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ORIGINAL ARTICLE

Intraoral versus extraoral photobiomodulation therapy in the prevention of oral mucositis in HSCT patients: a randomized, single-blind, controlled clinical trial

Mariana Bitu Ramos-Pinto[1] · Teresa Paula de Lima Gusmão[1] · Jayr Schmidt-Filho[2] · Graziella Chagas Jaguar[1] · Manoela Domingues Martins[3] · Fábio Abreu Alves[1,4,5]

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Abstract

To compare the efficacy of intraoral and extraoral photobiomodulation (PBM) protocols for the prevention of oral mucositis (OM) in hematopoietic stem cell transplantation (HSCT) patients. A total of 60 patients was randomized into intraoral PBM (IOPBM) and extraoral PBM (EOPBM) groups. Both PBM protocols were well tolerated and no side effects were observed. EOPBM session times were one fourth of IOPBM durations. Of 60 patients, 35 (58.3%) developed ulcerated OM between day +3 and day +12. No intergroup difference was observed in OM healing times ($p=0.424$). The lateral border of the tongue was the most common site affected in both groups. However, the incidence of mucositis on buccal mucosa was significantly reduced in the EOPBM group ($p=0.021$). Young patients (OR.5.35, 95%CI 0.94–30.4, $p=0.058$) and those who had received myeloablative conditioning (OR.55.1, 95%CI 2.69–1129.3, $p=0.009$) were more likely to develop ulcerated OM, whereas autologous HSCT recipients (OR 0.079, 95% CI 0.009–0.67, $p=0.021$) had a lower probability of developing ulcerated OM independent of PBM protocol. EOPBM protocol was as effective as IOPBM in the management of OM in HSCT patients, with the advantage of shorter treatment sessions.

Trial registration number: RBR-7nww56.

Date of trial registration submission: 30th September 2019.

Keywords Oral mucositis · Mucositis · Side effects · Photobiomodulation · Hematopoietic stem cell transplantation

Introduction

The management of side effects caused by hematopoietic stem cell transplantation (HSCT) conditioning regimens has a major impact on quality of life. Oral mucositis (OM) is a debilitating complication in 70–100% of HSCT recipients undergoing high-dose chemotherapy (CT) and total body irradiation (TBI). OM may impair oral function, thereby necessitating parenteral nutrition, opioid analgesia, changes in treatment protocols, prolonged hospitalizations, and increased financial burdens [1–3].

An understanding of the pathobiology and prognostic factors of OM is essential to design effective medical interventions [4]. Preventive measures include oral hygiene, keratinocyte growth factor therapy, cryotherapy for patients receiving high doses of melphalan, and photobiomodulation (PBM) [5]. The later therapy promotes beneficial therapeutic effects including pain relief, immunomodulation, wound healing, and tissue regeneration. Moreover, PBM stimulates collagen synthesis by fibroblasts, angiogenesis, and myofibroblast differentiation improving the characteristics of the newly formed tissue [6, 7]. Most studies have used low-level laser therapy (LLLT) and light-emitting diode (LED) to achieve PBM. However, few studies have reported the benefits of high-level laser therapy (HLLT) [8–12].

✉ Fábio Abreu Alves
falves@accamargo.org.br

1 Stomatology Department, A.C. Camargo Cancer Center, Sao Paulo, Brazil

2 Hematology Department, A.C. Camargo Cancer Center, Sao Paulo, Brazil

3 Department of Oral Pathology, School of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil

4 Stomatology Department, School of Dentistry, Sao Paulo University, Sao Paulo, Brazil

5 Departamento de Estomatologia, AC Camargo Cancer Center, R: Prof. Antônio Prudente, 211, Bairro: Liberdade, São Paulo, SP CEP: 01509-900, Brazil

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Patient characteristics, laser parameters, and application methods may influence PBM outcomes [13, 14]. According to a Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology systematic review, intraoral PBM (IOPBM) using varying doses of LLLT reduces OM incidence, severity, and pain in adults undergoing HSCT [15].

Recent in vivo and clinical studies have yielded promising results of extraoral PBM (EOPBM) [8, 16–18]. This technique requires less time per application than IOPBM, thus minimizing patient discomfort. Moreover, EOPBM may also allow the simultaneous management of esophageal mucositis [16, 19]. Thus, the aim of the present study was to compare the efficacies of EOPBM and IOPBM in the prevention of OM in HSCT patients. In addition, mean exposure times and discomfort related to both methods were also evaluated.

Patients and methods

Characterization of the study

This study consisted of a randomized, single-blind, controlled clinical trial comparing the efficacies of IOPBM and EOPBM for the prevention of OM in adult HSCT patients. The study was approved by the Ethics Committee of the A. C. Camargo Cancer Center, Sao Paulo, Brazil (no.2569/18). Register Number of Trial (REBEC): RBR-7nww56. Written informed consent was obtained from all participants.

Inclusion criteria

Patients of both sexes aged 18 years or older with hematologic malignancies submitted to autologous or allogeneic HSCT were eligible for enrollment.

Exclusion criteria

Patients who had undergone HSCT previously were excluded.

Study design

A total of 63 patients had criteria to participate of the study; however, 3 patients refused. Then, 60 patients were enrolled in this study between September 2018 and December 2019, and randomized to IOPBM and EOPBM groups matched to sex, age range (≥ 18 yo and < 40 yo or ≥ 40 yo), type of HSCT (autologous or allogeneic), and conditioning regimen (myeloablative conditioning [MAC]; non-myeloablative conditioning [non-MAC]; or reduced-intensity conditioning [RIC]) by an institutional app based on the sequential allocation process.

All patients were given oral assessment, which included oral and radiographic evaluation. Moreover, oral hygiene instruction and oral care (periodontal treatment, restoration of caries, endodontic treatment, and/or extraction of teeth with poor prognosis) were performed before HSCT as routinely provided by our department. During the transplantation period, the patients were orientated to use 0.12% chlorhexidine rinse twice a day to maintain oral health.

Experimental groups/PBM protocols

IOPM and EOPM preventive protocols were performed daily by a single trained professional, starting on the first day of the conditioning regimen and ending on the fifth day after transplantation (d + 5). Session durations were measured, and both the professional and the patient wore protective eyewear. All PBM parameters used in the study are presented in Table 1.

IOPBM consisted of LLLT utilizing continuous InGaAlP diode laser applications delivered perpendicularly to four mucosal sites. Patients were irradiated on 34 points: 18 on the buccal mucosa (9 on each side), 4 on the lips (2 upper and 2 lower), 8 on the tongue (3 on the right lateral border, 3 on the left lateral border, and 2 on the ventral surface), 2 on the floor of the mouth (1 on each side), and 2 on the soft palate (Supplementary material—Fig. 1).

EOPBM was performed with a pulse diode laser (Gemini®, Azena Medical, LLC, distributed by Ultra dent Products, Inc.) with dual wavelengths of 810 and 980 nm. The adopted protocol was based on the method of a feasibility study using extraoral appliances [19] and consisted of the irradiation of 6 points on the face (2 on both right and left cheeks, and 1 on each lip) and three points on the anterior neck (right and left submandibular spaces, and submental space) (Supplementary material—Fig. 1).

All patients who developed ulcerated mucositis (≥ grade II on the World Health Organization (WHO) scale) received our institution's curative protocol that uses continuous indium–gallium–aluminum–phosphide (InGaAlP) diode laser (MM Optics Ltd., Sao Carlos, Brazil) LLLT delivered perpendicularly to lesions daily until wound healing (Fig. 1). The IOPBM laser parameters were used in the curative protocol (Table 1).

Oral mucositis assessment

OM was evaluated daily from the first day of the conditioning regimen until healing by a blinded observer who did not provide PBM and was scored according to WHO criteria: grade 0 (none), grade I (oral soreness, erythema), grade II (oral erythema, ulcers, solid and liquid diet tolerated),

Table 1 PBM parameters of IOPBM and EOPBM groups

Parameters	Preventive Protocols		Curative Protocol
	IOPBM	EOPBM	
Center wavelengths (nm)	660	810 + 980 (50%/50%)	660
Operating mode	Continuous	Pulsed	Continuous
Frequency (Hz)	~ 50/60	50	~ 50/60
Pulse duration (ms)	Continuous	2	Continuous
Duty Cycle (%)	–	10	–
Peak power (W)	–	20	–
Average power (mW)	100	2000	100
Polarization	Yes	No	Yes
Spot size (cm^2)	0.03	4.91	0.03
Irradiated area (cm^2)	0.03	4.91	0.03
Beam shape	Round	Round	Round
Beam profile	Gaussian	Gaussian	Gaussian
Irradiance (mW/cm^2)	3300	407	3300
Fluence (J/cm^2)	33.3	4.07	33.3
Exposure duration (s)	10	10	10
Total radiant energy (J)	1	20	1
Application form	Contact	Contact	Contact
Number of points irradiated	34	6	On the lesions
Frequency of sessions	Daily	Daily	Daily
	From the first day of conditioning until d + 5	From the first day of conditioning until d + 5	OM grade II until wound healing

grade III (oral ulcers, liquid diet only), and grade IV (oral alimentation impossible). Moreover, the National Cancer Institute (NCI) scale (NCI - *Common Terminology Criteria for Adverse Events)* was also used: grade 0 (none),

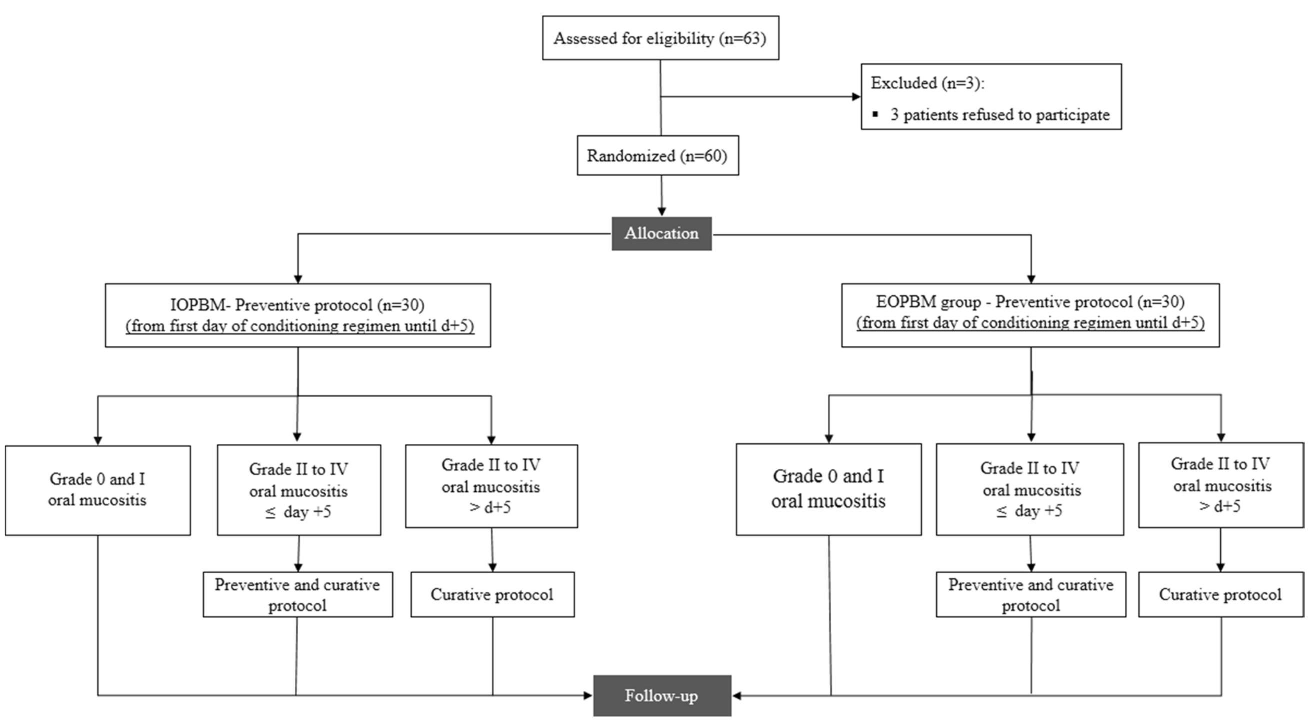

Fig. 1 Flowchart which shows the study design

grade I mucosal erythema), grade II (patchy ulcerations with pseudomembranes), grade III (confluent ulcerations or pseudomembranes, bleeding with minor trauma), and grade IV (tissue necrosis, significant spontaneous bleeding). In addition, oral mucosal sites affected by ulcerated OM were recorded.

Pain scoring

Oral and throat pain levels were evaluated during 10 post-transplant days through visual analogue scale (VAS) OM assessments. The VAS scale quantifies the patient's self-reported pain intensity by using a numerical score; 0 indicates the absence of pain and 10 is the maximum score.

Statistical analysis

Data were analyzed descriptively by calculating median, mean, and standard deviation of the mean considering day 0 (day of transplant) as the beginning of analysis. The Chi-square and Fisher's exact tests were applied to verify associations between covariables (demographic and clinical features) and the outcomes of OM, to verify the distribution of oral mucosal sites affected by ulcerated mucositis (II to IV), and to verify the mean intensity of oral and throat pain. The Mann-Whitney correlation test was used to evaluate the mean time to OM development in both groups, and the healing time of ulcerated mucositis. Simple and multiple logistic regression analyses were performed to obtain odds ratios (ORs) with 95% confidence intervals (CIs) to ascertain differences between the two groups, as well as to compare the WHO and NCI mucositis scores (≥ grade II OM). Covariables that presented significant p values (< 0.050) and those with p values <0.200 were included in multiple modeling. A stepwise technique was used, with testing from the lowest to the highest p value. The final model was built with the following assumptions: (1) no change in ORs > 10%, (2) improvement in accuracy by 95% CI, (3) total degrees of freedom allowed for each outcome variable, and (4) quality of the final model. The data were analyzed using IBM SPSS Statistics software version 25.0 and the significance level of 5% ($p < 0.05$) was used.

Results

A total of 60 patients were evaluated in this study. Demographic and clinical characteristics are presented in Table 2. Both PBM protocols were well tolerated, and no side effects were reported. However, three patients, two in the IOPBM group and one in the EOPBM group, refused one PBM session each, due to oral pain and malaise.

The mean durations of PBM sessions were 5.97 and 1.67 min in the IOPBM and EOPBM groups, respectively ($p < 0.001$). Thirty-eight patients (18 IOPBM and 20 EOPBM recipients) (63.3%) developed OM of any WHO grade. Three patients (one IOPBM and 2 EOPBM recipients) (5%) had WHO grade I, 23 patients (11 IOPBM and 12 EOPBM recipients) (38.4%) developed WHO grade II, and 11 patients (6 IOPBM and 5 EOPBM recipients) (18.3%) WHO grade III OM. Only one patient (1.6%) developed WHO grade IV OM. This patient had received EOPBM and declined one PBM session. Results graded by the NCI and WHO scales were similar. No significant differences were observed between the IOPBM and EOPBM groups in all OM grades (Figs. 2a–b). The lateral border of tongue was the most common site affected by ulcerated mucositis in both groups. The incidence of buccal OM was significantly lower in the EOPBM group ($p = 0.021$). The distribution of affected mucosal sites in both groups is shown in Fig. 3.

The highest oral pain scores occurred in the eighth day after HSCT (day +8) in IOPBM group and in the seventh day (day +7) in EOPBM group. There was no statistical difference in the mean daily oral pain intensity between groups ($p = 0.535$). The highest throat pain scores occurred on day +10 in the IOPBM group and on day +9 in the EOPBM group ($p = 0.382$).

Time to OM development and healing

There were no significant differences in the mean times to development of OM of any WHO severity grade between the IOPBM and EOPBM groups. Patients in the IOPBM group presented with WHO grade I OM between day +4 and day +12 (mean time of 7.7 days), whereas the EOPBM group exhibited grade I OM between day +2 and day +10 (mean time of 6.1 days) ($p = 0.112$). Grade II mucositis was observed between day +5 and day +10 (mean time of 7.9 days) and day +3 and day +11 (mean time of 6.8 days) in the IOPBM and EOPBM groups, respectively ($p = 0.134$). Grade III mucositis developed in the IOPBM group between day +6 and day +11 (mean time of 8.5 days) and in the EOPBM group between day +4 and day+12 with (mean time of 7.6 days) ($p = 0.699$). Similar results were also observed according to the NCI scale (Supplementary material- Table 1). Healing times for patients with ulcerated (grades II to IV) mucositis averaged 9.35 days (6–16) after transplantation (day 0) in the IOPBM group and 8.44 days (3–15) in the EOPBM group ($p = 0.424$).

Logistic regression model

Simple logistic regression showed a similar incidence of ulcerated (grades II to IV) OM in the IOPBM and

Table 2 Demographic and clinical characteristics of 60 participants

	IOPBM $n=30$		EOPBM $n=30$		Total $n=60$		*p*- value
	n	%	n	%	n	%	
Sex							0.790
Male	18	60.0	19	63.3	37	61.7	
Female	12	40.0	11	36.7	23	38.3	
Age							0.770
≥ 18 e < 40 years	8	26.7	9	30.0	17	28.3	
≥ 40 years	22	73.3	21	70.0	43	71.7	
Ethnic							0.770
Caucasian	21	70.0	23	76.7	44	73.3	
Non-Caucasian	9	30.0	7	23.3	16	26.7	
Diagnosis							0.300
Multiple myeloma	8	26.7	13	43.3	21	35.0	
Leukemias	11	36.7	5	16.7	16	26.7	
Lymphomas	10	33.3	11	36.7	21	35.0	
Germ cell tumors	1	3.3	1	3.3	2	3.3	
Type of HSCT							0.170
Autologous	17	56.7	23	76.7	40	66.7	
Allogenic	13	43.3	7	23.3	20	33.3	
Treatment modality							0.340
CT only	21	70.0	26	86.7	47	78.3	
CT + TBI 2 or 4 Gy	4	13.3	2	6.7	6	10.0	
CT + TBI 12 Gy	5	16.7	2	6.7	7	11.7	
Type of conditioning Regimen							0.671
MAC	26	86.7	28	93.3	54	90.0	
RIC	4	13.3	2	6.7	6	10.0	

CT Chemotherapy, *TBI* Total body irradiation, *MAC* Myeloablative Conditioning, *RIC* Reduced intensity conditioning

EOPBM groups. Young patients (from 18 to 39 years old) and patients who had undergone MAC were at higher risk of developing ulcerated OM (OR 4.88 95% CI 1.22–19.48 $p=0.025$, OR 8.5 95% CI 0.92–78.02 $p=0.058$, respectively). Caucasians, autologous HSCT recipients, and patients treated only with melphalan had lower probabilities of developing ulcerated OM (OR 0.23 95% CI 0.05–0.92 $p=0.038$, OR 0.022 95% CI 0.06–0.79 $p=0.021$, OR 0.22, 95% CI 0.05–0.90, $p=0.035$, respectively). Multiple logistic regression revealed that young patients (OR 5.35 95% CI 0.94–30.4 $p=0.058$) and MAC recipients (OR 55.1 95% CI 2.69–1129.3 $p=0.009$) were

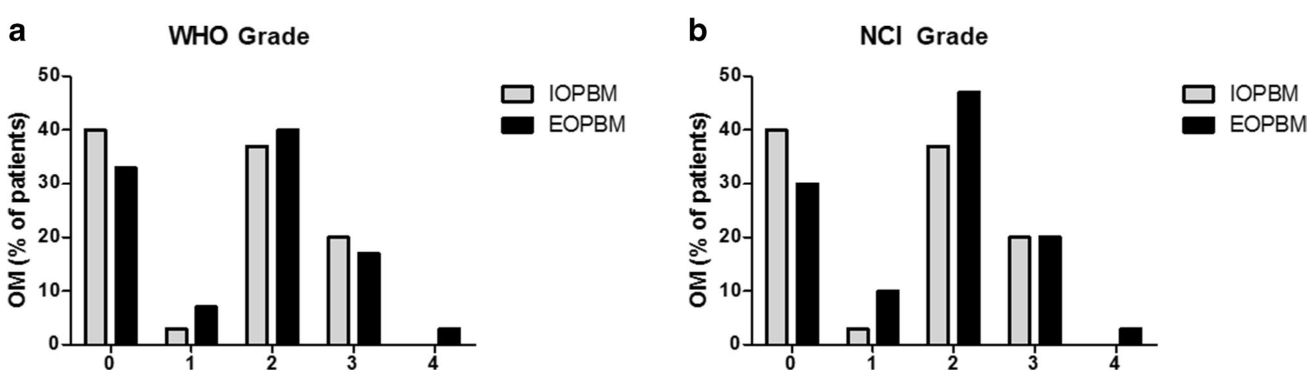

Fig. 2 Comparison of OM incidence between IOPBM and EOPBM groups. **a** WHO scale. **b** NCI scale

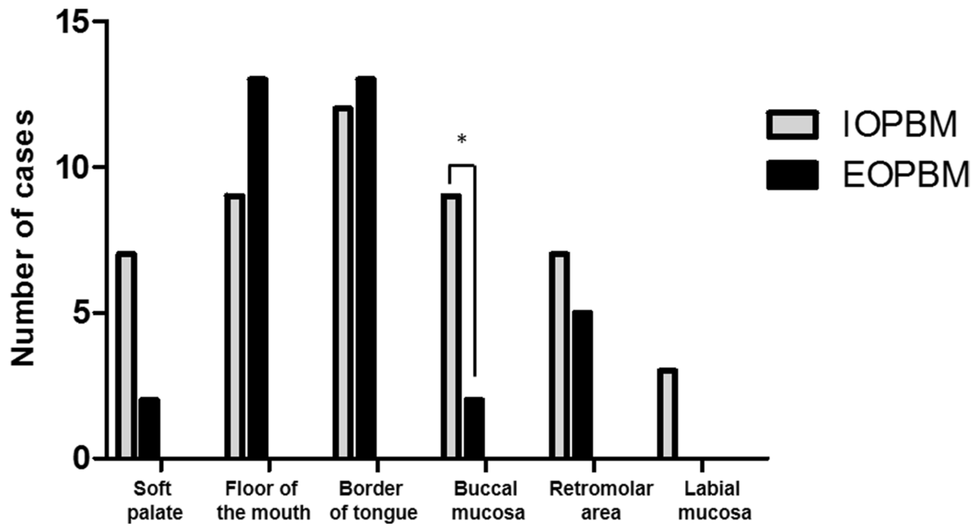

Fig. 3 Comparison of anatomic sites of ulcerated mucositis according to IOPBM and EOPBM groups

more likely to develop ulcerated OM, while autologous HSCT recipients were at lower risk (OR 0.079 95% CI 0.009–0.67 $p=0.021$) (Table 3).

Discussion

IOPBM using diode lasers has been recommended for the prevention of OM in adult HSCT patients [15]. Most studies have demonstrated that IOPBM is effective for the amelioration of OM. However, PBM parameters reported in the literature are highly variable [9, 10, 12, 16, 20, 21]. In addition, restricted mouth opening due to severe OM can compromise IOPBM application [17]. To obviate these limitations, we explored the clinical utility of EOPBM for the prevention of OM. To the best of our knowledge, this study is the first randomized, single-blind, controlled clinical trial to compare the efficacies of IOPBM and EOPBM for the prevention of OM in HSCT patients.

Both diode laser treatments were well tolerated, and no toxicity was reported. Both protocols (IOPBM and EOPBM showed similar efficacies for the prevention of oral mucositis. However, EOPBM reduced the duration of laser sessions by an average of 4 min. Similar data were also observed in a pilot study that evaluated the feasibility of EOPBM in pediatric HSCT patients [19]. In addition, no intergroup differences were detected in the mean times to OM development and healing, independent of OM grade and scale. Only 6 patients in IOPBM group and 5 in EOPBM group experienced grade III OM and one patient developed grade IV mucositis in later group (such patient was the one who refused one laser session). The EOPBM group had a lower incidence of buccal mucositis than the IOPBM group. However, other oral mucosal sites such as the floor of the mouth, the lateral borders of the tongue, and soft palate showed similar incidence rates in both groups. In a literature review, it was also emphasized that EOPBM may be effective for controlling OM on buccal mucosa and lips [22].

Acute oral pain caused by OM exacerbates cancer morbidity and worsens quality of life [23]. PBM has been considered as an alternative to opioid analgesia for the palliation of OM-related pain [20]. In this study, both groups displayed low and similar OM-related pain scores.

OM severity may be influenced by the type of HSCT (autologous or allogeneic), conditioning regimen (MAC, RIC, or non-MAC), and the pharmacokinetics of CT agents [24]. Logistic regression analyses showed that the incidence of ulcerated OM (grade II to IV) in our study was similar in the IOPBM and EOPBM groups. However, higher rates of ulcerated OM were observed in young patients, MAC recipients, and allogenic HSCT patients. These findings are concordant with the results of an earlier study in which OM was more severe in allogeneic than autologous HSCT recipients and attributed to the higher intensity of conditioning regimens, particularly in MAC protocols using high-dose CT and TBI [25].

Another innovation of this study was the comparison of extra-oral HLLT using infrared wavelengths in defocused mode to visible-wavelength LLLT delivered in direct contact to mucosal surfaces. Intraoral and extraoral PBM have been correlated with lower scores of OM and enhanced biostimulation without cytotoxicity. In addition, HLLT modulates inflammation and accelerates healing more effectively than LLLT [12, 18]. Infrared wavelengths have better tissue penetration than visible-spectrum light, thus enhancing submucosal laser-tissue interactions to

Table 3 Association of demographic and clinical characteristics to the incidence of ulcerated mucositis (grade II to IV), as determined by simple and multiple logistic regression

Variables	Oral mucositis									
	Simple logistic regression						Multiple logistic regression			
	N	Y	OR	95% CI		*p* value	$OR_{adjusted}$	95% CI		*p* value
	n (%)	n (%)		Lower	Upper			Lower	Upper	
Groups										
IOPBM	13 (43.3)	17 (56.7)	0.87	0.31	2.43	0.793				
EOPBM	12 (40)	18 (60)	1							
Sex										
Male	15 (40.5)	22 (59.5)	1.12	0.39	3.23	0.822				
Female	10 (43.5)	13 (56.5)	1							
Age (years)										
≥ 18 < 40	3 (17.6)	14 (82.4)	4.88	1.22	19.48	0.025*	5.35	0.94	30.4	0.058*
≥ 40	22 (51.2)	21 (48.8)	1							
Diagnosis										
Multiple myeloma	12 (57.1)	9 (42.9)	1							
Leukemia	3 (18.8)	13 (81.3)	1			0.999				
Lymphomas	10 (47.6)	11 (52.4)	1			0.999				
Germ cell tumors		2 (100)	1			0.999				
HSCT										
Autologous	21 (52.5)	19 (47.5)	0.22	0.06	0.79	0.021*	0.079	0,009	0.67	0.021*
Allogeneic	4 (20)	16 (80)	1							
Treatment										
CT only	22 (46.8)	25 (53.2)	1							
CT/TBI 2 or 4 Gy	3 (50)	3 (50)	1			0.999				
CT/TBI 12 Gy		7 (100)	1			0.999				
Conditioning regimen										
MAC	20 (37)	34 (63)	8.5	0.92	78.02	0.058*	55.1	2.69	1129.3	0.009*
RIC	5 (83.3)	1 (16.7)	1							

CT Chemotherapy, *TBI* Total body irradiation, *MAC* Myeloablative conditioning, *RIC* Reduced intensity conditioning; * Statistically significant (Chi-Square and Fisher's exact tests)

N No, *Y* Yes, *OR* Odds ratio

improve wound healing [26]. The extraoral application of high-energy infrared wavelengths in defocused mode may be the key to target deeper tissues and improve PBM efficacy [18].

In conclusion, both EOPBM using HLLT and IOPBM utilizing LLLT protocols presented similar results for preventing OM in HSCT patients. Approximately 37% of the patients did not present any grade of OM. EOPBM protocol reduced application times (4-min decrease in duration of the laser session). However, further prospective, randomized, controlled studies are encouraged to define optimal laser parameters of EOPBM and further develop this modality as possible standard care for the prevention and treatment of OM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-021-06228-3.

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Authors' contributions Study design and concepts: Fabio Alves, Manoela Martins, Jayr Schmidt-Filho, Graziella Jaguar.

Data collection: Marianna Ramos-Pinto, Teresa Gusmão, Graziella Jaguar.

Data analysis: Marianna Ramos-Pinto, Teresa Gusmão, Fabio Alves.

Manuscript draft: Mariana Ramos-Pinto, Fabio Alves, Manoela Martins.

Manuscript final and approvement: All authors.

Data availability The authors have full control of all primary data and agree to allow the journal to review our data if requested.

Code availability Our data were registered in REDCap (A.C Camargo) and they are available if requested.

Declarations

Ethics approval and consent of participate The study was approved by the Ethics Committee of the A. C. Camargo Cancer Center, Sao Paulo, Brazil (no.2569/18). Register Number of Trial (REBEC): RBR-7nww56. Written informed consent was obtained from all participants.

Consent to participate Written informed consent was obtained from all participants; this document is in Portuguese (Native language of the participants).

Consent for publication All authors agree with publication of this manuscript.

Conflict of interest None of the authors have a financial relationship with the organization that sponsored the research. All authors have full control of all primary data and agree to allow the journal to review their data if requested.

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