Preventive versus curative photobiomodulation for oral mucositis in patients with multiple myeloma undergoing hematopoietic stem cell transplantation: which approach is more effective?

Katia Rupel[1] · Arianna Cornacchia[1] · Monica Poiani[2] · Sara Mohamed[2] · Eleonora De Bellis[2] · Mario Ballerini[2] · Theodora Magdalena Bogdan Preda[1] · Augusto Poropat[1] · Roberto Di Lenarda[1] · Francesco Zaja[1,2] · Matteo Biasotto[1] · Giulia Ottaviani[1]

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Abstract

Purpose There is increasing evidence that photobiomodulation (PBM) therapy is both an effective and safe approach in hematopoietic stem cell transplantation (HSCT) for both prevention and management of oral mucositis (OM), but its use in clinical practice is still limited and the timing of application is under discussion. The aim of this retrospective study was to evaluate possible differences between patients treated either with preventive or curative PBM therapy.

Methods The retrospective case series included 24 patients suffering from multiple myeloma who underwent the same conditioning and transplantation protocol. Patients were treated either with preventive PBM starting from the first day of conditioning up to two days post-HSCT or with curative PBM (starting at OM onset for four consecutive days). OM score, pain, and functional parameters were recorded.

Results All patients developed OM. Preventive PBM was significantly more effective in reducing OM severity ($p < 0.0001$) and pain ($p < 0.0001$) post-HSCT than curative PBM. Furthermore, we found a lower number of patients reporting discomfort in all subjective parameters (pain during swallowing, chewing, and speaking) in the preventive PBM group. No adverse events related to PBM therapy were recorded in both groups.

Conclusion The timing for PBM therapy in patients undergoing HSCT is crucial: when started on the first day of conditioning, it significantly reduces both pain and OM severity, providing an important benefit also in subjective oral functions such as speaking, swallowing, and chewing, thus increasing the overall adherence to the oncological therapies.

Keywords Photobiomodulation · Oral mucositis · Hematopoietic stem cell transplantation · Supportive care in hematological cancer · Laser therapy · Multiple myeloma

Introduction

Mucositis is a common and feared adverse effect of oncological patients undergoing anticancer treatments; it can develop throughout the gastrointestinal tract, from mouth to anus, and symptoms may vary depending on the affected site [1]. While gastrointestinal mucositis is often associated with nausea, vomiting, diarrhea, bloating, intestinal cramps, and anal pain [2], oral mucositis (OM) is associated to pain, difficulty in eating and in swallowing, need for enteral or parenteral nutrition, and sometimes with a need to increase opioid use and discontinue anticancer therapy [3, 4]. Furthermore, mucositis is a threat to the effectiveness of therapy because it may cause local or systemic infections and frequently lead to dose reduction, increase health costs due to hospitalization and antibiotics need, and compromise patients' quality of life and patients' outcome [5, 6].

The incidence of OM is about 30–40% in oncological population in general [7]; however, multiple myeloma (MM) patients undergoing high-dose chemotherapy (CT)

Katia Rupel and Arianna Cornacchia contributed equally to this work.

✉ Katia Rupel
krupel@units.it

[1] Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

[2] UCO Hematology, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

based on melphalan 200 mg/m^2 before autologous hematopoietic stem cell transplant (HSCT) have a mean incidence of 76% [8]. Conditioning regimens for autologous HSCT trigger OM in about 35–75% of patients, while in allogeneic transplant, the incidence rises up to 75–100%, depending on the type of disease, transplantation procedure, and conditioning regimen [9]. For neutropenic patients, due to CT conditioning, it represents a significant risk for the development of systemic infection [6] with twice the risk of infection and four times the risk of death compared to patients without OM.

Pain evoked by the presence of OM can impact on oral nutritional status, since food intake may prove difficult, thus worsening patient's general health. A proper management of OM would also reduce analgesic necessity and reduce the duration and the costs of hospitalization [10, 11].

For all these reasons, the clinical approach should include both the prevention and the treatment of early oral manifestations, according to the latest MASCC guidelines [12]. Prevention includes various measures such as maintaining good oral health, chlorhexidine or sodium bicarbonate rinses, cryotherapy [13], and administration of intravenous KGF-1 [14].

Recently, several studies confirmed the beneficial role of PBM in the management of OM [15]; particularly, daily sessions of PBM following OM onset up to 4 days later elicited immediate pain relief and decreased severity and duration of OM [16–18]. However, attention has been recently focused on PBM preventive strategies, which demonstrated further efficacy: MASCC guidelines, indeed, recommend PBM use in patients undergoing HSCT [12]. However, despite such evidences and recommendations, the application of PBM for the prevention and treatment of OM in HSCT patients is undervalued, and there is still a lack of universally accepted disease-specific PBM protocols [19], either considering wavelength choice and fluence parameters, or the timing of application (preventive or curative intent) [20].

Furthermore, the application of PBM presents resistance of different kinds: cost of the instruments, need for operator training, and clinical time required to carry out the treatment. For several structures, this effort is not sustainable; therefore, one of the possibilities could be to start performing PBM only at the appearance of signs of OM. It is still unclear what could be the difference in terms of the severity of the mucositis itself and the pain developed by the patient, so here we present a retrospective case series study that aims at comparing OM grade and associated pain in a cohort of patients affected by MM undergoing autologous HSCT, treated either with preventive or curative PBM.

Materials and methods

Patients

The present retrospective non-randomized case series study was performed according to the ethical standards of the 1975 Declaration of Helsinki (7th revision, 2013) upon approval by the ethical committee of the University of Trieste (n. 115/2021). The study included 24 adult patients with MM who underwent a single autologous HSCT with melphalan 200 mg/m^2 at the Transplant Unit of the UCO Hematology, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy, and were evaluated and treated with PBM at the Oral Medicine and Pathology Unit (Ospedale Maggiore, Trieste, Italy).

Treatment

Among the 24 patients included, 12 underwent PBM starting from the first day of conditioning regimen up to the second day after transplantation (group Preventive PBM, PrPBM) following the MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy [12], while 12 patients underwent PBM starting from the onset of OM for four consecutive days (group Curative PBM, CuPBM). In both groups, PBM was delivered for four consecutive days. The total number of days depends mainly on the length of conditioning and for all the patients included in the study it lasted 1 day.

Both groups were treated with the following PBM protocol: diode laser source, 660 nm and 970 nm combined wavelengths, irradiance 100 mW/cm^2, fluence 2 J/cm^2, spot size 0.8 cm^2, continuous wave, and 18 sites throughout the entire oral cavity (K-Laser Cube 3, Eltech K-Laser s.r.l., Strada Castagnole 20/H, Treviso, Italy). The protocol was defined according to previous studies performed by our research group [18, 21] and literature evidence [22–24]. Both patients and operators wore protective glasses during the treatment to avoid possible eye damage. PBM was provided using a rotatory motion all over the oral cavity to cover both ulcerated and healthy areas, keeping a 1-cm distance between the probe and the tissue.

Patients were evaluated daily by both hematologists and oral medicine specialists daily, and clinical variables were recorded at the following time points: at T0 (first day of PBM therapy, i.e., at the timing of OM onset for CuPBM group and at the first day of the conditioning regimen for PrPBM group), T7 (7 days after T0 in both groups), and T14 (14 days after T0 in both groups). At each time point, experienced clinicians registered information about patients' clinical variables and scored OM severity

according to the World Health Organization (WHO) oral mucositis grading [25]. OM severity is assessed on a scale from 0 to 4, where (0) no findings; (1) erythema and soreness, no ulcers; (2) oral erythema, ulcers, solid diet tolerated; (3) oral ulcers, liquid diet only; and (4) not able to tolerate a solid or liquid diet. A 0–10 numerical rating scale (NRS) was employed to quantify pain. Additional functional oral parameters recorded were difficulties in swallowing, speaking, and chewing. At each time point (T0, T7, and T14), patients were asked to respond dichotomously (yes/no).

In addition, the percentage of engraftment was recorded, and the days required to reach a count of neutrophils > 500/mm^3 and of platelets > 20.000/mm^3.

Sample size calculation

Primary endpoint was difference in OM severity. Sample size was therefore calculated considering an expected difference in the mean OM grading of 1 ± 1.5 at T7 (7 days after starting PBM) between groups. Sample size calculation was performed employing the ClinCalc tool (Kane SP. Sample Size Calculator. https://clincalc.com/stats/samplesize.aspx. Updated July 24, 2019). The significance level and test power were 95% and 90%, respectively. Sample size was calculated to be 12 patients for each group.

Statistical analysis

The Prism 6.0 software (GraphPad Software, La Jolla, California, USA) was used to perform statistical analysis. All statistical assessments were two-sided, and a p value < 0.05 was used for the rejection of the null hypothesis. Descriptive variables are reported using percentages, mean, and standard deviation. Friedman's test was employed to test significance of changes over time in NRS and OM grading, while Dunn's multiple comparison test was used as post hoc to compare each pair of time points. The Mann–Whitney U test was employed to evaluate differences between groups at each time point and to evaluate differences between groups in numerical variables. Chi-squared test was used to evaluate significance of differences between groups in categorical variables.

Results

Patients

All patients completed the HSCT transplantation procedures with 100% of engraftment. There were no significant differences between groups in the number of days required to reach a count of neutrophils > 500/mm^3 and of platelets > 20.000/mm^3. There was a significantly lower mean age in the CuPBM group ($p = 0.0052$), while no differences were found in gender distribution. PBM was very well tolerated, and no adverse events related to PBM therapy were recorded in both groups. Demographic and clinical characteristics of the patients who underwent PrPBM and CuPBM are described in Table 1.

Effect of PrPBM and CuPBM on OM severity and pain

All patients developed OM following the conditioning regimen and HSCT, with statistically significant differences between groups (Table 1). All patients who underwent PrPBM therapy developed OM (measured using the WHO OM grading 0–4) with grade 0–1 (66.7%) or 2 (33.3%), while patients who were treated with CuPBM developed OM with higher severity grades. Over 50% of patients treated with CuPBM developed OM with grade 3 or 4. The difference in the distribution of OM grades in the two groups was statistically significant (Chi-squared test $p = 0.0035$).

OM severity grading changed significantly over time in both groups (Friedman's test $p < 0.01$ for PrPBM and $p < 0.0001$ for CuPBM), which is consistent to the fact that all patients developed OM. At T7, OM severity was significantly lower in the PrPBM group (Mann–Whitney's U test $p < 0.0001$). Median OM severity at T7 was 1 (range 0–2) in the PrPBM group and 3 (1–4) in the CuPBM group. Dunn's post hoc test performed on the CuPBM group showed significant changes from T0 to T7 ($p < 0.0001$) and from T7 to T14 ($p < 0.05$), while in the PrPBM group, we only observed a significant increase from T0 to T7 ($p < 0.01$).

Considering pain experienced by patients measured using NRS score (0–10), we observed a significant

Table 1 Descriptive variables of the subjects included. SD, standard deviation; *N*, number of subjects; neutrophils and platelets: days necessary to increase, expressed as median (range). [a]Mann–Whitney U test. [b]Chi squared test

	Preventive PBM	Curative PBM	p value
Number of subjects	12	12	
Age (mean ± SD)	59.3 ± 8.4	55.9 ± 7.6	0.0052[a]
Gender (*N*, %)			
Male	8 (66.7%)	5 (41.7%)	NS[b]
Female	4 (33.3%)	7 (58.3%)	
Engraftment	12 (100%)	12 (100%)	NS[b]
Neutrophils > 500/mm^3	+ 10 (9–13)	+ 10 (9–13)	NS[a]
Platelets > 20.000/mm^3	+ 14 (11–24)	+ 13 (11–18)	NS[a]
Oral mucositis grade			
0–1	8 (66.7%)	1 (8.3%)	0.0035[b]
2	4 (33.3%)	3 (25%)	
3	0 (0%)	6 (50%)	
4	0 (0%)	2 (16.7%)	

increase over time in the CuPBM group (Friedman's test $p < 0.0001$), whereas in the PrPBM group, no significant variations were detectable (Friedman's test $p =$ NS). Dunn's post hoc test performed on the CuPBM group showed significant changes from T0 to T7 ($p < 0.0001$) and from T7 to T14 ($p < 0.01$). Comparing the two groups, pain score at T7 in the PrPBM group was significantly lower (Mann–Whitney's U test $p < 0.0001$). Mean NRS pain score at T7 was 1.1 ± 1.7 in the PrPBM group, whereas it was 6.7 ± 2.4 in the CuPBM group.

At T14, no significant differences between groups were recorded for both variables. Data are represented in Table 2 and Fig. 1A, B.

Effect of PrPBM and CuPBM on functional variables

There was a lower proportion of patients reporting discomfort in all subjective pain parameters (swallowing, chewing, and speaking) at T7 in the PrPBM group. In particular, the difference was statistically significant for swallowing (Chi-squared test $p = 0.0405$) and chewing parameters (Chi-squared test $p = 0.0247$). Data are represented in Fig. 1C–E.

Overall, the results show how PrPBM, i.e., with the first session starting on the first day of conditioning until day + 2 post-HSCT, significantly reduces the severity of OM and subjective pain. It is important to point out that the recovery of the number of neutrophils after the transplantation is contained in the range of days 9–13 post-HSCT in both groups; therefore, the effects on OM and pain were not related to

Table 2 OM severity values reported as median and range of WHO grading. Pain severity values reported as mean ± standard deviation of NRS scores; [a]Friedman's test; [b]Mann–Whitney U test; ***$p < 0.0001$; **$p < 0.001$; *$p < 0.05$; NS, not significant

	OM severity (WHO grading)				Pain severity (NRS scale)			
	T0	T7	T14	p value[a]	T0	T7	T14	p value[a]
PrPBM	0 (0–0)	1 (0–2)	1 (0–2)	*	0 ± 0	1.1 ± 1.7	0.3 ± 0.8	NS
CuPBM	0 (0–0)	3 (1–4)	1 (0–2)	***	0 ± 0	6.7 ± 2.4	1.2 ± 1.9	***
p value[b]	NS	***	NS		NS	***	NS	

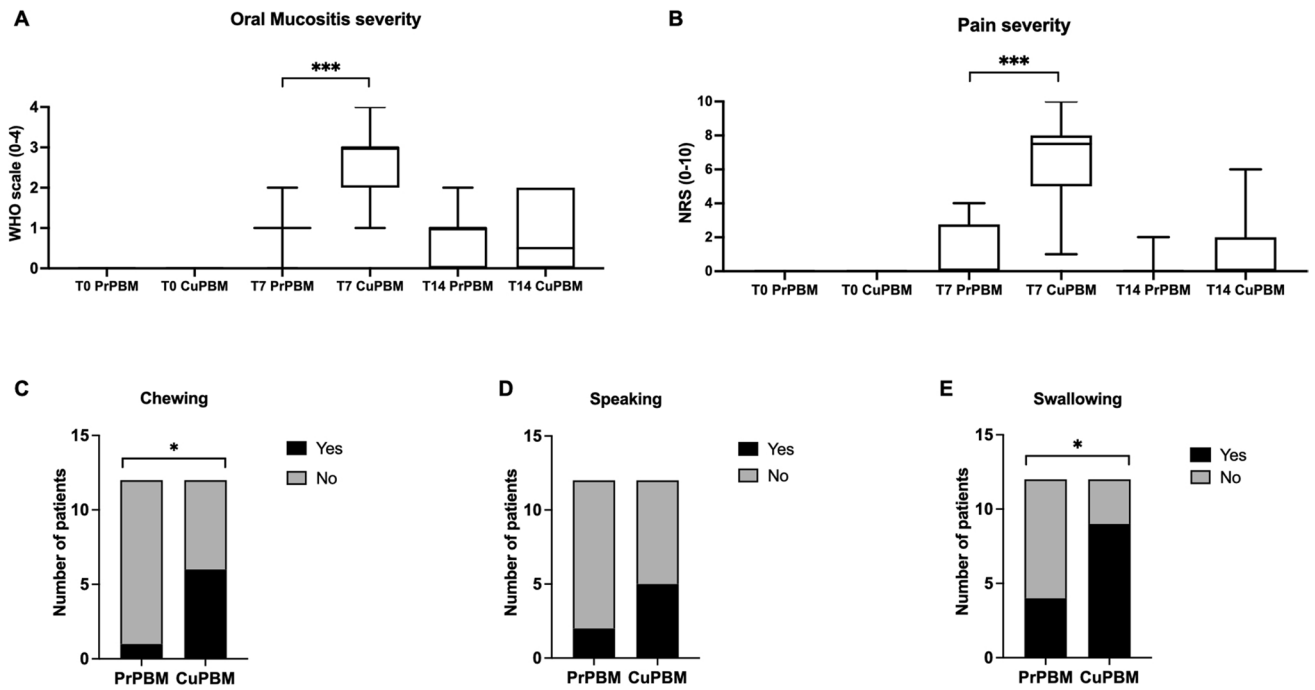

Fig. 1 Effect of PBM on clinical parameters in MM patients undergoing HSCT treated with Preventive or Curative protocols. **A** Evaluation of OM severity by CTC score at T0, T7, and T14 for the PrPBM and CuPMB groups. **B** Evaluation of pain severity by NRS score at T0, T7, and T14 for the PrPBM and CuPMB groups. ***Mann–Whitney U test PrPBM versus CuPBM at T7 with $p < 0.0001$. **C–E** Percentage of patients indicating presence (black bars) or absence (gray bars) of either pain or functional alterations in chewing, speaking, or swallowing at T7. Fisher's exact test confronting PrPBM versus CuPBM is not significant for all variables

any differences in the efficacy of the transplantation itself as PBM was concluded before day + 9 in all patients.

Discussion

Chemo and radio-induced OM appear to be caused by a combination of several pathways, including direct damage to DNA and mucosa, increased production of reactive oxygen species (ROS), transcription factors, and pro-inflammatory cytokines. As a result, loss of epithelial integrity, increased apoptosis, and cell necrosis are followed by various degrees of bleeding, ulceration, bacterial colonization, and increased risk of systemic infection [5]. In addition, pain evoked by the presence of OM during cancer therapy can be a debilitating side effect that noteworthy impacts on patients' quality of life. PBM is a phototherapy that employs light through specific sources to relieve pain and speed up the metabolic processes, thus acting on biological systems through faster wound healing [15, 26, 27]. Among the main effects of PBM, there is a marked reduction in nociception through the elimination of acute inflammatory mediators associated with axonal activity, as well as some selective inhibitory effects on axonal transmission [28, 29].

There is increasing evidence that PBM is both an effective [21, 30] and safe approach in HSCT patients [15, 31, 32] for the prevention and treatment of OM. Recently, novel PBM perspectives have emerged with the extraoral PBM approaches that minimize the mouth opening discomfort for patients [33], which can be used alone or in combination with intraoral PBM in case or worsening of signs and symptoms.

However, PBM is still rarely used in routine practice, related to several issues: it requires the availability of dedicated devices and the setting of specific parameters (wavelength, irradiance, fluence, frequency, and spot size) to optimize the effects. Moreover, PBM therapies are time-consuming and require the direct involvement of specialized personnel, not always available in all centers. In addition, one of the possible variations is the timing of PBM with respect to the different phases of transplantation procedure: it can be delivered either to prevent OM [23, 24, 33–35], usually starting on the first day of conditioning therapy, or to treat OM as its earliest clinical signs appears [10]. Advantages of the latest approach are to submit a smaller number of patients to PBM therapy, thus requiring a lower number of trained healthcare personnel.

The aim of this retrospective research was to evaluate possible differences in OM severity, pain, and functional parameters in HSCT patients treated either with preventive or curative PBM, using the same diode laser device and irradiation protocol (660 nm and 970 nm combined wavelengths, irradiance 100 mW/cm^2, fluence 2 J/cm^2, spot size 0.8 cm^2, continuous wave, and 18 sites throughout the entire oral cavity). All patients suffered from the same hematological malignancy (multiple myeloma) and underwent the same conditioning and transplantation protocol.

Our results show how preventive PBM was significantly more effective in limiting OM severity and pain post-HSCT than curative PBM. In addition, a lower proportion of patients reported discomfort in speaking (8% versus 21%), swallowing (17% versus 38%), or chewing (8% versus 50%) in the preventive PBM group. No adverse events related to PBM therapy were recorded in both groups. To our knowledge, this is the first study comparing the efficacy of preventive and curative PBM in HSCT patients.

The limitations of this retrospective single-center study are the limited number of patients included and the absence of randomization.

Conclusions

With the limitation of the sample size, our results show how the timing for the beginning of PBM therapy in patients undergoing HSCT is crucial: when started on the first day of conditioning, it significantly reduces both pain and OM severity, providing an important benefit also in subjective oral functions such as speaking, swallowing, and chewing and increasing overall tolerance of the procedure.

Author contribution Conceptualization: Giulia Ottaviani; methodology: Katia Rupel; formal analysis and investigation: Arianna Cornacchia, Theodora Magdalena Bogdan Preda, Augusto Poropat, Monica Poiani, Sara Mohamed, Eleonora De Bellis, and Mario Ballerini; writing—original draft preparation: Katia Rupel and Arianna Cornacchia; writing—review and editing: Giulia Ottaviani and Francesco Zaja; revision of the manuscript: Katia Rupel; funding acquisition: Giulia Ottaviani; supervision: Giulia Ottaviani, Francesco Zaja, Matteo Biasotto, and Roberto Di Lenarda. All listed authors should have seen and approved the final version of the manuscript.

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Data availability All data supporting the findings are available upon request to the Authors.

Declarations

Ethics approval All study procedures complied with the ethical standards and the guidelines of the 1964 Declaration of Helsinki. There were no invasive procedures planned for human beings during the study period. The study received approval from the ethics committee of the University of Trieste (n. 115/2021). Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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