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ORIGINAL ARTICLE

Oral Mucositis in Children with Leukemia Undergoing Chemotherapy: A Case Series

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ABSTRACT

Objective: To report nine cases of pediatric patients with Acute Lymphoid Leukemia (ALL) or Acute Myeloid Leukemia who developed severe oral mucositis (SOM) at the first week of chemotherapy. **Material and Methods:** The cases were selected from a sample of 105 children followed for 10 consecutive weeks. Hematological and personal data were obtained from the patient's medical records. The oral cavity was examined weekly using the modified Oral Assessment Guide. **Results:** More of the patients were male (55.6%), had black/brown skin (55.6%), with ALL (66.7%), and the mean age was 5.55. Two patients had values below normal for leukocytes, platelets, and creatinine over the follow-up. However, all patients showed changes in the normality of hematological data in most weeks. The most used chemotherapeutic agents were aracytin, etoposide, and methotrexate, known for their high stomatotoxic potential. Patients had 2 to 6 (mean of 4) episodes of SOM and 4 to 7 (mean of 5.5) episodes of OM. One patient at week 7, one patient at week 5, and one patient at weeks 2 and 10 did not have OM. Saliva (84 times) and lips (44 times) were the most affected items. **Conclusion:** The patients showed oscillations in the severity of oral mucositis and hematological parameters over the follow-up. All patients were exposed to stomatotoxic drugs during the initial phase of cancer treatment.

Keywords: Mucositis; Stomatitis; Hematologic Diseases; Child; Drug Therapy.

Introduction

Leukemias are hematological tumors of unknown origin which transform normal blood cells in the bone marrow into non-functional and rapidly proliferating cells through a genetic mutation. Acute Lymphoid Leukemia (ALL) is the most common in young children and Acute Myeloid Leukemia (LMA) affects children and adults, but its incidence rises with increasing age. Acute injuries are treated through a combination of chemotherapy drugs and conducted in stages according to the type of tumor [1].

Oral mucositis (OM) is the most common local adverse event of chemotherapy treatment in children and adolescents; however, it also affects the patient's systemic condition, leading to a debilitating condition from the patient's perspective. In this regard, appropriate management of OM must be taken into account during the course of therapy [2-4]. Oral mucosal damage caused by chemotherapy tends to be acute, reaching its peak within two weeks after starting treatment [4].

Younger individuals are more likely to develop oral mucositis than adults because of the rapid epithelial mitotic rate; however, the healing process occurs more rapidly than in adults for the same reason [5]. There are different risk factors potentially involved in the development of oral mucositis in pediatric patients, being considered a multifactorial event. The risk factors considered are chemotherapeutic agents, underlying disease [6], specific individual characteristics, hematological, renal, and hepatic parameters [7], genetic profile and biomarker factors [8], and oral microbiota [9,10].

Understanding how risk factors relate to the occurrence and duration of OM is crucial to prevent the interruption of medical treatment and increase the likelihood of a patient's cure. Therefore, the aim of this study was to report nine cases of pediatric patients with leukemia who developed severe oral mucositis (SOM) at the first week of chemotherapy.

Material and Methods

Ethical Clearance

The procedures performed in this study were observed by the Ethics Committee for Research with Human Beings of the Health Sciences Center of the Federal University of Paraíba under the protocol CAAE: 64249317.3.0000.5188 and conducted in accordance with the ethical principles of the Declaration of Helsinki. All the children gave their assent to participate and informed consent was obtained from all their parents or legal guardians.

Data Collection

Medical reports of nine patients of both genders, between 2 and 16 years old, were included, diagnosed with Acute Lymphoid Leukemia (ALL) or Acute Myeloid Leukemia (AML) and were followed for 10 consecutive weeks between April 2013 and July 2015 in the Pediatric Oncology sector at Napoleão Laureano Hospital, a reference center for prevention, diagnosis and cancer treatment, located in the northeast region of Brazil.

The reported cases are part of a sample of 105 patients between 2 and 18 years old with a diagnosis of solid and hematological tumors but did not develop the severe form in the initial days of treatment. The primary outcomes results have been previously published [11].

Prior to the study, the patients should not have started antineoplastic treatment; they were expected to exclusively undergo chemotherapy treatment for the next 10 weeks, not have mucosal inflammation before starting chemotherapy, and have severe oral mucositis (SOM) in the first week of follow-up.

Monitoring of the oral cavity was performed weekly using the modified Oral Assessment Guide (OAG) by a calibrated researcher (Kappa>0.85). Patients who developed OM were treated with a multi-component solution [12] and with low-level laser therapy until complete remission of signs and symptoms of the lesions according to the protocol: wavelength of 670nm, power of 40mW, and dose of 4J/cm², applied locally for 30s on reddish, erosive and/or ulcerated regions [11]. In addition, all patients received oral care instructions (brushing and dental floss technique, alcohol-free chlorhexidine solution, and lip hydration) or treated other problems in the oral cavity.

The OAG is a simple and fast instrument applicable to children that assesses the following items through scores of 1 to 3: voice, swallowing, lips, tongue, saliva, oral/mucosal palate, labial mucosa, and gums. Scores 1 and 2 indicate normal and slight changes in oral structures and functions without lesions, respectively, while score 3 represents severe alterations in one or more items [13].

Serum rates were categorized as altered to values below 3,500 or above 10,000 for leukocytes and below 150,000 or above 450,000 for platelets. Creatinine concentrations below 0.5mg/dl or above 1.0 mg/dl were also considered altered.

Results

More of the patients were male (n=5, 55.6%), had black/brown skin (n=5, 55.6%), with ALL (n=6, 66.7%), and the mean age was 5.5±4.4. Diagnosis of tumor type, chemotherapy regimen, type of blood, and presence of metastasis were collected from medical records. Table 1 describes the characteristics of each patient.

All patients were newly diagnosed with the tumor and were in the induction phase of cancer treatment. Aracityn (ARAC), Aracityn associated with Etoposide (AE), and Methotrexate (MTX) were the most commonly administered drugs during the 10 weeks. Patients 4 and 6, both with AML, only used ARAC, while patient 1 (with ALL) only used MTX during data collection.

Table 1. Characterization of patients with leukemia and severe oral mucositis.

Patient	Gender	Age (Years)	Skin Color	Hematological Tumor	Chemotherapy Regimen
1	Male	2	Black	ALL	MTX
2	Male	16	Black	ALL	AD/ARAC/AE
3	Male	4	Black	ALL	AE/ARAC
4	Male	3	Brown	AML	ARAC
5	Female	6	Brown	ALL	VD/ARAC/CP
6	Female	3	White	AML	ARAC
7	Female	9	White	AML	ARAC/AD
8	Female	3	White	ALL	MTX/AMC/ARAC/CP/PM
9	Male	4	White	ALL	AE/ARAC

ALL = Acute Lymphoid Leukemia; AML = Acute Myeloid Leukemia; MTX = Metotrexate; AD = Aracityn+Daunoblastin; ARAC = Aracytin+Cytarabine; AE = Aracityn+Etoposide; VD = Vincristine+Daunorubicin; CP = Cyclophosphamide; AMC = Aracytin+Metotrexate+Cyclophosphamide; PM = Purinethol+Metotrexate.

The hematological status of patients was collected weekly from medical records (Table 2). Patients 4 and 6 had values below normal for leukocytes, platelets, and creatinine over the 10 weeks of follow-up. However, all patients showed changes in the normality of hematological data in most weeks.

Patients had 2 to 6 (mean of 4) episodes of SOM and 4 to 7 (mean of 5.5) episodes of OM during the 10 weeks of follow-up. Patient 2 at week 7, patient 6 at week 5, and patient 8 at weeks 2 and 10 did not have oral mucositis (OAG=8). Lips and saliva were the most affected items (Table 3).

Table 2. Leukocyte count, platelet count, and creatinine levels of patients with leukemia.

Patient	Week																													
	1			2			3			4			5			6			7			8			9			10		
	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C	L	P	C
1	N	↑	N	N	N	N	N	N	N	↓	↓	↓	↓	↓	↓	N	N	↓	↓	N	↓	↑	↓	N	↑	N	N	N	N	N
2	↓	N	↑	↓	N	N	N	N	↓	↓	↓	↓	N	N	↓	N	N	↓	N	↓	N	↓	N	N	↓	N	N	↓	N	N
3	N	↑	↓	N	N	N	↓	↓	↓	N	↓	↓	N	N	↓	↓	N	↓	N	N	N	↓	N	↓	N	N	N	N	N	N
4	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
5	N	↑	↓	N	↑	↓	↓	↓	↓	↓	↓	↓	↓	N	↓	↓	N	↓	↓	↓	↓	↓	↓	↓	↓	N	↓	↓	N	↓
6	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
7	↓	N	↑	↓	↓	N	↓	↓	N	↓	N	N	↓	N	N	↓	↓	↓	↓	↓	N	N	N	↓	N	↑	↓	N	↑	↓
8	↓	N	↓	N	↑	N	N	N	N	↓	↓	N	↓	↓	↓	↓	↓	N	↓	↓	N	↓	N	N	↓	N	N	↓	N	N
9	N	↑	↓	N	N	N	↓	↓	↓	N	↓	↓	N	N	↓	↓	N	↓	N	N	N	↓	N	↓	N	↑	N	N	N	N

L = Leukocyte count; P = Platelet count; C = Creatinine; ↓ = Below normal value; N = Normal value; ↑ = Above normal value.

Table 3. Occurrence of oral mucositis, severe oral mucositis, and affected sites of patients with Leukemia.

Patient	Affected Sites by SOM and OM									
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	Tongue, saliva, gums	Lips, saliva	Saliva	Lips, saliva, labial mucosa	Lips, saliva	Saliva	Saliva	Lips, saliva	Saliva	Lips, saliva, labial mucosa
2	Lips, saliva	Lips, saliva	Lips, saliva	Saliva, oral mucosa	Lips, saliva, labial mucosa	Lips, saliva	No mucositis	Lips, saliva	Lips, saliva	Lips, saliva
3	Lips, saliva	Lips, saliva, labial mucosa	Lips, saliva, labial mucosa	Saliva	Lips, saliva	Saliva, labial mucosa	Saliva	Lips, saliva	Lips	Saliva
4	Saliva	Saliva	Lips, saliva	Saliva	All sites	Saliva	Saliva	Saliva	Saliva	Saliva
5	Lips, saliva	Lips, saliva	Lips, saliva	Lips, saliva	Lips, saliva	Lips, saliva	Saliva	Saliva	Lips, saliva	Saliva
6	Saliva, gums	Saliva, labial mucosa	Lips, tongue, saliva, oral mucosa, labial mucosa, gums	Lips, saliva	No mucositis	Saliva	Saliva	Saliva	Saliva	Saliva
7	Lips, saliva	Lips, saliva	Lips, saliva, oral mucosa, gums	Saliva	Lips, saliva	Lips, saliva	Lips, saliva, oral mucosa, labial mucosa, gums	Saliva	Saliva	Saliva, labial mucosa, gums
8	Lips, tongue, saliva	No mucositis	Saliva	Lips, saliva, labial mucosa	Saliva	Swalling, lips, tongue, saliva, labial mucosa, gums	Tongue, saliva, oral mucosa	Saliva	Tongue, saliva	No mucositis
9	Swalling, saliva	Saliva	Lips, saliva, labial mucosa	Lips, saliva	Lips, saliva	Lips, labial mucosa	Saliva	Lips, saliva	Saliva	Saliva

SOM = Severe Oral Mucositis (in Blue); OM = Oral Mucositis (in Green).

Discussion

In the present study, nine patients with ALL or AML who developed severe oral mucositis in the first week of chemotherapy treatment were selected. These patients showed oscillations between the mild/moderate and severe forms of the lesion over the 10 weeks of follow-up.

Systematic reviews show that the incidence of oral mucositis is high among oncopediatric patients, ranging from 20% to 80% [10] and 16.7 to 91.5% [6]. Oral mucositis is the result of the stomatotoxic action of chemotherapy or radiotherapy drugs on the DNA of the basal cells of the oral epithelium, as well as from damage to the adjacent connective tissue, leading to a series of biological events that culminate in the appearance of ulcerations [14].

Burning, dryness, erythema, edema, changes in the papillae, hoarseness, and difficulty in swallowing are observed in the early stages [15,16]. Therefore, daily oral health surveillance is necessary when the objective is to prevent or minimize the clinical signs of oral mucositis [17].

On the other hand, we suggest that there are variables related to cancer treatment and variables related to the patient, which apparently allow similar individuals to present different oral complications and intensity. The selected individuals in this study were similar in age, tumor type, and chemotherapy regimen.

With regard to treatment-related variables, the occurrence of oral mucositis varies between 20% and 100% depending on the type of malignancy, chemotherapeutic drug type, and chemotherapy regimen [18,19]. Patients with hematological tumors are also at higher risk of developing oral mucositis when compared to patients with solid tumors [11].

Although treatment protocols for ALL and AML are different, the goal of treatment in the early stage is to achieve complete disease remission through a combination of chemotherapy. Then, treatment is continued according to the type of cancer [1].

The drugs used in the treatment of the nine cases included the classes of alkylating, antimetabolites agents, natural products, and miscellaneous. According to Sonis [4], ARAC, MTX, and Etoposide present a risk of 20, 23 and 20%, respectively, of developing severe oral mucositis. These were the drugs most used in the treatment of reported cases. Patients who undergo the same chemotherapy regimen may experience oral complications in different degrees depending on the dose and frequency of drug administration [6,15].

The cytotoxic effect of chemotherapeutic agents also depends on their mechanism of action, which may be specific for a phase of the cell cycle that requires prolonged exposure or repeated doses or unspecific for the phase of the cell cycle and, therefore, more dose-dependent [20].

Patient-related variables such as age, nutritional status, type of mucosa, oral microbiota, oral health and hygiene status, salivary secretory function, neutrophil counts, molecularly targets, and genetics can increase or reduce the risk for the severity of oral mucositis [8,21,22]. The variability in the factors that lead the patient to develop oral mucositis, even in homogeneous and controlled samples, is a challenge in determining their risk [4]. The authors, in a recent systematic review with meta-analysis, highlighted the association of MTX with other drugs, oral microbiota, and gene variants as important risk factors in the development of oral mucositis [10].

Garrocho-Rangel et al. [23] described a case series of 11 children with ALL followed for 14 days after being treated with MTX as a chemotherapy agent. However, none of them presented SOM. The changes occurred in the lips, tongue, buccal mucosa, and gingiva. In our study, children were followed for 10 consecutive weeks after starting chemotherapy (including methotrexate) and developed severe oral mucositis in the first week of cancer treatment.

Some hematological parameters such as neutrophil, platelet, and creatinine counts are possible risk factors for oral mucositis [10]. As the neutrophil count decreases, the severity of oral mucositis increases in pediatric oncology patients who have received chemotherapy [24]. Neutropenic children are 7.5 times more likely to develop oral mucositis [25]. However, it is not possible to establish any association of hematological parameters with the occurrence and severity of oral mucositis in this study. The occurrence of oral mucositis was observed even in the patients whose blood rates were within the reference values.

The onset of oral mucositis may be early (4 to 7 days) or later, and its complete remission within 7 to 14 days after discontinuing the therapy [16]. The cases reported show alterations in the oral cavity between 1 and 11 days after the last dose of the chemotherapy. However, the brief appearance of such changes was due to the frequency of doses. Patient 3 received three doses of AD in the first week of treatment.

Damascena et al. [2] found that the remission time of severe oral mucositis was 30.6 days in oncopediatric patients. They also found that age (over 10 years old) and the absence of metastasis increase the duration of MOG by 1.4 times and 1.7, respectively. Several methods have been used to manage OM, including Low-Level Laser Therapy, which has been found to reduce the incidence of any grade of OM by 90% (95% CI 0.81-1.00; p=0.06) and can reduce SOM duration [3].

Although the patients appeared to develop some degree of oral mucositis during the 10 weeks of follow-up, even with weekly applications of laser therapy, the clinical improvement of the patients was notable when compared to the time when the research group did not use this technology. Peng et al. [3] highlighted that the risk of developing SOM was not significantly lower (p=0.13) with laser applications at 2-day intervals compared with that in the control group.

The Oral Assessment Guide (OAG), as well as the main toxicity scales, combine objective, functional, and symptomatic aspects, applying them to eight specific anatomical areas [4]. Therefore, it is necessary to check the affected sites at each new exam to verify the improvement or worsening of the patient's clinical condition when using the OAG or a similar scale. In this study, the reduction in the OAG values was due to clinical improvement in the same affected sites, while worsening was due to the involvement of new sites in the oral cavity. Guimarães et al. [26] highlighted the importance of monitoring the likely sites most affected by SOM so that the strategies are more effective.

Most oral complications related to chemotherapy occur within the second week after starting treatment. The establishment of ulcerations causes discomfort and pain when speaking, swallowing, drinking, and eating. In addition, the exposure of connective tissue associated with reduced care with oral hygiene due to pain makes the individual susceptible to infections in the oral cavity. Thus, the patient's systemic condition can worsen and lead to interrupting cancer treatment. However, it is possible to plan more effective actions from the knowledge of the possible risk factors for oral mucositis to reduce the incidence of this condition.

Conclusion

The patients showed oscillations in the severity of oral mucositis and hematological parameters over the 10 weeks of follow-up, making it impossible to assign risk factors for the occurrence of oral mucositis in the first week of chemotherapy treatment; however, all patients were exposed to stomatotoxic drugs during the initial phase of cancer treatment. Due to the risk of oncopediatric patients presenting severe oral mucositis early in treatment, well-designed observational studies are needed to better understand the risk factors for developing oral mucositis and the need for a multidisciplinary team to monitor pediatric patients undergoing chemotherapy to prevent and avoid the worsening of this expected condition.

Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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