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Oral mucositis in paediatric acute lymphoblastic leukemia patients receiving methotrexate-based chemotherapy: case series

ABSTRACT

Aim *Oral mucositis (OM) is a painful and inflammatory ulcerative lesion occurring as an adverse effect during chemotherapy in children with acute lymphoblastic leukemia (ALL). This condition may cause significant systemic anomalies such as malnutrition, opportunistic infections, and delay in the chemotherapy course. This report aims to describe a case series of 11 ALL patients treated with methotrexate as chemotherapy agent.*

Case series *Each patient was carefully followed-up and orally examined for 14 days after their chemotherapy session. OM occurred in all children. Then, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) management protocol for OM was applied to them. The mean time of the lesion total resolution was 3.7 days.*

Conclusions *It is necessary to emphasise the importance of early detection of OM through a close clinical oral examination of children and adolescents with ALL undergoing methotrexate chemotherapy. Pain/infection control and the maintenance of good levels of oral hygiene are fundamental during the management of OM. Therefore, paediatric dentists need to be part of the oncology care team, and thus contributing and helping with ALL treatment.*

Keywords *Acute lymphoblastic leukemia, Chemotherapy, Children, Methotrexate.*

Introduction

Cancer in children and adolescents is currently considered as a major public health issue worldwide, with an incidence rate increasing 1% every year [Ghandi et al., 2017]. According to recent report it is estimated that during 2017, 10,270 children aged 0 to 14 years were diagnosed with cancer and 1,190 of them died due to the disease. The most common types of cancer in children are leukemias, followed by brain and other central nervous system tumors, lymphomas, soft tissue sarcomas, neuroblastomas, and kidney tumors [Siegel et al., 2017]. Leukemia is considered the most prevalent underlying disease in paediatric patients. It is a malignancy of the bone marrow and blood, characterised by the uncontrollable and excessive production of immature leukocytes, hindering the normal production of red and white cells, as well as platelets [Javed et al., 2012; Morais et al., 2014; Ribeiro et al., 2017]. Out of leukemias, 60-85% are cases of acute lymphoblastic leukemia (ALL). ALL accounts for three fourths of all newly diagnosed leukemias and one fourth of all cancers in childhood, with a peak incidence at 4 years of age [Arora et al., 2009; Ponce-Torres et al., 2010; Ribeiro et al., 2017]. Common manifestations of ALL in the oral cavity are gingival bleeding, hyperplasia, opportunistic infections, and bone alterations [Javed et al., 2012; Azher and Shiggaon, 2013; Morais et al., 2014].

Two treatment modalities widely accepted for ALL are chemotherapy alone, or combined with radiation [Azher and Shiggaon, 2013]. The main choices of chemotherapy drugs for children include adriamycin, cytarabine, etoposide, and methotrexate [Fong-Cheng et al., 2011]. Methotrexate (MTX) is a folate analog widely used anticancer drug for childhood malignancies, which possess anti-proliferative activity in malignant cells through the inhibition of the dihydrofolate reductase enzyme; this process inhibits the synthesis of thymidine, thereby stopping cell replication [Chu and Sartorelli, 2007]. This agent can completely erase most of cancer cells, but it is not exempt of early and long-term cytotoxic effects, such as damage to normal tissues, particularly those characterised by rapid cell division rates, like the oral mucosa proper [Ghandi et al., 2017].

Around 40% of children treated with MTX chemotherapy suffer mild to severe oral complications, such as mucositis, infection, trismus or xerostomia [Azher and Shiggaon,

2013]. The most common of these adverse effects is oral mucositis (OM) or the inflammation and ulceration of the oral mucosa [Moslemi et al., 2016]. The frequency of OM has been reported to be around 65% in paediatric cancer patients [Harris et al., 2008; Didem et al., 2014], and is clinically manifested as oedematous, erythematous, atrophic, and friable areas, commonly associated with white desquamative patches in the oral mucosa [Figliolia et al., 2008]. It results in pain, discomfort, and dysphagia, together with difficulties in swallowing, eating, drinking, talking, poor nutrition, systemic weakness, and, in severe cases, life-threatening infections [Figliolia et al., 2008; Moslemi et al., 2016]; these conditions can cause psychological distress and impairment of quality of life and functional status [Mendonça et al., 2015; Ribeiro et al., 2017]. OM appears 3 to 7 days after chemotherapy initiation and persists up to 3 weeks, reaching its peak between 7-14 days, and then resolves slowly [Rimulo et al., 2011; Mendonça et al., 2015].

The aim of the present report is to describe and discuss the clinical oral presentation and management evolution of a case series of paediatric patients affected from mild to severe OM during the chemotherapy, employing MTX as an anticancer agent during the induction phase.

Case series

Eleven patients diagnosed with ALL under 17 years old were orally examined for the presence of mucositis after receiving at least one methotrexate chemotherapy session, between July and December 2017, in the Paediatric Oncology Clinic (Hospital Central "Ignacio Morones Prieto", San Luis Potosí, México). After the necessary permission from the institution's Research Ethics Committee, written informed consent was obtained from the parents of each patient; confidentiality was warranted about a child's identifying or personal information.

During the initial interview, a personal information was filled out that identified the demographic characteristics of the patient and her/his family. Each child was examined in detail (lips, tongue, palate, buccal mucosa, labial mucosa, and gums) five times in a period of 14 days: day 0 (basal) and days 1, 3, 7, and 14 after the chemotherapy session. Presence, anatomical characteristics, grade of OM, and other findings were evaluated according to WHO Oral Mucositis Assessment Scale [WHO, 1979] developed to describe toxicities associated with a particular chemotherapy agent or regimen (Table 1) [Sonis et al., 1999; Didem et al., 2014]. This process was performed by a same researcher, who was pre-calibrated by means of intra and inter-observer Cohen's Kappa tests (0.89 and 0.93, respectively). In this case, clinical photographs were taken and supportive treatment was provided, according to the recommendations from Moslemi et al. [2016]; each patient was followed-up until lesion resolution.

Six girls and five boys were examined. The age range of the patients was 3-12 years, with a mean of 8.01±2.6 years (female = 7.6±1.8; male = 8.5±2.1). The mean age when the ALL diagnosis was performed was 6.5 years. One patient was in chemotherapy induction phase and 10 in consolidation (maintenance) phase; the latter reported an average of 4.3 chemotherapy cycles. The mean time for the lesion total resolution was 3.7 days after initial detection.More than half of patients exhibited grade 1 OM (Fig. 1), and the rest a grade 2 (Fig. 2). None of them presented grades 3 or 4. In general, the most common oral anomalies observed in this small sample were painful ulcers on the lower lip mucosa surrounded by an erythematous/edematous halo, erythematous gums, dehydrated lips, and tongue or buccal mucosa erosions. Most children manifested poor oral hygiene levels and dental caries.

Table 2 summarises the principal clinical oral findings of each patient at the different days of evaluation.

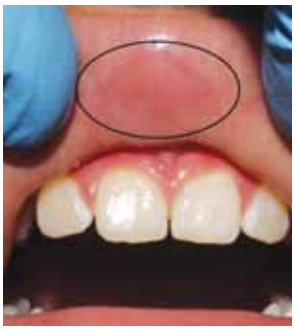

FIG. 1A

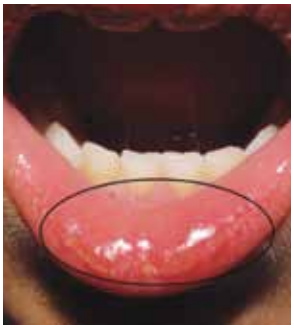

FIG. 1B

FIG. 1 Representative images of grade 1 OM. One typical finding is the presence of painless mild erythema in the vermilion border of one or both lips. In this particular case it was evident an angular cheilitis on the right side.

Grade	Characteristics
0	No mucositis present
1	Irritation of OM with pain
	No overt ulceration
	Normal diet
2	Sores evident in oral mucosa
	Patient still able to swallow solid food
3	Extreme sensitivity when swallowing solid food
	Liquid diet necessary
4	Inability to swallow
	Parenteral nutrition or tube feeding necessary

TABLE 1 The WHO system criteria for grading OM. Taken and adapted from Moslemi et al., 2016.

Discussion

Chemotherapy is employed to treat approximately 70%

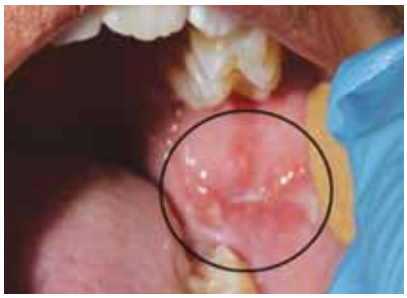

FIG. 2A

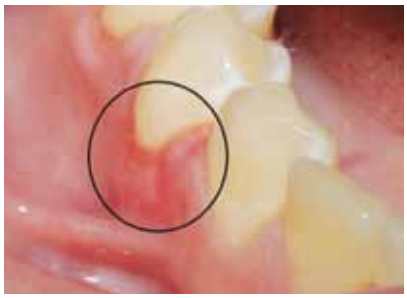

FIG. 2B

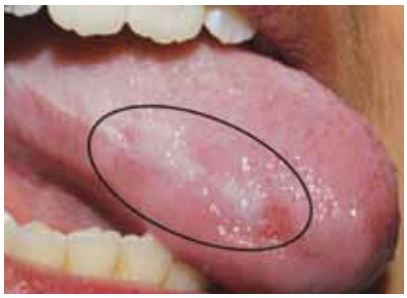

FIG. 2C

FIG. 2 Representative images of OM grade 2. It was evident the presence of sore ulcerations and erosions in different soft-tissue areas of the oral cavity.

Patient no.	Basal characteristics	Day 1	Day 3	Day 7	Day 14	OM grade
1	DHL, PalGum, PaleMuc	DHL, EL, EG, FT	DHL,	DHL	DHL, ACh	1
2	DHL	DHL, EG, FT	DHL	DHL	DHL, EMB	2
3	DHL, DBP, POH	DBP, DHL, EL, Ulc, POH	EMB, Ach, Ulc, POH	EMB, Ach, Ulc, POH	EMB, Ach, POH	2
4	DBP, POH	DHL	DHL, EL	DHL, EL, FT	DHL	1
5	NAPD	Ulc, EMB	Ulc, tongue Er	Ulc, tongue Er	NAPD	2
6	DBP, DHL	EL	Ulc, EL, EG	Ulc, EL	Ulc	2
7	DBP, POH	NAPD	EL, Er	EL, Er	NAPD	1
8	POH	EL, EG	EL, EG	EL, EG	EL	1
9	DHL, POH	EMB, EG, Er	EMB, EG,	EMB, EG,	NAPD	1
10	DHL, PalGum	Ulc, Er	Ulc, Er	Ulc, Er, EL	Ulc	2
11	DHL, POH	NAPD	EL, EMB, EG	EL, EMB, EG	EL	1

Abbreviations: DHL= dehydrated lips, EL= erythematous lips, EMB= Erythematous buccal mucosa EG= Erythematous gums, PalGum= pale gums, PalM= pale mucosa, Ulc= ulcer (s), POH= poor oral hygiene, DBP= evident dentobacterial plaque, ACh= angular cheilitis, Er= erosion, FT= furry tongue. NAPD= no apparent pathological data

TABLE 2 Principal oral findings detected during the follow-up period.

of cancer patients [Velten et al., 2017]. Diverse previous studies have demonstrated direct stomatotoxic effects of the anticancer chemotherapy or radiation over the mitosis of proliferating oral basal epithelium [Fong-Cheng et al., 2011]. Although the individual risk of occurrence of OM cannot be predictable in children undergoing chemotherapy, several risk factors, related to both therapy and patient, have been associated with this condition, including age, female gender, time of ALL diagnosis, pre-treatment body weight, blood type, underlying malignant disease, serum creatinine levels, baseline neutropenia, poor oral hygiene, alterations in salivary productions, concomitant presence of herpes simplex virus, renal and liver dysfunction, and specific chemotherapy regimen or protocol [Fong-Cheng et al., 2011; Ye et al., 2013; Mendonça et al., 2015]. In this regard, it has been mentioned that the risk of OM is increased during the treatment of ALL with those cell-cycle specific and myeloablative chemotherapy agents (that kills cells in the bone marrow, including cancer cells), such as MTX, and also with the use of pro and antiinflammatory mediators (cytokines or pro-LL37) based-therapies [Fong-Cheng et al., 2011; Ye et al., 2013; Velten et al., 2017]. Additionally, recent studies have suggested that differences in the expression of genes related to chemotherapy and OM pathogenesis may increase the risk of the condition; however, this theory still remains unclear [Fong-Cheng et al., 2011].

In spite of the very small sample of patients reported here, our findings about OM incidence in children with ALL treated with chemotherapy are consistent with previous studies, in which this parameter was reported as moderately high [Mendonça et al., 2015]. For example, Figliolia et al. [2008] estimated that among 169 ALL children treated with diverse chemotherapy protocols in a Brazilian hospital during 1994 to 2005, 77 of them (46%) developed OM. The higher incidence of OM reported in children than in adults can be explained by the higher mitotic rate of basal cells exhibited in children, which causes the loss of the ability of the oral mucosa epithelium to renew itself and consequently in atrophy, thinning, and symptomatic ulceration of the soft tissues [Figliolia et al., 2008].

The main impact related to OM is that the presence of this condition often interrupts the chemotherapy process, and this means that the affected children reduce their chances

to be cured. As a consequence, the chemotherapy cycles cannot continue until the lesions have healed [Ribeiro et al., 2017]. Therefore, the continuous and watchful oral status monitoring of these patients is crucial for the prevention or treatment of inflammatory lesions or ulcers, particularly on the lower lip mucosa and tongue, which can reduce functions such as chewing, swallowing, or speaking [Harris et al., 2008; Ribeiro et al., 2017]. However, and according to the paediatric dentistry literature, there is a lack of consensus about an accepted management strategy or a specific drug capable to effectively prevent or treat OM in children [Cheng et al., 2004; Harris et al., 2008; Rimulo et al., 2011]. According to Didem et al. [2014], 29 different types of interventions for treating OM were reported in a Cochrane review performed in 2014 from 71 published randomized clinical trials, most of them carried out in adult samples. These included amifostine, chlorhexidine gluconate, ice chips chewing, tablets with antibiotics, topical anesthetics, moisturizers, and diverse oral care protocols. As mentioned above, in the present study we adopted the conventional management protocol for OM in children recently recommended by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) [Moslemi et al., 2016]. In general, the protocol comprises patient education and supportive care: use of non-medicated saline rinses, topical and systemic pain management, hydration, nutritional support, and infection control; besides, the patient must be entered into a rigorous oral hygiene programme, incorporating training and frequent practice of tooth brushing with soft bristles, dental flossing, and the use of gentle non-medicated mouth washes. On the other hand, the Basic Oral Care Group [McGuire et al., 2006] has suggested other additional measures. Because OM may significantly delay the chemotherapy drug control process and increase the treatment and hospital supportive care costs, this disorder should be prevented or opportunely managed. Thus, the Paediatric Dentist must be part of the multidisciplinary medical team contributing and helping with the treatment of cancer-affected paediatric patients in the clinical setting. This specialist should be aware of oral anomalies associated both to ALL and also to the treatment provided, in order to improve the child's oral health status.

Conclusions

It is strongly recommended that the paediatric dentist performs frequent clinical assessments of the oral health status of children with ALL after the start of chemotherapy, in order to early recognize the possible occurrence of OM. The adequate management of this painful condition may prevent significant comorbidities and interruption of the chemotherapy course. Pain/infection control and the maintenance of oral hygiene are essential. Therefore, the Paediatric Dentist needs to be included in the oncological care team during the management of children and adolescents suffering ALL. The final and most important goal when applying a therapeutic intervention to decrease the impact of OM is to improve the quality of life of these patients and their families.

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