Long-Term Safety of Photobiomodulation Therapy for Oral Mucositis in Hematopoietic Cell Transplantation Patients: A 15-Year Retrospective Study

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Abstract

Photobiomodulation therapy (PBMT) has demonstrated efficacy in the prevention and treatment of oral mucositis (OM) in hematopoietic cell transplantation (HCT). However, based on the cell stimulation properties, its long-term safety has been questioned, mainly in relation to risk for secondary malignancies in the oral cavity. The aim of this study was to investigate if different PBMT protocols for OM control have association with immediate and late adverse effects in HCT patients. Data on autologous and allogeneic transplantation, conditioning regimen, PBMT protocols, and OM severity were retrospectively collected from medical and dental records. Presence of secondary malignancies in the oral cavity was surveyed during a 15-year follow-up. Impact of OM on overall survival was also analyzed. Different PBMT protocols for prevention and treatment of OM were recorded over the years. Severe OM (grades 3 and 4) was infrequently observed. When present we observed a significant decrease of the overall survival. No immediate adverse effect and secondary malignancy was associated to PBMT. In conclusion, the PBMT protocols used in the study were considered safe. The low frequency of severe OM observed encourages the implementation of this technique, with a special emphasis on the dosimetry adjustments focused on the HCT context.

Introduction

Hematopoietic cell transplantation (HCT) is a consolidation treatment for diseases in which there is a failure and/or deficiency of the hematopoietic system, including both neoplastic and non-neoplastic disorders. HCT procedure includes the reduction of bone marrow cellularity by means of conditioning with high doses of chemotherapy and or radiotherapy, followed by an infusion with normal stem cells. The stem cells will replace the original hematopoietic cells precursors, improving the free-disease survival.

The HCT conditioning causes high toxicity and prolonged immunosuppression, predisposing the patient to infections and injuries in several tissues. The digestive system is particularly affected by conditioning-induced toxicity, being the oral cavity one of the most affected site. Oral mucositis (OM) is an important dose-limiting adverse event that occurs immediately after the HCT. OM is a painful inflammatory condition that can impair the oral intake, and compromise the patient´s quality of life. Difficulties of eating and swallowing often predispose a significant loss of body weight and a nutritional imbalance (Eduardo et al., 2018). In addition, ulcerated OM favors secondary oral infections, increasing the risk of bacteremia and sepsis in the immunocompromised patients (Elad et al, 2015).

Currently, photobiomodulation therapy (PBMT) protocols have been proposed for OM prevention and treatment in different phases of the transplantation procedure. The majority of studies have used laser devices and a great variability of the light dosimetry. **Table 1** shows studies published in the last 10 years focused in HCT patients and the PBMT effect on preventing or reducing oral mucositis severity and oral pain. Despite the dosimetry variation and the type of light used, all of them showed efficacy of PBMT.

However, in these studies the frequency of immediate and late side effects was not reported, leading to questions about the safety of this therapy in the immunocompromised individual.

Some authors have raised questions about the role of PBMT on those patients exposed to mutagenic agents, such as chemotherapy and radiotherapy, based on the principle that PBMT, depending of the dose, can induce modulation of oxidative stress, cell proliferation, growth factors release, and several transcriptional pathways of activation, among other mechanisms that could favor tumor recurrence or the development of secondary malignancy (Sonis et al., 2016; Zecha et al., 2016a). Systematic reviews and retrospective investigations evaluated the PBMT safety in oncologic patients, addressing mainly individuals who underwent chemotherapy and radiotherapy or radiochemotherapy for tumors of the head and neck (Brandão et al., 2018; de Pauli Paglioni et al., 2019; Bensadoun et al., 2020). These studies concluded that PBMT is safe. However, because there is a great variability in the parameters used (dosimetry, wavelength, time and protocols of application), further clinical investigation is necessary.

To the best of our knowledge, there is no study addressing the PBMT safety for HCT patients. During the HCT procedure, the patient is exposed to high doses of chemotherapy and radiotherapy with few fractionations, inducing a high mutagenic stress in the majority of the body tissues. Moreover, these patients are immunosuppressed for a long time, increasing significantly the risk of secondary malignancies (Heydari et al., 2020). The oral cavity is one of the most affected sites by secondary tumors (Santarone et al., 2020), probably due to a persistent genomic instability in the oral mucosa after the transplantation (Khan et al., 2010).

The aim of this study was to investigate the safety of PBMT in HCT patients. We analyzed different PBMT protocols for OM prevention and treatment. This single HCT center retrospective study aimed to determine whether there is an association of PMBT with immediate and late adverse effects or the development of secondary malignancies in the head and neck region. We also evaluated the development of OM in all the patients exposed to PBMT and the impact of this condition on the overall survival.

Materials And Methods

This was a single center retrospective, observational study carried out using data collected from medical and dental records of patients treated at the Bone Marrow Transplant Center at Hospital Israelita Albert Einstein (HIAE). The methodology described below was previously approved by the Research Ethics Committee of our institution (Project #3471-18) 98904918.4.0000.0071

Oral Care Protocol

The study was conducted by dental professionals with expertise in oncology working in the oral oncology section of the Bone Marrow Transplant Center. Prior to start conditioning, all patients were evaluated by the oral oncologists and treated as needed for stabilization of oral disease. Dental and periodontal infection, elimination of areas that could produce trauma to the oral tissues, extraction of hopeless teeth and implementation of the institutional oral care protocol were conducted. Patients were educated about

the importance of maintaining oral hygiene and the procedures associated with PBMT protocol, including patient acceptance.

Eligibility criteria

All available medical and dental records of patients who underwent HCT during the period of January 2004 to December 2019 were surveyed. Inclusion criteria were: any age, both sexes, autologous or allogeneic HSCT, prescription of oral care protocols in the pre, trans, and post-transplantation periods until marrow engraftment, prescription of PBMT, description of frequency and severity of oral mucositis throughout transplantation, description of the conditioning regimen and graft-versus-host disease (GVHD) prophylaxis. Records must have had a description of the patient's general systemic condition. Exclusion criteria were: medical records of patients who did not adhere to the protocol of oral care, absence or insufficient information about the oral conditions, PBMT protocol, and oral mucositis, death before the neutrophil engraftment, and graft failure.

Data collection

We collected data on age, sex, primary diagnosis, transplantation type, conditioning regimen, GVHD prophylaxis, and day of neutrophil engraftment (>500 neutrophils/mm^3). The conditioning regimen was classified accordance with the risk for oral mucositis as follows**:** ***high risk*** - BEAM (carmustine, etoposide, cytarabine, and melphalan); R-(rituximab)-BEAM; regimens containing busulfan, total body irradiation (TBI), and melphalan; ***low risk*** - other regimens. The GVHD prophylaxis with methotrexate, was considered high risk for OM. The medical informatics service of HIAE provided data for secondary malignancies, date of transplantation, date of death and the date of last follow-up.

Data about oral mucositis, oral care protocol prescription, and type of PBMT protocol were collected from the dental records. The data on the oral care protocol and the use of PBMT protocols was collected by the same team of dental professionals who have been performing patient care since 2004 when the oral oncology service was implemented at the HCT center at HIAE. Therefore, the information obtained on oral health status and oral mucositis, as well as the utilization of the PBMT protocol, was standardized. This team also inquired the patient about adverse effects immediately after the PBMT procedure, such as, oral discomfort, tingling in the irradiated site, burning sensation etc. Absence or presence of these events were registered in the dental records.

Oral mucositis was classified in accordance with WHO classification (WHO, 1979), as follows: 0 – without lesions; 1 – oral soreness, only erythema; 2 – oral erythema and ulcers, but solid diet is tolerated; 3 – oral ulcers, only liquid diet is tolerated; 4 – oral ulcers, artificial nutrition is needed. The oral oncology team collected oral mucositis grade daily. After healing occurred, only the highest degree of OM was considered and the number of days with oral mucositis were also recorded.

Statistical analysis

Categorical data is presented in absolute and relative (%) frequencies. Numerical data is shown in median and minimum/maximum values. Overall survival was calculated using Kaplan-Meier curve. The follow-up was from the first day of transplantation to the last day of contact with the patient (censored cases) or the death day. The impact of oral mucositis on overall survival was calculated by means of Cox proportional hazards regression. For this, oral mucositis degrees were classified as absent (grade 0), mild (grade 1), moderate (grade 2), and severe (grades 3 and 4). The level of significance was set as 5%.

Results

Medical records selection

From 2004 to 2019, 841 medical records of patients who underwent HCT were surveyed. Of these, 148 were excluded due to patient´s death before the engraftment (n=18), graft failure (n=27), and absence of enough medical and dental data (n=103) **(Figure 1).**

Patient and transplantation characteristics

A total of 693 records were reviewed. The majority of patients were male (59.0%), with a quite variable age frequency, including 3-11y.o. children (12.0%), and 31-60y.o. adults (42.5%). A significant frequency of >60y.o. patients (24.5%) was also included. Leukemias (28.1%), lymphomas (21.6%) and multiple myeloma (18.2%) were the most common primary disease groups **(Table 2).**

Patients received autologous (42.7%) and allogeneic (57.3%) HCT; in allogeneic HCT, there was a predominance of matched unrelated donor transplantation (26.7%). Conditioning regimens of high risk for oral mucositis were the most frequent, mainly melphalan alone (30.4%), and regimens containing busulfan (30.6%) and TBI (16.2%). For allogeneic transplantation, GVHD prophylaxis with methotrexate was prescribed with high frequency (52.6%) **(Table 1).**

Photobiomodulation therapy protocols

All patients included in the study were treated with PBMT. The same professional applied the PBMT therapy and the oral care protocol. During the years of patient care, the laser machine and the PBMT protocols were modified. Different parameters were used due to the modifications required by the laser machine. Four time periods were established in accordance with the PBMT protocol characteristics: 2004-2006; 2007-2014; 2015-2016; and 2017-2019. In addition, two different basic protocols of PBMT application were used, one for prevention of oral mucositis and other for the treatment when lesions developed. **Table 3** describes the information of the various PBMT protocols used throughout the 15 years of patient follow-up.

Oral mucositis prevention protocol

Laser parameters used for PBMT prevention started on the first or second day of the HCT conditioning and ended at neutrophil engraftment. The oral mucosal tissues had to be clear of any abnormalities or

any suggestion of OM (oral mucositis grade 0). Prevention protocol was done using red lasers (650nm or 660nm), with a lower energy density. The entire oral mucosa was irradiated (right and left buccal mucosa, upper and lower lip mucosa, lateral borders and ventral surface of the tongue, floor of mouth, and soft palate), with exception of tongue dorsum and hard palate, sites considered of low risk for oral mucositis. Comparing 2004-2006 with 2007-2014 period, the laser power increased from 0.04 to 0.1W. This higher power was maintained in the following periods. The time of irradiation also varied from 2s in 2004-2006 to 10s in 2017-2020. These variations in the laser parameters changed significantly the power and energy densities per point in the subsequent periods (**Table 3**).

Oral mucositis treatment protocol

The protocol for oral mucositis treatment was implemented when the oral mucosal tissues started to show early signs of OM such as erythema (oral mucositis grade 1). While the development of OM continued with atrophy, erosion or ulceration (oral mucositis grades 2, 3 and 4), the PBMT continued to be used. PBMT was also used when the patient reported oral discomfort or oral pain mainly during mastication and swallowing. The PBMT treatment protocol was applied only in areas with lesions. Areas around the lesions and the rest of the oral mucosa received parameters of prevention protocol. The laser parameters for oral mucositis treatment included both red and infrared wavelengths (650nm, 660nm, 780nm, and 808nm depending on the time of application **(Table 3).**

Laser equipment, power, spot area, and power density were the same used in the protocol for oral mucositis prevention. Irradiation time, energy per point, and energy density per point had higher values, in general double values **(Table 3).** The number of irradiation points were established in accordance with the size of each lesion. Starting in 2015, infrared lasers (808nm) were adopted for analgesia induction. During 2015-2016 period, lesions were first irradiated with 660nm and then with 808nm (consecutive irradiation). Starting in 2017, the laser machine was enhanced, allowing a 660nm and 808nm irradiation at the same time (simultaneous irradiation). This laser setting was indicated when patient reported extreme pain and discomfort. When the two wavelengths were used, the irradiated point received double energy, i.e., 2J derived from the 660nm and 2J derived from 808nm. Extraoral PBMT protocol was also used for patients with dysphagia, using infrared laser and a higher energy density (100J/cm^2 per point). The irradiation was performed in 12 points on the skin of the neck and in the region around the pharynx and esophagus (**Figure 2**)

There was no difference in the laser settings with regards to the patient´s age, type of conditioning and transplantation, as well as type of GVHD prophylaxis. Particularly to the pediatric patients with age <2y, some changes in the irradiation technique were implemented, such as performance of laser irradiation with the patient positioned on the mother´s lap. These adaptations were previously published (Eduardo et al., 2015).

Oral care protocol

The PBMT was adjuvant to a standardized oral care protocol, which was described in all the eligible medical records. All patients underwent dental and radiographic examination prior to transplantation. Oral infectious foci and traumatic surfaces were eliminated before the start of conditioning. From all the enrolled patients, 58% underwent some dental intervention in the pre-transplantation period, which included dental plaque prophylaxis, caries removal, scaling and root planning, occlusal adjustment, dental extractions, and prosthesis adjustments. During HCT, a dental professional performed daily oral examination to confirm the maintenance of oral health status, the absence of infection and to monitor the quality of oral hygiene. When oral fungal infections were suspected, a topical application of nystatin suspension 4 times/day was prescribed. When other opportunistic infections were suspected, the dentist performed appropriate diagnostic test and instituted indicated treatment. For the patients who received melphalan conditioning, an oral cryotherapy protocol was adopted during the conditioning, as previously described (de Paula Eduardo, 2015) in order to decrease the incidence of OM.

Adverse effects related to photobiomodulation therapy

No undesired adverse reactions could be seen during or after PBMT. The medical records reviewed did not reveal any documentation of adverse reactions. In addition, in the analyzed period, the department of health quality and safety at HIAE did not identify any adverse event related to the PBMT.

Oral mucositis severity

The majority of patients (90.1%) had some degree of oral mucositis. Mild to moderate severity (grades 1 and 2) was observed in 68.0%, and more severe OM (grades 3 and 4) was described in 12.0% of the patients (Supplementary Table 1). The frequency of severe (grades 3 and 4) OM in autologous and allogeneic HCT was 6.7% and 16.0% respectively. The median day of OM onset was at day +4, and the median time duration of the lesions was 6 days.

Secondary neoplasms after transplantation

Only 7/693 patients (1.0%) had a secondary neoplasm after transplantation, 2 in patients who received autologous and 5 in patients who received in allogeneic HCT (Supplementary Table 2). All cases occurred in adult patients. One case was a myelodysplastic syndrome and the other 6 cases were solid tumors: breast cancer (2), pancreatic cancer (2), and head and neck cancer (2). Head and neck cancers affected the tongue and esophagus.

The tongue cancer was diagnosed in 50 y.o. male, who received an allogeneic transplantation with R-BEAM conditioning. The neutrophil engraftment occurred on Day+15, and the maximum degree of OM was grade 1. Treatment included a partial glossectomy followed by radiotherapy (60Gy). Until the end of the study the patient was well and had no history of recurrence. Oral GVHD was not detected during this period.

Impact of oral mucositis in the overall survival

The median follow-up in the study was 84.5 months (3-405 range). Considering all enrolled patients, the five-years overall survival was 62.6% (95%IC=58.0-67.0%). When the patients were stratified in accordance with the oral mucositis severity, moderate (HR=1.61, p=0.025) and severe (HR=1.96, p=0.008) oral mucositis reduced significantly the overall survival **(Figure 3).**

Discussion

In this retrospective study, we aimed to evaluate the short and long-term safety of the PBMT in prevention and treatment of OM in HCT patients. We evaluated the development of adverse reactions of PBMT in the oral cavity and the occurrence of secondary malignancies. To our knowledge this is the first single-center long-term study with a high number of patients (693) focused on the analysis of the safety of PBMT in HCT.

The analysis of early and late oral complications PBMT-induced did not reveal any harm, suggesting that PBMT is a safe therapy in this patient population. There were also no associated systemic side effects. The frequency of the secondary malignancies in the head and neck region, particularly in the oral cavity, was low not revealing a specific association with PBMT. Another important finding was that moderate and severe OM affected the overall survival of these patients.

The variation of PBMT parameters

This was a long-term study over a period of 15 years. During this period of time, several changes occurred in the type of laser wavelength and parameters used in the delivery of PBMT. Most of the variations in parameters involved the increase of power and energy density delivered to the oral tissues and OM lesions. A significant variation was the implementation of a laser device that could deliver light in the red and infrared wavelengths simultaneously.

The increase of energy and power densities were related to two specific facts: first, the majority of low intensity laser machines in Brazil have the power fixed at 0.1W, not allowing adjustments of this setting; second, the clinicians observed that the clinical outcomes of the PMBT protocol with higher energy and power density produced better effect in the treatment of OM. The laser machine that emits the red and infrared wavelengths simultaneously promotes healing of inflammation and pain control. This is desired when delivering care at bedside. In addition, the PBMT protocol was adjusted over time based on the evidence of increased OM risk.

The prevention and treatment protocols for OM

The HCT patients enrolled in the present study were treated with two different PBMT protocols, one for prevention and other for the treatment of oral mucositis. The two protocols involved energy densities considered high (from 8J/cm^2 to 22.2J/cm^2) when compared to the literature for oral mucositis control.

The prevention protocol involved shorter irradiation time per point, leading to a lower energy density (up to 11.1J/cm^2). The main objective of this protocol was to maintain the epithelial and connective tissue integrity by stimulating keratinocytes and fibroblasts renewal (George et al., 2018). Moreover, a prevention protocol can reduce the risk of oral mucositis in the critical periods of the transplantation. Recent systematic reviews and meta-analyses (He et al., 2018; de Lima et al., 2020; Peng et al., 2020) have demonstrated efficacy of PBMT in the prevention of oral mucositis severity, although more clinical studies focused on HCT patients are necessary for improving the scientific evidence of this therapy.

The treatment protocol was indicated when clinical signs of oral mucosal injury were present. This protocol increased the irradiation time and used a higher energy density (up to 22.2J/cm^2). In addition to higher doses, the laser machine delivered 660nm and 808nm wavelengths simultaneously, aiming to improve the photon interaction with different chromophores and promoting the photon resorption at different depth levels (Hamblin, 2017). The main objective of this protocol was to induce analgesia, for the reestablishment of oral intake and the improvement of patient´s quality of life.

Past studies have demonstrated efficacy in reducing pain caused by oral mucositis in HCT patients (Schubert et al., 2007, Ferreira et al., 2016), but their protocols used red lasers and lower energy densities. A previous study demonstrated a significant reduction of oral mucositis severity and analgesics prescription in cancer patients submitted to radiotherapy in the head and neck region when 660nm and 808nm were associated with a higher energy density (300J/cm^2) (Soares et al., 2018). Furthermore, the association of red and infrared wavelengths can improve tissue repair by the increasing the collagen matrix and reducing inflammation (Santos et al., 2011); Nevertheless, more comprehensive clinical studies involving the oral mucosa, variations on the dosimetry, and association of the two wavelengths are necessary to confirm this trend.

Scientific evidence has suggested that dosimetry up to 6J/cm^2, 150mW, and use of 633-685nm and 780-830nm wavelengths is safe (Zecha et al., 2016b). Systematic reviews of PBMT used to prevent and control oral mucositis recommended higher values, including 12, 35, and 70J/cm^2 (Migliorati et al., 2013, Zadik et al., 2019). Others showed that PBMT applied in patients who underwent radiotherapy in the head and neck region was not associated to any adverse effects (Antunes et al., 2017; de Pauli Paglioni et al., 2019). Another study used 10J/cm^2 daily, without adverse events and safety issues reported in H & N cancer patients (Brandão et al., 2018). However, the majority of the studies in the current literature had short follow-ups. Therefore, the question about the risk of secondary malignancies or tumor recurrence in the head and neck region needs further investigation (de Pauli Paglioni et al., 2019).

In the current study, the highest doses were 11,1J/cm^2 and 22,2J/cm^2, which were compatible with the range of dosimetry values reported in other studies with HCT patients **(Table 1).** Based on the absence of adverse effects, no association with secondary malignancies in the head and neck region, and low frequency of severe of oral mucositis (grades 3 and 4) we can consider the parameters used in the present study to be safe.

Secondary malignancies

Secondary malignancies are the one of the most important late complications in post-HCT period, affecting mainly patients receiving allogeneic transplantation (Heydari et al., 2020). Second primary oral cancers are one of the most frequent neoplasms in the HCT patients (Santarone et al., 2020). A study showed 2.7% incidence of oral squamous cell carcinoma as a second primary malignancy in allogeneic HCT. Risk factors associated with the malignancy development included myeloablative conditioning and presence of chronic GVHD in the oral cavity (Santarone et al., 2020).

In the present study, only 1/693 (0.01%) patient developed a secondary malignancy in the oral cavity. We were not able to find any association of PBMT adverse reactions with the development of this neoplasm.

Overall survival and oral mucositis

The frequency of severe oral mucositis was low (12.0%). A comprehensive systematic review (Chaudhry et al., 2016) showed frequencies of severe oral mucositis varying from 19.4 to 83.0% and from 23.5 to 90.6% in allogeneic HCT performed with myeloablative conditioning and reduced intensity conditioning, respectively. Although oral care protocols and oral cryotherapy were used, none of them implemented the use of PBMT. In the current study, a daily specialized oral care protocol was done for all HCT patients. In addition, oral cryotherapy was used in patients who underwent melphalan conditioning. Therefore, based on the very low frequency of grades 3 and 4 oral mucositis, the implementation of oral care, cryotherapy when indicated and PBMT use can be recommended in the transplant setting (Bezinelli et al., 2014). Further clinical studies with HCT patients are necessary to confirm this hypothesis.

Although the frequency of severe oral mucositis was low, grades 3-4 oral mucositis reduced significantly the overall survival, suggesting that the prevention and control of OM is one of the most important steps in transplantation. New PBMT strategies focused on the patients at high risk for severe oral mucositis, such as those receiving allogeneic transplantation, myeloablative regimens, and with GVHD prophylaxis using methotrexate, must be investigated.

A significant limitation of this study was the absence of a control group, not allowing a complete extrapolation regarding to the PBMT safety. Absence of oral GVHD data is also an important limitation, because the oral mucositis is considered a possible risk factor for this complication, and probably the PBMT may have a positive role on oral acute and chronic GVHD. The use of PBMT for other oral conditions, such as infectious, traumatic, and immune-mediated lesions, was not addressed, limiting also the knowledge about the PBMT effect and safety in these circumstances.

In conclusion, the PBMT protocols for oral mucositis prevention and treatment in the HCT patients were not associated with immediate and late adverse effects and were not related to the development of secondary malignancies in the oral cavity. The low frequency of severe OM detected in this study encourages the implementation of these protocols, with a special emphasis on the need for the correct use of dosimetry in PBMT.

Declarations

Funding - the study did not have any funding

Conflict of interest - The authors declare that there is no conflict of interests as regards the publication of this paper.

Availability of data and material - All the data showed in the study support our claims and comply with field standards.

Code availability: N/A

Ethics approval - This retrospective chart review study involving human participants is in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. The Human Investigation Committee (IRB) of Hospital Israelita Albert Einstein approved this study (#3471-18 – HIAE).

Authors' contributions:

- Letícia Mello Bezinelli - contributed with study conception and design, data acquisition and interpretation, and critical review of the manuscript.
- Luciana Corrêa - contributed with study design, data interpretation, and manuscript draft.
- Cristina Vogel - contributed with study conception and design, data acquisition and interpretation, and review of the manuscript..
- Jose Mauro Kutner - contributed with data interpretation and critical review of the manuscript.
- Andreza Feitosa Ribeiro - contributed with data interpretation and critical review of the manuscript.
- Nelson Hamerschlak - contributed with study design and critical review of the manuscript.
- Carlos de Paula Eduardo- contributed with study conception and design, data acquisition and interpretation, and critical review of the manuscript.

Cesar Augusto Migliorati- contributed with study conception and design, and with a critical review of the manuscript.

Fernanda de Paula Eduardo - contributed with study conception and design, data acquisition and interpretation, and critical review of the manuscript.

Consent to participate: An informed consent to participate in this study was not signed by the patients because the data were collected from archived medical records, being impossible to contact the majority of the patients or their legal guardian. Principles of confidentiality, privacy, and data protection were entirely adopted in the study and in the manuscript.

Consent to publish: Informed consent to publish this study was not signed by the patients because the data were collected from archived medical records, being impossible to contact the majority of the patients or their legal guardian. Principles of confidentiality, privacy, and data protection were entirely adopted in the study and in the manuscript.

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Tables

Table 1
– Efficacy of photobiomodulation therapy for reduction of oral mucositis severity and oral pain reported in clinical studies*.

Patients (number and age range)	Type of HCT	PBMT protocol	Outcomes for oral mucositis severity	Outcomes for oral pain	Reference
N = 49 (24 laser and 25 control)	Autologous and allogeneic	InGaAlP laser, 660 nm, 10 mW, 10s irradiation per point, 2.5J/cm^2	Reduction, but not significant, on the frequency of severe oral mucositis in the laser group	Significant reduction of oral pain in the laser group	Jaguar et al. (2007)
N = 70 (23 laser 650nm, 23 laser 780nm, 24 control)	Autologous and allogeneic	InGaAlP laser, 650 nm, 40 mW, and InGaAlP laser, 780nm, 60 mW; both arms with 2J/cm^2; irradiation time per point and spot area not informed	Significant reduction on the frequency of severe oral mucositis in the 650nm laser group	Significant reduction of oral pain in the 650nm laser group	Schubert et al. (2007)
N = 42 (21 laser and 21 control)	Autologous and allogeneic	InGaAlP laser, 660 nm, 0.04 cm^2 spot area, 40 mW, 0.16J per point, 4s irradiation per point, 4J/cm^2	Significant reduction on the frequency of severe oral mucositis in the laser group	Not evaluated	Santos et al. (2011)
N = 80 (40 laser and 40 control)	Autologous and allogeneic	LED, 670nm, 50mW/cm2, 80s irradiation per point, 4J/cm^2, extraoral application (cheeks and throat region)	Reduction, but not significant, on the frequency of severe oral mucositis in the laser group	Significant reduction of pain in the laser group	Hodgson et al. (2012)
N = 24 (12 laser and 12 control)	Autologous and allogeneic	InGaAlP laser, 685 nm, 35 mW, 0.35J per point, 10s irradiation per point, energy density not informed	Significant reduction on the frequency of severe oral mucositis in the laser group	Not evaluated	Silva et al. (2015)
N = 35 (17 laser and 18 sham)	Autologous and allogeneic	InGaAlP laser, 650 nm, 0.028 cm^2 spot area, 100 mW, 2J per point, 20s irradiation per point, 70J/cm^2	Significant reduction on the frequency of severe oral mucositis in the laser group	Significant reduction of oral pain in the laser group	Ferreira et al. (2016)

Patients (number and age range)	Type of HCT	PBMT protocol	Outcomes for oral mucositis severity	Outcomes for oral pain	Reference
N = 68 (34 laser and 34 control)	Autologous and allogeneic	InGaAlP laser, 660 nm, 0.04 cm^2 spot area, 40 mW, 0.16J per point, 4s irradiation per point, 4J/cm^2	Significant reduction on the frequency of severe oral mucositis in the laser group	Not evaluated	Salvador et al. (2017)

* Only studies with control group and information about the photobiomodulation therapy were included.

Table 2
– Main clinical characteristics of the patients and transplantation.

Sex	**N**	**%**
Male	409	59.0
Female	284	41.0
Age	N	%
0-2y	47	6.8
3-11y	83	12.0
12-20y	46	6.6
21-30y	52	7.5
31-40y	80	11.5
41 – 50	92	13.3
51-60y	123	17.7
61-70y	136	19.6
71-76y	34	4.9
Primary disease group	N	%
Anemias	33	4.8
Autoimmune diseases	31	4.5
Genetic syndromes	20	2.9
Immunodeficiencies	53	7.6
Leukemias	195	28.1
Lymphomas	150	21.6
Multiple myeloma	126	18.2
Other myeloproliferative disorders	57	8.2
Solid tumors	28	4.0
Type of transplantation	N	%
Autologous	296	42.7
Allogeneic	397	57.3

Sex	N	%
Matched related donor	115	16.6
Matched unrelated donor	185	26.7
Haploidentical	97	14.0
Conditioning regimen	N	%
BEAM or R-BEAM	73	10.5
Melphalan	211	30.4
Containing busulfan	210	30.3
Containing total body irradiation	112	16.2
Other	87	12.6
Graft-versus-host disease prophylaxis	N	%
Containing methotrexate	209	52.6
Other	188	47.4
Neutrophil engraftment (day+)	Median	Range
	11	7–43

BEAM (carmustine, etoposide, cytarabine, and melphalan); R- (rituximab).

Table 3

– Laser parameters indicated for oral mucositis prevention and treatment in accordance with different periods of the HCT patients survey.

	Periods (years)			
Indication for oral mucositis	2004–2006	2007–2014	2015–2016	2017–2020
Prevention				
Equipment	Twin laser (MMO, São Carlos, SP, Brazil)	Therapy (DMC, São Carlos, SP, Brazil)	Therapy XT (DMC, São Carlos, SP, Brazil)	Therapy EC (DMC, São Carlos, SP, Brazil)
Type	diode	diode	diode	diode
Power (W)	0.04	0.1	0.1	0.1
Wavelength (nm)	650nm	660nm	660nm	660nm
Spot area (cm^2)	0.04	0.04	0.04	0.09
Mode	punctual	punctual	punctual	punctual
Energy (J) per point	0.08	0.3	0.4	1
Irradiation time (s) per point	2	3	4	10
Power density (W/cm^2)	1	2.5	2.5	1.1
Energy density (J/cm^2)	2	8	10	11.1
Therapy frequency	Daily	Daily	Daily	Daily
Beginning and ending of the therapy	From first day of conditioning to neutrophil engraftment	Second day of conditioning; neutrophil engraftment		
Treatment				
Equipment	Twin laser (MMO, São Carlos, SP, Brazil)	Therapy (DMC, São Carlos, SP, Brazil)	Therapy XT (DMC, São Carlos, SP, Brazil)	Therapy EC (DMC, São Carlos, SP, Brazil)
Type	diode	diode	diode	Diode
Power (W)	0.04 and 0.06	0.1	0.1	0.1

	Periods (years)			
Wavelength (nm)	650nm and 780nm	660nm and 808nm	660nm and 808nm	660nm and 808nm
Spot area (cm^2)	0.04	0.04	0.04	0.09
Mode	punctual	punctual	punctual	punctual
Number of points in the oral mucosa	In accordance with the lesion area; 1cm distance between each point			
Energy (J) per point	0.08	0.5	2	2
Irradiation time (s) per point	2	5	8	20
Power density (W/cm^2)	1	2.5	2.5	1.1
Energy density (J/cm^2)	2	12.5	20	22.2
Therapy frequency	daily	daily	daily	daily
Beginning and ending of the therapy	From first day of clinical sign and symptoms onset to two days after the clinical sign and symptoms disappearance			

The description of dose parameters was individual for each wavelength.

* From 2010y, it was adopted an extraoral PBMT protocol for patients with dysphagia, performed in the neck region around the pharynx and esophagus with the following parameters: 808nm, 0.1W, punctual, 40s, 0.04 spot area, $2.5W/cm^2$, 4J per point, $100J/cm^2$ per point.

Figures

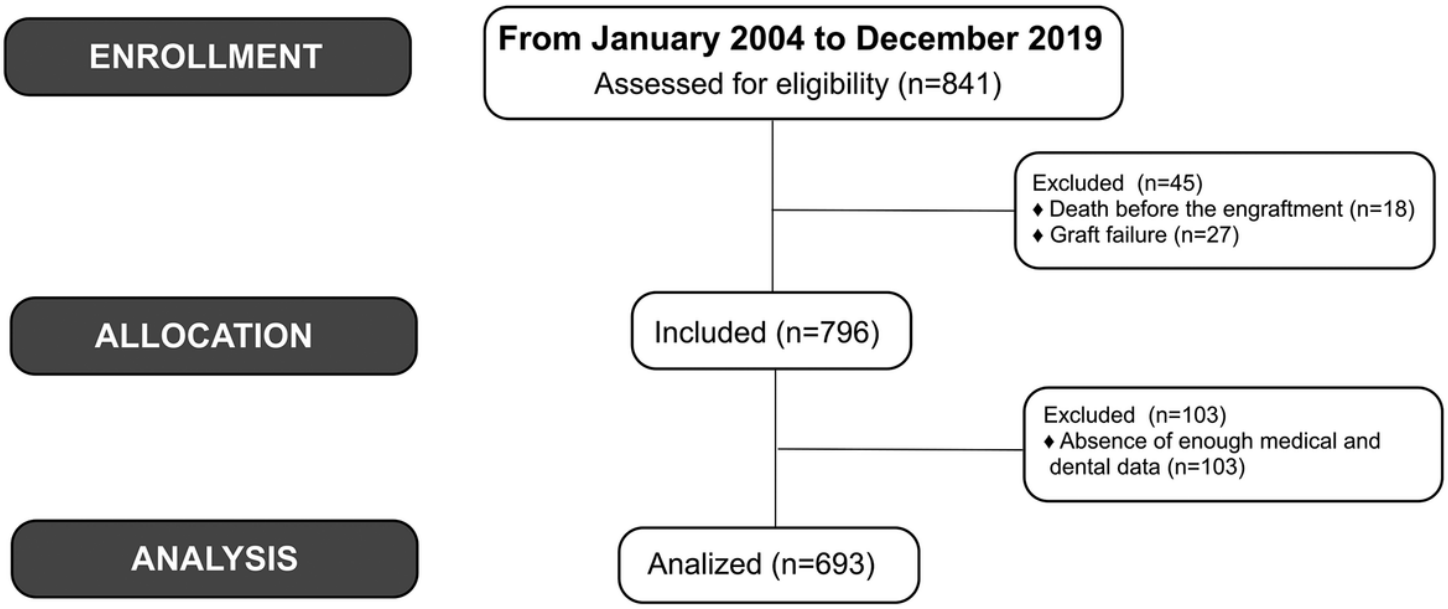


Figure 1

Flow chart of the patients in accordance with the inclusion and exclusion criteria.

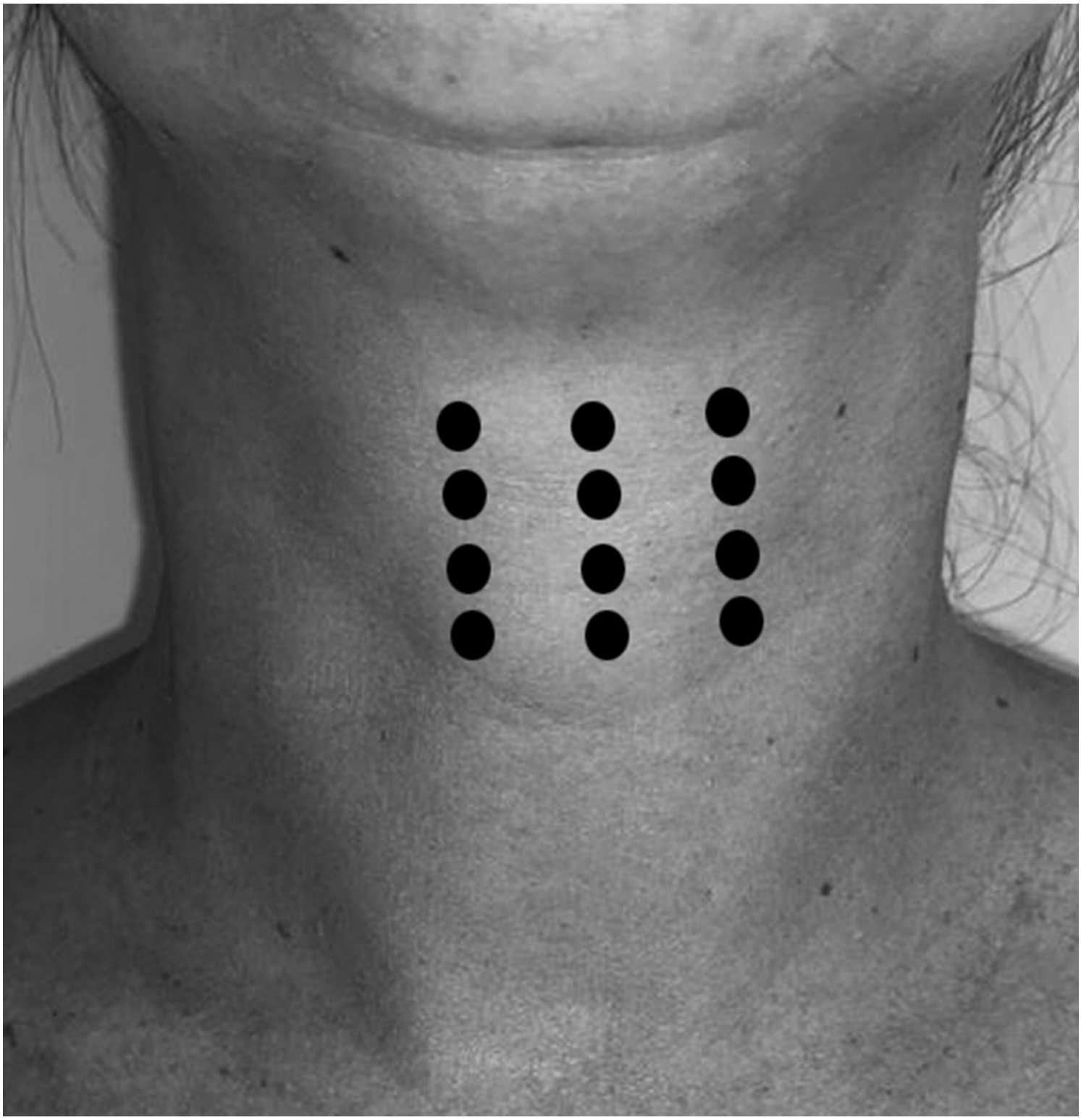
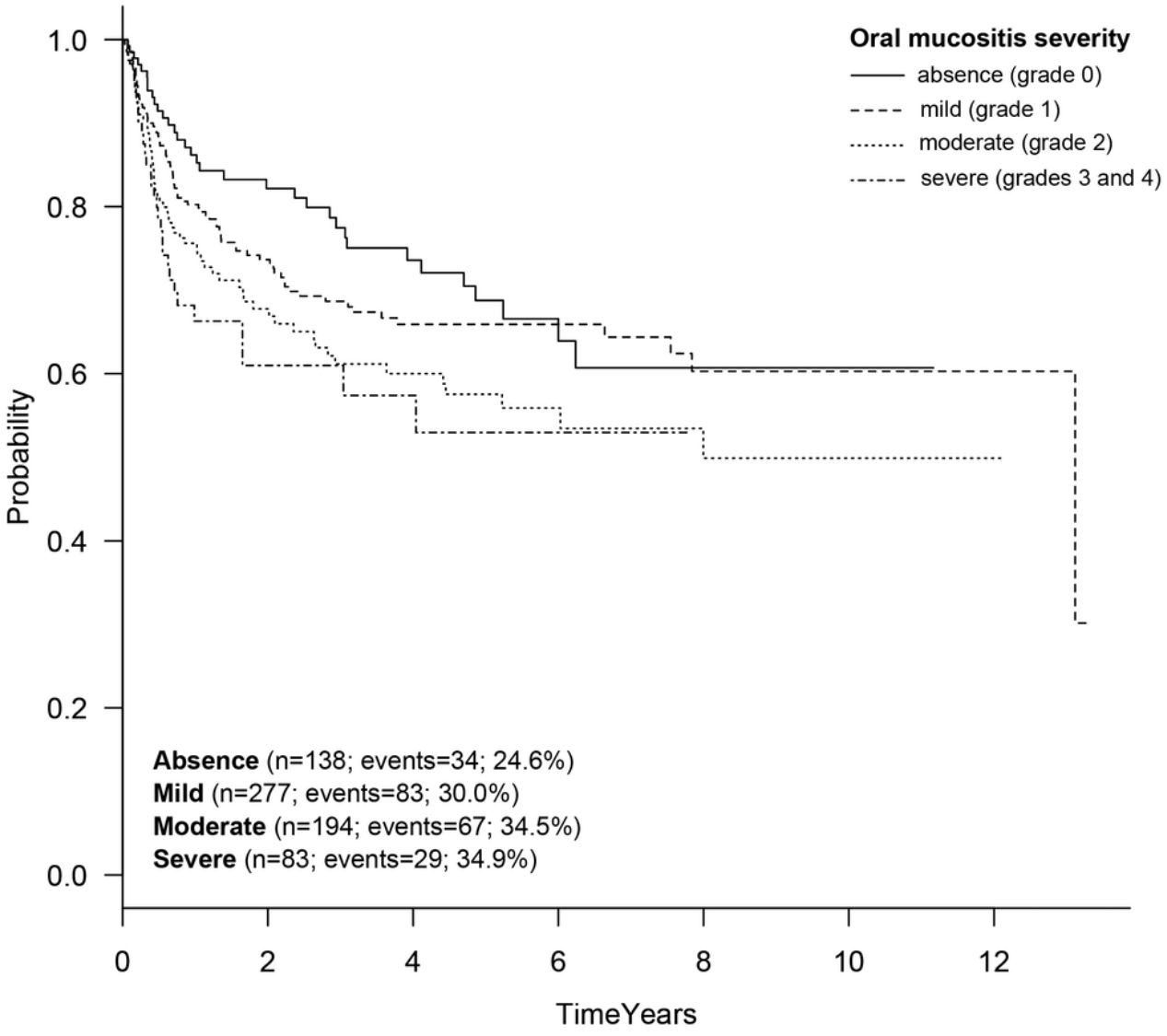


Figure 2

Irradiation points for photobiomodulation therapy in the extraoral region in patients with pharyngeal and esophageal mucositis.



Cox regression - final model

Oral mucositis severity	Overall survival (95%CI)	HR	p
Absence	7.9 (6.9-8.8)	1.00	
Mild	8.8 (8.0-9.6)	1.21 (0.81-1.80)	0.353
Moderate	7.1 (6.1-8.0)	1.61 (1.06-2.43)	**0.025**
Severe	4.7 (3.8-5.6)	1.96 (1.19-3.22)	**0.008**

Figure 3

Kaplan-Meyer curve and Cox regression final model for overall survival in accordance with oral mucositis severity in patients who underwent hematopoietic cell transplantatio

Supplementary Files

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- SupplementaryTable1.docx
- SupplementaryTable2.docx