agents*									
Week		*Actinomicin D*	*Ara C*	*Cyiclophosphamide*	*Daunorrubicin*	*Doxorrubicin*	*Ifosfamide*	*Interferon*	*Methotrexate*	*Vincristine*	*Cisplatin*
1	Yes	0 (0.0%)	3 (15.8%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	4 (21.0%)	3 (15.8%)	0 (0.0%)
	No	5 (5.9%)	11 (12.8%)	5 (5.9%)	5 (5.9%)	3 (3.5%)	2 (2.3%)	1 (1.2%)	17 (19.8%)	23 (26.9%)	1 (1.2%)
2	Yes	0 (0.0%)	7 (21.2%)	1 (3.0%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	8 (24.3%)	8 (24.2%)	2 (6.0%)
	No	4 (5.6%)	7 (9.7%)	1 (1.4%)	1 (1.4%)	3 (4.2%)	2 (2.8%)	1 (1.4%)	14 (19.5%)	17 (23.6%)	2 (2.8%)
3	Yes	0 (0.0%)	2 (6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	21 (20.0%)	8 (27.5%)	1 (3.4%)
	No	4 (5.3%)	11 (14.5%)	5 (6.5%)	1 (1.3%)	3 (3.9%)	2 (2.6%)	0 (0.0%)	15 (19.7%)	18 (23.6%)	0 (0.0%)
4	Yes	0 (0.0%)	5 (18.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	4 (14.8%)	7 (25.9%)	0 (0.0%)
	No	4 (5.1%)	10 (12.8%)	1 (1.3%)	1 (3.7%)	3 (3.8%)	0 (0.0%)	1 (1.3%)	21 (26.9%)	14 (18.0%)	1 (1.3%)
5	Yes	0 (0.0%)	4 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (47.7%)	3 (14.3%)	0 (0.0%)
	No	4 (4.8%)	14 (16.7%)	2 (2.4%)	1 (1.2%)	3 (3.6%)	2 (2.4%)	1 (1.2%)	22 (26.2%)	13 (14.3%)	3 (3.6%)
6	Yes	4 (12.9%)	12 (38.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (16.1%)	5 (16.1%)	1 (3.2%)
	No	0 (0.0%)	12 (16.2%)	2 (2.8%)	1 (1.4%)	3 (4.1%)	2 (2.7%)	1 (1.4%)	17 (23.0%)	19 (25.8%)	2 (2.8%)
7	Yes	4 (18.2%)	7 (31.8%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	3 (13.6%)	3 (13.6%)	0 (0.0%)
	No	0 (0.0%)	15 (18.1%)	2 (2.4%)	0 (0.0%)	3 (3.6%)	0 (0.0%)	1 (1.2%)	18 (21.6%)	18 (21.6%)	3 (3.6%)
8	Yes	4 (12.1%)	4 (12.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.0%)	0 (0.0%)	8 (24.3%)	8 (24.3%)	0 (0.0%)
	No	0 (0.0%)	16 (22.2%)	4 (5.6%)	1 (1.4%)	3 (4.2%)	2 (2.8%)	1 (1.4%)	14 (22.2%)	13 (18.1%)	3 (2.8%)
9	Yes	0 (0.0%)	4 (23.5%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	3 (17.6%)	0 (0.0%)
	No	4 (4.5%)	8 (9.1%)	3 (3.4%)	2 (2.3%)	3 (3.4%)	1 (1.1%)	1 (1.1%)	24 (27.3%)	20 (22.6%)	3 (3.4%)
10	Yes	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.8%)	7 (41.1%)	0 (0.0%)
	No	4 (4.5%)	11 (12.5%)	5 (5.6%)	1 (1.1%)	3 (3.4%)	1 (1.1%)	2 (2.2%)	23 (26.2%)	14 (15.9%)	4 (4.5%)

The absolute and percent frequencies distributed in this table do not correspond to the totality of drugs used in the different chemotherapy protocols instituted to the patients of this study. The drugs listed here are included in the following classes according to ANVISA (BRAZIL. 2013): alkylating agents (cyclophosphamide; ifosfamide); antimetabolites (Ara C; methotrexate); natural products (actinomycin D; daunorubicin; doxorubicin; vincristine); miscellaneous (cisplatin)

Table 3: Median, mean, and standard deviation values for the time since the last chemotherapy and for the frequency of chemotherapy administration in the time intervals between the evaluations for the oral mucositis grade in the different evaluation periods distributed as to who had or did not have severe oral mucositis

Severe oral mucositis for follow-up week		*Time median/mean (standard deviation)*	*Frequency median/mean (standard deviation)*
1	Yes	8.00/8.53 (±4.94)	1.00/5.53 (±3.61)
	No	5.00/6.48 (±5.65)	1.00/1.40 (±0.88)
2	Yes	7.00/11.58 (±15.89)	1.00/3.76 (±2.53)
	No	7.00/8.60 (±6.73)	1.00/1.50 (±1.16)
3	Yes	9.00/10.03 (±6.33)	1.00/1.34 (±0.72)
	No	7.00/8.26 (±6.54)	1.00/1.88 (±2.00)
4	Yes	8.00/8.37 (±5.00)	1.00/1.59 (±1.11)
	No	8.00/11.31 (±7.21)	1.00/1.86 (±1.99)
5	Yes	8.00/8.86 (±6.11)	1.00/1.62 (±1.11)
	No	8.50/12.44 (±10.22)	1.00/1.81 (±1.78)
6	Yes	13.00/12.19 (±6.12)	3.00/2.55 (±1.52)
	No	10.00/14.09 (±12.53)	1.00/6.80 (±2.96)
7	Yes	14.00/13.82 (±8.42)	2.00/2.55 (±1.53)
	No	8.00/15.29 (±15.94)	1.00/2.02 (±2.04)
8	Yes	9.00/8.76 (±4.71)	1.00/1.67 (±1.10)
	No	10.00/18.93 (±27.12)	1.00/1.97 (±1.91)
9	Yes	12.00/10.41 (±5.08)	1.00/1.88 (±1.31)
	No	8.00/18.66 (±35.29)	1.00/1.61 (±1.29)
10	Yes	8.00/8.06 (±4.64)	1.00/1.88 (±1.16)
	No	9.00/20.29 (±42.88)	1.00/1.86 (±1.82)

Table 4: Absolute frequency and percentage values for the distribution of patients who had interrupted treatment during the different periods, owing to severe oral mucositis or other causes, for those who had or for those who did not have severe oral mucositis

Treatment week	*Interruptions in treatment due to severe oral mucositis n (%)*	*Interruptions in treatment due to other reasons n (%)*
1	0 (0.0%)	0 (0.0%)
2	1 (3.0%)	1 (3.0%)
3	3 (10.3%)	2 (6.9%)
4	0 (0.0%)	0 (0.0%)
5	2 (9.5%)	0 (0.0%)
6	2 (6.5%)	1 (3.2%)
7	2 (9.1%)	1 (4.5%)
8	0 (0.0%)	0 (0.0%)
9	0 (0.0%)	0 (0.0%)
10	0 (0.0%)	0 (0.0%)

findings of Camargo et al.[21] and they have presented values close to those found by Cheng et al.,[18] which verified an average of 7.6 and a standard deviation of 5.2 for the 102 patients evaluated in their study.

The percentage of solid tumors of this study resemble that reported by Kung et al.[20] when evaluating 69 patients, 43.4% of basic diseases constituted solid tumors and other tumors. It can be observed that there was a slight difference between solid tumors and tumors that reach the blood and lymph tissues ($n = 54$; 51.4%). Other studies have also shown a greater prevalence of involvement of children and adolescents in hematology-based diseases than in solid tumors.[8,20,22]

The average time of the induction phase of the remission of tumors under a chemotherapy regime lasts from 1 to 2.5 months; generally, it is after this period that chemotherapy in combination with other treatments such as radiotherapy and surgery[13] are considered. Moreover, the main complications of oral mucositis usually appear in this initial treatment period.[7,8] For these reasons, the evaluations were chosen for the first 10 weeks of treatment, including an average of 2.5 months, where it was possible to assess at what times of the chemotherapy treatment severe oral mucositis was present.

Although Mendonça et al.[23] have conducted a study assessing only two moments for the occurrence of severe oral mucositis in children and adolescents under the chemotherapy treatment regime, the same periods of time were evaluated (14th and 56th days), and the occurrence of an even greater number of cases (63.1% and 36.9% of 103 evaluated patients, respectively) were found. The study in question evaluated only patients with LLA and included cases of inflammation in the oral mucosa, the absence of ulceration, in addition to the cases considered in the present study as oral mucositis, which Mendonça et al.[23] considered as severe mucositis. This last fact may be the reason why the percentage of involvement shown by the patients included in this study is greater for the two periods of time.

In the present study, the result obtained during the first period of evaluation of the occurrence of severe oral mucositis is in accordance with the results found by Cheng et al.,[8] which was one of the few studies in literature to discriminate against mucositis ulceration of the other types of mucositis. In a period of 14 days, a rate of 2–18% of the occurrence of severe oral mucositis was noted after initiating the chemotherapy treatment, corroborating the findings of this study for the initial treatment period.

Although they studied the oral mucositis and the severity of oral mucositis, the two studies cited earlier[8,23] were the most approached in methodological terms of the present study because they had conducted a prospective study from the initial moment of the chemotherapy treatment and to have studied variables nearby and conducted statistical analyses similar to the present study. However, the follow-ups were short, with daily reports being made by the patients themselves and their caregivers, during the first 14 days of the therapeutic treatment[8] and with evaluations on the 14th and 56th days after the onset of chemotherapy,[23] which can demonstrate the importance of the novelty of this present study in performing evaluations for 10 consecutive weeks, in a time of ±70 days ±2.5 months, corresponding to one of the most critical stages of the antineoplastic treatment, which is the induction phase of the remission of the tumors,[13] with an extensive margin for the protocols that may have been interrupted for some reasons, including the occurrence of the severe oral mucositis.

As presented in the methodology of this study, as well as in the study of Cheng et al.,[8] not only ulcerative lesions were considered as characterized by a severe oral mucositis, but also the pain and difficulty of speaking,[24] the inability to swallow;[6] the total absence of saliva, and bleeding gums.[6] Such factors limit the quality-of-life and the survival rate of these patients, on the grounds that the pain and difficulty to speak are associated with inflammation/loss of tissue continuity of mucosal linings.[6,26] Similarly, the inability to swallow is closely associated with changes in the tissue, according to Scully, Epstein, and Sonis.[25] Malnutrition retards the healing process

of lesions of oral mucositis, which makes a worrisome clinical picture of the patient . Nutrition is crucial in all stages of the antineoplastic treatment[27] and the treatment may be conditional on the limitations arising from injuries in the oral mucositis cavity.[6,28] These factors can affect the patient's health status in reason of difficult to nutrition before the diagnosis inherent to cancer in development.[29]

When initiating treatment, the ideal is that pediatric oncology patients get an oral nutritional diet, which may not be possible if some of these comorbidities for severe oral mucositis come to occur. As pain and discomfort may arise during feeding in the absence of saliva, with pain to swallow or to chew/move food, a change in any of the factors evaluated in this study by the modified OAG can contribute to reducing the frequency and acceptance of oral foods.[6]

In the face of these facts, in the present study, treatment measures for the severe oral mucositis have been imposed over the evaluation periods for all patients who are presented with severe oral mucositis. The treatment protocol of these injuries comprised the use of the laser therapy of low potency, which has been regarded as an efficient therapy in the treatment of the oral mucositis,[30,31] and there is still no consensus regarding the amount of energy to be used, but the wavelength in general is between 660 nm and 670 nm, and the potency between 40 mW and 60 mW.[32] For the children presented with severe oral mucositis, a low-power laser (ECCO fibers and devices/Brazil; N/S—040401; Model—BM0004A) calibrated for a wavelength of 670 nm, a power of 40 mW, and a dose of 4 J/cm^2 was applied for 30 seconds. in the reddish and ulcerated regions with or without pseudomembrane.

In addition to the treatment protocol for active injuries, during monitoring of the presence/absence of oral mucositis, there has been a constant counseling of the child/adolescent and/or the caregiver responsible for oral hygiene care. Brushing with soft brushes in light, circular movements, with the bristles passing through the teeth and gums was performed whenever the patient feeds. In addition, a careful use of yarn or dental ribbon at night; use of mouthwash with a 0.12% alcohol-free chlorhexidine solution once a day (for patients above 2 years old); the orientation for a frequent intake of water; and the use of a lip moisturizer are also recommended.

It was not the objective of this study to assess the progression of oral mucositis, preventing possible treatments from being imposed, as the main objective was to predict the occurrence of severe oral mucositis in different periods so as to assist the team involved in treating these children and adolescents to prevent the occurrence of these injuries. In this study we adopted a protocol for prevention, weekly surveillance and treatment of oral mucositis lesions. On the contrary, the fact that children and adolescents have received treatment only for injuries reinforces the thesis that the occurrence rates in each evaluation period are worrisome, since most children were treated for injuries in a week, and in the next evaluation (one week after), these lesions were usually healed or included as an oral mucositis degree "2" by OAG modified, indicating the possibility that at the second time of evaluation (with a 7-day interval), those who presented themselves with severe oral mucositis could be new patients.

The class of alkylating agents (10.5–20.0%) was the therapeutics least administered to patients, together with the class of the miscellaneous type (14.3–17.1%). Treatment with antimetabolites constitute 40.0–54.3% in all evaluation periods. The chemotherapeutic class is mostly used in the 5th, 7th, 8th, 9th, and 10th evaluation periods.

Natural-type pharmaceutical products were the most widely used in the chemotherapy of children and adolescents included in this study, with a rate of utilization ranging from 44.8% to 57.1%. This class was even more administered than the antimetabolites. There is a current trend for the use of antineoplastic medications included in the group of natural products because recent surveys have permitted the production of less-aggressive chemotherapeutic agents to the organism as a whole, with more selectivity for tumor cells.[33,34]

This study was conducted in 10 consecutive weeks, featuring 10 different periods of time. This study was conducted for 10 consecutive weeks, with 7-days of interval between evaluations. However, the time between chemotherapy doses varied within the evaluation weeks. This is because for each child/adolescent, the treatment protocols vary according to the time interval given for the administration of antineoplastic drugs mainly in this study, where all children with cancer were included, and there is no selection of subtypes. Moreover, depending on the results of blood tests, nutritional condition, and the existence of oral or systemic infections, the chemotherapy treatment needs to be interrupted until there is a reversal or improvement in patients' clinical status. Such disruptions resulted in larger time intervals between the last time the evaluated patient received chemotherapy and the period in which he was evaluated. However, temporary interruptions between chemotherapy and another did not constitute a limiting factor for the evaluations of this study in relation to the variable "time" in view that, if all children/adolescents make use of the chemotherapeutic with the same interval of time, it would not be possible to test the hypothesis that time is a conditioning factor for the emergence of severe oral mucositis, as did Cheng et al. Testing time as influence of the emergence of the mucositis and finding that the average time for the occurrence of the oral mucositis was 4.7 ± 2.7 days.

The main chemotherapeutic agents used in the patients in this study and the presented percentage frequencies of use greater than those of other types for patients with MOG in the different periods (methotrexate, Ara C, and vincristine) are also described in the literature as the most associated with adverse effects, including the oral mucositis.[4,5,25] Furthermore, one of the chemotherapeutic agents (the cisplatin) that has shown a lower frequency of use among the patients who presented MOG in different periods is also described by Albarran[5] as the antineoplastic is less aggressive and less associated with adverse reactions, such as the oral mucositis.

It was concluded that the chemotherapeutic agents most related to severe oral mucositis and to the interruption in chemotherapy due to this condition are those of the class of antimetabolites, especially the methotrexate and the Ara C. This study suggests that it is necessary to conduct a major surveillance in oral health to pediatric oncology patients who will be submitted to antineoplastic treatment with these drugs.

Highlights

This study is the one of a kind in the international literature that evaluated pediatric patients for a follow-up of 10 weeks after the start of chemotherapy treatment. This study suggests that it is necessary to conduct a major surveillance in oral health to pediatric oncology patients who will be submitted to antineoplastic treatment with methotrexate and the Ara C.

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