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ORIGINAL ARTICLE

Prophylactic photobiomodulation therapy using 660 nm diode laser for oral mucositis in paediatric patients under chemotherapy: 5-year experience from a Brazilian referral service

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Abstract

The use of photobiomodulation therapy (PBMT) in the prevention of oral mucositis (OM) in paediatric care has increased. In this article, we report data of paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients treated with PBMT to prevent chemotherapy-induced OM. A retrospective study was conducted at a Brazilian referral service. Prophylactic PBMT was used in children and adolescents (≤ 17 years) following the protocol: InGaAlP, 660 nm, 100 mW, 2 J, 3.33 W/cm^2, and 20 s per point. Demographic data and OM severity scores were assessed. A regression model tested the association between OM with prophylactic PBMT and antineoplastic therapy. A total of 148 individuals who had undergone 358 chemotherapy cycles were analysed. A higher occurrence of OM was observed in HSCT and osteosarcoma (OS) patients. Except for HSCT, OM was associated with methotrexate (MTX) use in all disease groups. PBMT significantly reduced OM severity in acute lymphoblastic leukaemia (ALL) and OS patients. OM grade was 3.16 and 5.45 times higher among individuals with ALL and OS, who had not undergone prophylactic PBMT compared with those who had undergone prophylactic PBMT ($p < 0.001$). PBMT prevented chemotherapy-induced OM. Individuals who used MTX and did not undergo prophylactic PBMT were at increased risk of OM.

Keywords Cancer · Chemotherapy · Haematopoietic stem cell transplantation · Methotrexate · Oral mucositis · Paediatric oncology

Introduction

Paediatric cancers are a significant cause of the global burden of disease, even when compared with other disorders of youth or with adult cancers [1]. Despite the differences of the global epidemiological aspects across countries, childhood cancer is the sixth leading cause of total cancer burden and the ninth leading cause of childhood disease burden worldwide [1],

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with an incidence of 155.8 cases per million yearly [2]. In Brazil, the median incidence rate of childhood cancer is 154.3 per million, and the most common cancer types among children and adolescents are leukaemia, lymphoma and central nervous system tumours [3]. Treatment protocols vary widely according to the type of disease and staging. Nearly 50% of children and adolescents undergoing cancer treatment, particularly 5-fluorouracil (5-FU), busulfan, cisplatin, doxorubicin, etoposide, melphalan, methotrexate (MTX), taxanes and vinblastine, have developed oral complications [4–7].

Oral mucositis (OM) is a significant cause of morbidity in patients submitted to chemotherapy before haematopoietic stem cell transplantation (HSCT) despite the marked improvements in supportive care [8]. Almost 70% of individuals receiving HSCT develop OM and, particularly in the paediatric group, severe mucositis has been observed [9]. Generally, the high severity of OM is more associated with allogeneic than autologous transplantation, mainly due to the conditioning regimen and the graft-versus-host disease prophylaxis [8]. A high risk of oral and gastrointestinal mucositis has been reported in paediatric patients undergoing HSCT due to the use of busulfan, thiotepa, melphalan, etoposide and total body irradiation [10].

The inflammatory process and loss of epithelial barrier in OM generates intense pain and discomfort, impairing speech, swallowing and eating, and also causing oral ulceration. Chemotherapy-associated immunosuppression also increases the risk of fungal/viral infections [11], which may occur concomitantly with OM. It has been argued that microbiome can trigger the onset of OM. However, until now, what is understood is that all changes in both the microbiome and the mucosa are directly linked to the drugs used in the treatment [12]. Of note, these conditions directly affect the quality of life of individuals, influence the survival rates and increase cancer treatment costs [13]. For instance, in 2007, Elting et al. [14] reported that, depending on the grade of OM, an incremental cost of US$ 1700–6000 was needed due to increased use of resources, hospitalisation time, drug prescriptions and other reasons. Considering the Brazilian Unified Health System, Antunes et al. [15] reported that the incremental cost-effectiveness ratio was US$ 4961.37 per case of severe OM.

The well-established clinical efficacy of photobiomodulation therapy (PBMT) in the prevention of OM is leading to an increased use in Oncology and HSCT paediatric care [16–18]. PBMT is a safe, feasible and effective treatment because it accelerates mucosa recovery and reduces inflammation and pain [13, 15, 17–20]. Studies have reported inflammation as a central component of the pathogenesis of OM and have expanded the role of growth factors, inflammatory and proinflammatory cytokines, as well as transcription factors such as NF-κB [12, 21]. Mechanistically, PBMT protocols are helpful in reducing the severity of OM by modulating inflammatory pathways [13, 15, 21].

More recently, a systematic review conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) [20] stated that there were no guidelines for the use of intraoral PBMT in the prevention of OM in oncology individuals treated with chemotherapy. The lack of randomised clinical trials and the significant variability of the PBMT parameters preclude the definition of a reliable protocol [20]. Nevertheless, the benefits of wavelengths from 660 to 970 nm in the prevention of chemotherapy-induced OM in paediatric oncology patients have been reported elsewhere [20]. Intraoral PBMT is also highly beneficial for the prevention of OM and related pain in individuals undergoing HSCT conditioning regimens [20–23].

Although many studies on the prevention or minimisation of the severity of OM in individuals receiving chemotherapy have been published, most participants included in these assessments are adults [24]. Considering the paucity of studies in the literature in which prophylactic PBMT is only associated with chemotherapy-induced OM—in particular among children and adolescents with cancer and/or undergoing HSCT—the purpose of our study was to report a 5-year experience of prophylactic PBMT in chemotherapy-induced OM and associated factors in paediatric oncology/HSCT from a Brazilian referral service. Moreover, it is of clinical relevance to identify the most vulnerable groups in a routine service in order to intensify care for these individuals.

Methods

Study design and ethical considerations

In a retrospective analysis from 2012 to 2016, the medical records of patients who had developed chemotherapy-induced OM and had been treated at the Paediatric Oncology and Haematopoietic Stem Cell Transplantation services, Hospital das Clínicas, Universidade Federal de Minas Gerais (HC/UFMG), Belo Horizonte, Brazil, were evaluated. The report of this study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and statement [25]. The study was approved by the Ethics Committee of UFMG (No. 69069917.5.0000.5149).

Patients and data collection

Data on children and adolescents (up to 17 years) who had undergone cycles of chemotherapy and had received prophylactic PBMT were retrieved. Data of some individuals were collected when they had already started chemotherapy treatment; therefore, they were submitted only to therapeutic PBMT and no prophylactic PBMT had been provided to these

individuals. Information regarding sex, age, baseline disease and the chemotherapy protocol used was recorded. Cases with confirmed diagnosis of cancer were assigned according to the International Classification of Childhood Cancer [26]. Non-malignant cases diagnosed in individuals with HSCT were assigned according to the International Statistical Classification of Diseases and Related Health Problems (ICD-11) (e.g. severe haemoglobinopathies) [27]. In parallel, neutrophils counting and bone marrow engraftment in patients undergoing HSCT were also recorded [28, 29]. The chemotherapy protocols used for each disease are shown in Supplementary Table 1.

Information on the anatomical site of OM lesion was considered as follows: lips, labial mucosa, labial commissure, buccal mucosa, vestibule, floor of the mouth, tongue (lateral border, ventral, dorsal), retromolar trigone, palate and oropharynx. The anatomical location was not analysed in terms of number of patients, but rather in terms of number of lesions presented, i.e. the same patient may have been affected at more than one anatomical site.

Exclusion criteria were incomplete or illegible medical records, as well as records of patients who had received radiotherapy or those who had received concomitant chemoradiotherapy.

OM evaluation

Measurement of the severity of OM was scored according to the World Health Organization (WHO) classification [30], as follows: grade 0, no signs or symptoms; grade 1, erythema without lesions; grade 2, ulcerated mucosa, but the patient was able to feed normally; grade 3, individual with painful ulcers, individual who ingested only liquids; and grade 4, individual who required a parenteral diet. The clinical evaluation of OM and application of PBMT were undertaken by previously calibrated general dentists (LFMN and RCCS) from the HC/UFMG. Disagreements between assessors were solved upon discussion until a consensus emerged.

Device information, irradiation parameters and treatment standards

The device information of diode laser, irradiation parameters and treatment standards of the PBMT are described in Table 1 [31]. The irradiation parameters and treatment standards employed in PBMT according to previously published methods [22, 32].

Oral health care assessment

Preventive strategies were used prior to or during chemotherapy cycles to attenuate the severity of chemotherapy-induced OM. The strategies included the maintenance of adequate oral hygiene and oral hygiene protocols, such as daily tooth brushing, application of petroleum-based or lanolin-based lip care products and the control of oral conditions (e.g. dental caries, periapical disorders or periodontal infections).

Opportunistic infections associated with OM evaluation

Clinically suspected opportunistic infections associated with OM were confirmed by cytopathological examination.

Data analysis

The Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) was used for statistical analysis of the data. Descriptive statistics was carried out to characterise the distribution of chemotherapy-induced OM in individuals with malignant lesions/HSCT according to chemotherapy cycle. The chi-square test was used for analysis of categorical data. Univariate analysis was performed to describe the likelihood of individuals undergoing MTX treatment to present OM compared with individuals not undergoing MTX treatment. Due to clinical relevance, regression analysis was applied to evaluate the association between OM severity and PBMT, controlled for MTX administration. For all analyses, the level of significance was set at < 0.05.

Results

Characteristics of patients with chemotherapy-induced OM

Data of 148 children and adolescents who had undergone 358 cycles of chemotherapy were analysed. Eighty-two (55.4%) individuals were males and 66 (44.6%) were females (male-to-female ratio 1.2:1). Affected individuals' mean age was 9.2 (± 4.6) years (range 8 months to 17 years).

The most common malignant neoplasm was acute lymphocytic leukaemia (ALL), with information being available for 74 (50.0%) individuals who had experienced 190 cycles of chemotherapy. Data for 30 (20.3%) individuals with osteosarcoma (OS) who had performed 83 cycles of chemotherapy, 23 (15.5%) individuals with acute myeloid leukaemia (AML) who had undergone 51 cycles of chemotherapy, six (4.1%) individuals with Burkitt lymphoma (BL) who had undergone 18 cycles of chemotherapy and 15 (10.1%) individuals with HSCT who had performed 16 cycles of chemotherapy were also included (Table 2). Considering the number of chemotherapy cycles in each group, individuals with HSCT (87.5%) were most affected by OM, followed by individuals with OS

Table 1 Device information, irradiation parameters and treatment standards

Device information	
Manufacturer	MMOptics, São Carlos, SP, Brazil
Model identifier	Laser Duo
Number of emitters	Two
Emitter type	GaAlAs and InGaAlP laser
Spatial distribution of emitters	Elliptical
Beam delivery system	Fiberoptic
Irradiation parameters	
Parameter (unit)	**Measurement method or information value source**
Centre wavelength (nm)	660
Spectral bandwidth (nm)	660 ± 10
Operating mode	Continuous wave (CW)
Frequency (Hz)	Non related (CW)
Pulse on duration (s)	Non related (CW)
Pulse off duration (s) or duty cycle (%)	Non related (CW)
Peak radiant power (mW)	Non related (CW)
Average radiant power (mW)	Non related (CW)
Beam profile	Gaussian
Treatment standards	
Parameter (unit)	**Value**
Beam spot size at target (cm^2)	0.03
Irradiance at target (mW/cm^2)	3333
Exposure duration (s)	20
Radiant exposure (J/cm^2)	66.6
Radiant energy (J)	2
Number of points irradiated	22
Area irradiated (cm^2)	22
Application technique	Contact
Number and frequency of treatment sessions	Five sessions weekly (Monday to Friday), 1–14 days
Total radiant energy (J)	~ 440

(68.7%), BL (55.5%), AML (41.2%) and those with ALL (30.5%) (Table 2).

The association between the other chemotherapeutic agents and the potential risk factor for the development of OM was evaluated; however, no significant differences were observed ($p > 0.05$). Except for HSCT, OM was associated with MTX use in all other disease groups. Children and adolescents with ALL under treatment with intravenous MTX were 2.03 times more likely to have OM than those who were not under treatment with intravenous MTX ($p = 0.033$). We also observed

Table 2 Frequency of chemotherapy-induced oral mucositis in paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients according to chemotherapy cycles ($n = 358$)

Oral mucositis	Diagnosis				
	ALL ($n = 74$)[†]	OS ($n = 30$)[†]	AML ($n = 23$)[†]	BL ($n = 6$)[†]	HSCT ($n = 15$)[†]
Yes	58 (30.5%)[‡]	57 (68.7%)[‡]	21 (41.2%)[‡]	10 (55.5%)[‡]	14 (87.5%)[‡]
No	132	26	30	8	2
Total	190	83	51	18	16

[†] Number of affected individuals

[‡] Percentage refers to the number of chemotherapy cycles

ALL, acute lymphocytic leukaemia; *AML*, acute myeloid leukaemia; *BL*, Burkitt lymphoma; *OS*, osteosarcoma

that individuals with OS ($p = 0.029$), AML ($p < 0.001$) and BL ($p = 0.034$) under MTX treatment were 1.36, 1.82 and 1.56 times more likely, respectively, to have OM than those who were not under MTX treatment (Table 3).

With respect to anatomical location, buccal mucosa, labial mucosa, lateral border of the tongue, floor of the mouth and oropharynx were the most affected sites (Table 4).

Prophylactic PBMT efficiently prevented OM

The mean number of sessions of prophylactic PBMT was 3.5 (± 3.1) (range one to 15 sessions per chemotherapy cycle). In 127 of the 190 cycles of chemotherapy recorded, individuals with ALL under prophylactic PBMT did not develop OM ($p = 0.001$) (Table 5). All individuals who had developed OM received therapeutic PBMT. Overall, the mean number of sessions of prophylactic PBMT combined with therapeutic PBMT was 4.1 (± 4.2) (range one to 28 sessions per chemotherapy cycle).

Table 6 demonstrates that ALL and OS patients who had undergone PBMT developed grade 1 or 2 (mild) OM, while patients not submitted to prophylactic PBMT had more severe OM (grade 3 and 4) ($p < 0.05$). For AML, BL and HSCT patients, there was no statistically significant difference between those who had received PBMT and those who had not received PBMT ($p > 0.05$).

Regarding the association between severity of OM and prophylactic PBMT, controlled for MTX administration, the grade of OM was 3.16 times higher among individuals with ALL who had not undergone prophylactic PBMT than among those who had undergone prophylactic PBMT ($p < 0.001$). This was also observed in individuals with OS and BL, for whom the OM grade was 5.45 and 7.38 time higher, respectively, among individuals who had not been submitted to prophylactic PBMT in comparison with those who had been submitted to prophylactic PBMT ($p < 0.001$) (Table 7).

Table 3 Univariate analysis describing methotrexate (MTX)-induced oral mucositis in paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients

Disease		Ratio (95% CI)	*p* value
ALL	MTX		
	Yes	2.03 (1.06–3.90)	0.033
	No	1	
OS	MTX		
	Yes	1.36 (1.03–1.80)	0.029
	No	1	
AML	MTX		
	Yes	1.82 (1.58–2.08)	< 0.001
	No	1	
BL	MTX		
	Yes	1.56 (1.03–2.35)	0.034
	No	1	
HSCT	MTX		
	Yes	1.06 (0.75–1.51)	0.710
	No	1	

ALL, acute lymphocytic leukaemia; *AML*, acute myeloid leukaemia; *BL*, Burkitt lymphoma; *CI*, confidence interval; *OS*, osteosarcoma

The occurrence of opportunistic infections was reduced in children and adolescents who had undergone prophylactic PBMT

Within the 358 cycles of chemotherapy, the patients exhibited 40 (61.8%) episodes of fungal infection, followed by 17 (26.2%) episodes of viral infection and eight (12.3%) episodes of both types of infection. There were 28 (14.7%), 16 (19.3%), 14 (27.5%), four (22.2%) and three (18.8%) episodes of opportunistic infection among individuals with ALL, OS, AML, BL and HSCT, respectively. There was no significant association between OM and oral infections ($p > 0.05$); however, there was an association between prophylactic PBMT and a reduction of episodes of opportunistic infection in individuals with ALL ($p = 0.017$), while no association was observed for other diseases (Supplementary Table 2).

Discussion

The reduction in the severity and duration of OM and its consequences among children and adolescents undergoing chemotherapy cycles has a substantial impact on morbidity and mortality [33]. Since the early 1980s, PBMT (formerly called laser therapy) has been used for the management of OM. Working in France, Dr. Ciais and co-workers [34] were the pioneers in the use of PBMT for cancer patients who had received combined chemotherapy, including 5-FU. The authors reported a significant reduction in the severity of OM, with a reduced occurrence of oral complications from 43 to 6% [34].

The present study deals with the trends of prophylactic PBMT among paediatric patients with chemotherapy-induced OM. Currently, there is no standard treatment for OM therapy among paediatric cancer patients receiving chemotherapy because interventions predominantly aim to prevent or palliate symptoms [35]. Nevertheless, palifermin, a recombinant keratinocyte growth factor, has been reported to significantly reduce the incidence, severity and duration of OM among cancer patients [36]. According to Lucchese et al. [37], palifermin, 60 μg per kg per day, intravenously, for 6 days, prevented the recurrence of severe OM and improved the quality of life of paediatric patients affected by ALL. However, assessments of clinically significant end points and health care cost still need to be endorsed in the literature. In spite of this fact, the complex pathogenesis of the disorder requires full comprehension of inflammatory signalling [12]. Recently, targeting of downstream

Table 4 Distribution of oral mucositis over the cycles of chemotherapy in paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients according to affected site(s)

	Disease				
	ALL, n = 58 (%)	OS, n = 57 (%)	AML, n = 21 (%)	BL, n = 10 (%)	HSCT, n = 14 (%)
Anatomical location[†]					
Buccal mucosa	35 (60.3)	37 (64.9)	13 (61.9)	10 (100.0)	10 (71.4)
Labial mucosa	30 (51.7)	27 (47.4)	9 (42.8)	10 (100.0)	6 (42.8)
Lip	3 (5.2)	3 (5.3)	2 (9.5)	0 (0.0)	1 (7.1)
Floor of the mouth	13 (22.4)	13 (22.8)	7 (33.3)	7 (70.0)	8 (57.1)
Soft palate	1 (1.7)	3 (5.3)	2 (9.5)	2 (20.0)	2 (14.3)
Oropharynx	13 (22.4)	11 (19.3)	2 (9.5)	1 (10.0)	5 (35.7)
Retromolar trigone	3 (5.2)	5 (8.8)	2 (9.5)	4 (40.0)	3 (21.4)
Lateral border of the tongue	17 (29.3)	23 (40.3)	10 (47.6)	6 (60.0)	7 (50.0)
Ventral tongue	12 (20.7)	6 (10.5)	4 (19.0)	2 (20.0)	5 (35.7)
Dorsal tongue	6 (10.3)	0 (0.0)	3 (14.3)	0 (0.0)	2 (14.3)
Vestibule	5 (8.6)	9 (15.8)	2 (9.5)	3 (30)	2 (14.3)
Labial commissure	1 (1.7)	7 (12.3)	2 (9.5)	0 (0.0)	1 (7.1)

[†] The anatomical location was not analysed in terms of number of individuals but rather in terms of number of lesions presented, i.e. the same individual may have been affected at more than one anatomical site

ALL, acute lymphocytic leukaemia; *AML*, acute myeloid leukaemia; *BL*, Burkitt lymphoma; *OS*, osteosarcoma

mediators such as CXCLs, IL-1RA and IL-4 has supported the key role of chemokines and proinflammatory cytokines in OM [38, 39]. Contemporary upstream modulation of reactive oxygen species (ROS) through scavengers highlights potential new targets for mucositis prevention [40]. PBMT temporarily enhances ROS production by accelerating the mitochondrial respiratory chain [41]. In fact, during the optical absorption of cytochrome c oxidase, PBMT has a mechanism by which the energy of red/near-infrared photons will be absorbed by cytochrome c oxidase in the mitochondria of cells, playing an essential role in oxygenation metabolism and ATP production. In this regard, the accelerated oxygenation process and extra production of ATP will be helpful to cells and tissues [41–43].

Table 5 Association between prophylactic photobiomodulation therapy (PBMT) and occurrence of oral mucositis in paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients according to chemotherapy cycles (n = 358)

Disease	Oral mucositis	Prophylactic PBMT		p value*
		No (%)	Yes (%)	
ALL	No	5 (3.8)	127 (96.2)	0.001
	Yes	11 (19.0)	47 (81.0)	
OS	No	0 (0.0)	26 (100.0)	0.304
	Yes	4 (7.0)	52 (93.0)	
AML	No	4 (13.3)	26 (86.7)	0.702
	Yes	4 (19.1)	17 (80.9)	
BL	No	0 (0.0)	8 (100.0)	1.000
	Yes	1 (10.0)	9 (90.0)	
HSCT	No	0 (0.0)	2 (100.0)	1.000
	Yes	1 (7.1)	13 (92.9)	

*Fisher's exact test

ALL, acute lymphocytic leukaemia; *AML*, acute myeloid leukaemia; *BL*, Burkitt lymphoma; *OS*, osteosarcoma

Among the several prophylactic and therapeutic protocols that have been developed for the management of OM in patients undergoing HSCT, PBMT is one of the approaches recommended by a current guideline [20]. In contrast, no recommendation panel has been indicated for individuals treated with chemotherapy due to insufficient evidence [20]. While the premise that PBMT is effective in modulating multiple inflammatory processes is certain, the effects of therapy depend on distinct parameters considered critical for irradiation, including irradiance/power density, fluence/energy density and time per site [20]. We performed prophylactic PBMT with a wavelength of 660 nm in daily applications of continuous-wave diode laser with energy density of 2 J/cm^2 [4, 15, 16, 19]. Some studies have addressed intraoral PBMT for the management of OM and have supported the use of PBMT for all chemotherapy-treated individuals who experience OM [4, 15, 19], regardless of the type of malignant lesion and chemotherapy regimen [44].

HSCT is also a risky procedure because of the intense conditioning regimen required prior to transplantation and the fact that subsequent immune recovery is slow. OM is certainly one of the most debilitating outcomes among patients who undergo HSCT [8, 10, 16, 22]. In our study, due to the small sample size of patients undergoing HSCT, no statistical significance was achieved when patients who had

Table 6 Association between prophylactic photobiomodulation therapy (PBMT) and grade of oral mucositis in paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients according to chemotherapy cycles (n = 358)

Disease		Prophylactic PBMT		p value*
		No (%)	Yes (%)	
ALL	Grade			
	1	1 (6.7)	14 (93.3)	0.035
	2	4 (15.4)	22 (84.6)	
	3	3 (25.0)	9 (75.0)	
	4	2 (66.7)	1 (33.3)	
OS	Grade			
	1	0 (0.0)	20 (100.0)	0.031
	2	2 (7.7)	24 (92.3)	
	3	1 (20.0)	4 (80.0)	
	4	1 (33.3)	2 (66.7)	
AML	Grade			
	1	2 (25.0)	6 (75.0)	0.788
	2	1 (14.3)	6 (85.7)	
	3	1 (25.0)	3 (75.0)	
	4	0 (0.0)	2 (100.0)	
BL	Grade			
	1	0 (0.0)	2 (100.0)	0.600
	2	0 (0.0)	1 (100.0)	
	3	0 (0.0)	3 (100.0)	
HSCT	Grade			
	1	0 (0.0)	3 (100.0)	1.000
	2	1 (25.0)	3 (75.0)	
	3	0 (0.0)	5 (100.0)	
	4	0 (0.0)	2 (100.0)	

*Linear by linear test

ALL, acute lymphocytic leukaemia; *AML*, acute myeloid leukaemia; *BL*, Burkitt lymphoma; *OS*, osteosarcoma

Table 7 Regression analysis evaluating the association between oral mucositis severity and prophylactic photobiomodulation therapy (PBMT) in paediatric oncology/haematopoietic stem cell transplantation (HSCT) patients

Disease		Adjusted ratio† (95% CI)	p value
ALL	Prophylactic PBMT		
	Yes	1	< 0.001
	No	3.16 (1.86–5.37)	
OS	Prophylactic PBMT		
	Yes	1	< 0.001
	No	5.45 (2.60–11.44)	
AML	Prophylactic PBMT		
	Yes	1	0.738
	No	1.14 (0.51–2.55)	
BL	Prophylactic PBMT		
	Yes	1	< 0.001
	No	7.38 (2.47–22.10)	
HSCT	Prophylactic PBMT		
	Yes	1.24 (0.52–2.94)	0.612
	No	1	

† Adjusted for methotrexate administration

ALL, acute lymphocytic leukaemia; *AML*, acute myeloid leukaemia; *BL*, Burkitt lymphoma; *CI*, confidence interval; *OS*, osteosarcoma

received PBMT and those who had not received PBMT were compared. However, Bezinelli et al. [29] reported that PBMT and oral care contribute to reducing the morbidity resulting from OM and reduce the costs of medications and medical supplies in general (e.g. opioids), as well as nursing. Accordingly, Antunes et al. [22] reported that 63.2% of patients who had undergone HSCT did not develop OM due to the use of prophylactic PBMT. Moreover, the existing guideline recommends intraoral PBMT at wavelengths of 630 to 660 nm combined with high-dose chemotherapy, with or without total body irradiation for the prevention of OM in adult individuals undergoing HSCT [20]. A recent clinical study has shown that PBMT is effective in preventing OM in patients undergoing HSCT and receiving three PBMT sessions weekly using a continuous-wave diode laser at a wavelength of 660 nm and energy density of 6 J/cm^2 [23].

Herein, ALL was the most common malignant neoplasm, which conforms to the incidence of childhood cancer according to data from the Brazilian Population-Based Registry [3]. The rate of ALL is increasing worldwide and the therapeutic advances have led to longer survival rates of affected individuals [7, 11]. Thus, the involvement of paediatric dentists in the multidisciplinary team is essential [45]. MTX, a folic acid antagonist, inhibits cell reproduction and shows partial selectivity for tumour cells and toxicity against rapidly proliferating normal cells, as occurs in gastrointestinal tract cells. MTX is a cytotoxic agent for the oral mucosa, contributing to the onset of OM [5, 46]. MTX is a drug that has proved to be effective in a variety of childhood malignancies, including ALL, lymphomas and OS [4, 6, 7]. In particular, ALL and OS are neoplasms for which the highest dose of MTX is used [6, 7].

In the current study, risk factors likely to be associated with the development of OM have been assessed. Children and adolescents with ALL and OS who used MTX were 2.03 and 1.36 times, respectively, more likely to have OM than those who did not use MTX. Likewise, patients with these malignancies receiving MTX regimens and submitted to prophylactic PBMT had lower OM grades. This finding was expected because the first biological response to the toxic effects of chemotherapy begins shortly after the chemotherapy itself and the detection of clinical symptoms of OM at that time is unfeasible [12]. However, other alkylating therapeutic drugs that may also be involved in treatment cannot be excluded [5–7]. Collectively, our findings support the use of prophylactic PBMT among

paediatric ALL and OS patients under an MTX regimen since these individuals showed mild OM.

Interestingly, in our study, the occurrence of opportunistic infections was lower among children and adolescents who had undergone prophylactic PBMT. Gobbo et al. [19] used buccal swabs for microbiological culture in patients with OM treated with PBMT. In that Italian multicentre study, no differences were observed in *Candida* or herpes simplex virus positivity between PBMT and non-PBMT groups. An in vitro study demonstrated that the wavelength of 905 nm and energy of 7 J/cm^2 parameters considerably affected the survival and inflammatory potential of pathogenic *Candida* spp. [47] suggesting the use of PBMT as a co-adjuvant tool for children with OM complicated by *Candida* infections. For virus infection, further studies are still needed to better elucidate how PBMT affects virus cell survival.

The use of representative data from a Brazilian referral service, and the standard protocol for data collection throughout the study are strengths of the current study. Therefore, the findings support the use of prophylactic PBMT in chemotherapy-induced OM in children and adolescents with cancer and/or HSCT. This study also has shortcomings. Due to the retrospective nature of this study and ethical issues, there is no control group of individuals who are not receiving treatment. Thus, larger randomised controlled studies are warranted. Second, the influence of age, disease stage, nutritional status, duration of neutropenia and others factors on OM should be investigated further [6, 48–50]. Third, since it is challenging to assign individuals to particular ethnic groups, due to their heterogeneity as a result of many years of miscegenation [51], the influence of ethnicity cannot be ruled out as well. Finally, long-term details about the participant individuals are unavailable (i.e. alive with disease, disease-free survival or death).

Conclusions

In summary, prophylactic PBMT has been shown to be an effective and safe modality for the prevention of chemotherapy-induced OM in cancer and/or HSCT paediatric patients. PBMT effectively prevented OM in young individuals with ALL and OS, since patients undergoing PBMT developed mild OM, while patients not undergoing PBMT had severe OM. Regarding the severity of OM in children and adolescents receiving MTX and prophylactic PBMT regimens, the grade of OM was higher among children and adolescents with ALL, OS and BL who had not undergone prophylactic PBMT compared with those who had undergone prophylactic PBMT. Taken together, these data will assist paediatric dentists by providing trends in prophylactic PBMT among individuals undergoing chemotherapy cycles.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of Universidade Federal de Minas Gerais (No. 69069917.5.0000.5149).

Informed consent Consent was obtained from both the parents and children.

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