

Photobiomodulation: a promising innovative approach for preventing oral mucositis in patients undergoing hematopoietic stem cell transplantation

Nicolas Stocker (✉ nicolas.stocker@aphp.fr)

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Virginie Baltes

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Solal Bellaïche

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Flora Brouillard

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Nadia Belmoufid

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Céline Rousseau

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Agnès Bonnin

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Zoé Van de Wyngaert

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Laure Ricard

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Anne Banet

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Florent Malard

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Remy Dulery

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Mohamad Mohty

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Eolia Brissot

AP-HP, Hôpital Saint-Antoine, Service Hématologie Clinique et Thérapie Cellulaire

Keywords: Photobiomodulation, Hematological malignancies, HCT, Oral mucositis

Posted Date: May 24th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1674701/v1>

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Abstract

Purpose: The study aims to investigate the efficacy/acceptance of photobiomodulation by a quick and easy-to-use device for both preventing oral mucositis (OM) and reducing its severity in the setting of hematopoietic stem cell transplantation (HCT).

Methods: Twenty-five consecutive patients underwent autologous HCT for hematological malignancies between November 2020 and October 2021. Prophylactic photobiomodulation (PBM) was used daily from day 1 of conditioning until the day of neutrophil recovery at a dose of 3 J/cm². Curative PBM was started at a dose of 6 J/cm² when at least one grade 1 OM had occurred. For each OM case, time of onset, National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 grade for OM, analgesic dose, and time to resolution were reported.

Results: The median age of the 25 patients was 58 years (range, 39-74) and 14 (56%) were male. Twenty-one patients (84%) received a high dose melphalan conditioning regimen for multiple myeloma, and 4 (16%) patients received BEAM conditioning for aggressive lymphoma. A total of 178 CareMin650 sessions were performed, with a median of 7 days of application (range, 4-12), with no device-related adverse events (AEs). According to the NCI-CTCAE v5.0 scale, 76% (19 of 25) of patients presented grade 0 or 1 mucositis (no ulcers), five patients (20%) developed small ulcers (grade 2), and only one patient developed grade 4 mucositis. Satisfaction rates were high among patients and users.

Conclusion: Photobiomodulation provides excellent safety and tolerance, as well as promising efficacy, both as a preventive and curative strategy, in patients undergoing autologous HCT.

Introduction

Oral mucositis (OM) is among the most common and disabling side effects related to the toxicity of high-dose chemotherapy (CT) administered as a conditioning regimen prior to hematopoietic stem cell transplantation (HCT) [6]. OM often develops 5 to 7 days after the conditioning regimen, frequently continues for 6 days, and heals around day 14 after HCT administration [17, 18]. Depending on the type of disease, conditioning regimen, and transplantation procedure, the incidence of OM in autologous HCT patients varies between 35-75%, and it can rise to 75-100% in allogeneic HCT patients [6]. The severity of OM varies with the CT procedure, high-dose CT being known to cause severe OM [1]. As a result of OM (which causes dysphagia and pain), weight loss, dehydration, and malnutrition can occur. Consequently, life-threatening infections can develop, the use of opioid analgesics and artificial nutrition increases, hospital stays are prolonged, and healthcare costs increase while the patient's quality of life decreases [6, 13, 19]. To date, very few options have been shown to be effective in the prevention and/or treatment of OM, despite a wide range of experimental treatments, and there is no standardized protocol for OM in autologous or allogeneic HCT [2, 14, 19].

Low-level light therapy, now referred to as photobiomodulation (PBM), has demonstrated significant benefits in several randomized clinical trials which support the use of PBM to promote wound healing

and reduce pain and inflammation. Furthermore, according to recent guidelines, PBM is recommended for OM prevention in patients receiving high-dose CT as a conditioning regimen for HCT [11, 20]. PBM involves the absorption of red and near-infrared light by mitochondrial chromophores. The rate of electron transfer in the respiratory chain is increased, resulting in increased production of adenosine triphosphate, reactive oxygen species and nitric oxide, thereby stimulating genes involved in tissue repair. Factors involved in inflammation and immunity are recruited to act at the tissue level [10, 12]. Thus, PBM impacts all stages of wound repair and tissue regeneration. It also prevents fibrosis, reduces pain (energy absorption by nociceptors), and prevents tissue death [10, 12].

The CareMin650 (NeoMedLight, Villeurbanne, France) is a device that has been developed to improve the practical use of PBM. The emission of light from an LED (light emitting diode) source, emitted by a flexible surface (fabric made of woven optic fibers) in contact with the mucosa, is accurately controlled, reproducible and operator independent. The device consists of an electronic box generating the light, and pads connected to the box by a fiber optic cable: oral pads, measuring $2.6 \times 5.5 \text{ cm}^2$, emit light on both sides (**Figure 1**). The dose in J/cm^2 is selected on the light box, which automatically calculates the duration of the session to reach the chosen dose. The average irradiation times are 1 minute (min) 47 seconds (s) at a dose of $3 \text{ J}/\text{cm}^2$, and 3 min 34 s at a dose of $6 \text{ J}/\text{cm}^2$, respectively. Single-use disposable sleeves are placed over the pads before applying them to the mucosa.

OM remains a significant problem for patients undergoing HCT and there is a need for effective evidence-based methods to prevent and cure OM in these patients. The limited number of studies evaluating PBM in this setting prompted us to demonstrate the feasibility, safety, and tolerability of the CareMin650 lightsource, and to provide preliminary data on its efficacy in autologous HCT.

Patients And Methods

Study Design and Patients

This was a single-center retrospective study involving consecutive patients undergoing HCT after high dose CT conditioning and treated with PBM. From November 2020 to October 2021, 25 consecutive patients with hematological malignancies, who underwent autologous HCT, were analyzed. Eligible patients were at least 18 years of age, hospitalized for conditioning, and had an ECOG performance status ≤ 2 .

Ethical Considerations

All study procedures complied with ethical standards and the guidelines of the 1964 Declaration of Helsinki. There were no invasive procedures planned for human beings during the study period.

Photobiomodulation

CareMin650 was used daily from the first day of conditioning until the day of neutrophil recovery. The minimum number of sessions per week was 3; however, 5 sessions/week were recommended according to the manufacturer instruction. The treatment can be administered by any health care professional after appropriate training. Oral pads (50 cm² treatment area) delivered red light with a wavelength of 650 nm and an irradiance of 28 mW/cm². Doses for prophylactic and curative treatments were 3 J/cm² and 6 J/cm², respectively. If OM occurred in a patient, the dose was increased to 6 J/cm². Standard OM prophylaxis, including oral hygiene with a soft toothbrush and bicarbonate mouthwashes, was implemented according to our center's practice. In case of lesions, the usual local care, analgesics, and corticosteroids were initiated.

Assessment of OM

Safety was evaluated by chart review, and adverse events (AEs) were graded according to the NCI-CTCAE v5.0. An examination of the oral mucosa was performed at each CareMin650 session to assess local tolerance and detect any new OM lesions. For each case of OM, time of onset, grade according to the NCI-CTCAE v5.0, and Oral Assessment Guide (OAG) scales for mucositis, analgesic dose, and time to resolution were reported. At each session, data were collected on pain, using a visual analog scale (VAS) graduated from 0 (no pain) to 10 (intolerable pain), analgesic consumption, and in case of OM, consequences on food intake. Patient and user satisfaction were retrospectively analyzed through questionnaires completed at the end of the treatment.

Data Analysis

Analyses were descriptive only. Quantitative variables were described by their median, minimum, and maximum. Categorical variables were expressed as frequencies and corresponding percentages. No statistical tests were performed. Missing data were not imputed.

Results

Characteristics of Patients and CareMin650 sessions

Patient and CareMin650 session characteristics are summarized in Table 1. The median age of the 25 patients was 58 years (range, 39-74) and 14 (56%) were male. Twenty-one (84%) patients received a high dose melphalan conditioning regimen for multiple myeloma and 4 (16%) patients received a combination of BCNU, etoposide, cytarabine and melphalan (BEAM) conditioning for aggressive lymphoma. A total of 178 sessions were performed, with a median application time of 7 days (range, 4-12). The treatment was well tolerated, and no device-related AEs were recorded. Only two patients discontinued treatment due to painful OM.

Characteristics of OM lesions and analgesia

Using the NCI-CTCAE v5.0 scale, the median of OM severity was grade 1 (**Table 2**). The proportion of patients who developed grade 1 OM (no ulcers) was 48.0 % (12 of 25). Five (20%) patients had small ulcers (grade 2) and only one patient developed a grade 4 OM. Furthermore, evaluation using OAG criteria revealed a median score of 10 (range, 8-12). Analgesic consumption was available for all patients: 6 (24%) patients required level 2 analgesics (of which 3 quickly switched to level 3) and 13 (52%) patients required level 3 analgesics in total. The median duration of analgesic treatment was 2 days (range, 1-4) for patients on level 2 analgesics and 7 days (range, 4-14) for patients requiring level 3 analgesics.

Patients and users' satisfaction

Data on patient's satisfaction were available for 21 patients and are shown in **Table 3**. Most patients reported that the application of the device was not burdensome (76%), caused a slight but bearable discomfort (48%) or no discomfort (43%), and that the duration of the sessions was acceptable (62%). Overall, 90% of patients reported no pain during applications, while 2 (10%) reported mild but tolerable pain and in 95% of cases, the preference was to keep the device in contact with the mucosa themselves during the session. Based on their experience, 52% of the patients thought that they could comply with this treatment on their own, while 43% would need medical support during the first sessions. Overall, most patients were completely satisfied (71%) or somewhat satisfied (29%) with their use of the device. The application of CareMin650 was performed by physicians or nurses depending on our service organization. The installation and connection of the device were considered easy by all users (very easy for 86% and rather easy for 14%). Programming the device was considered very convenient and somewhat convenient in 86% and 14% of cases, respectively. The duration of the sessions was evaluated as short, rather short, or rather long in 24%, 62% and 14% of cases, respectively. Overall, users found the device very satisfactory (71%) or somewhat satisfactory (29%) and all said they would like to use it in routine practice.

Discussion

In our study, OM incidence was 72.0% with a median severity grade of 1 according to the WHO OM grading scale, in patients who received PBM by the CareMin650 device for prophylaxis of OM. This incidence is comparable to data in the literature reporting that OM develops in 70% of hematopoietic stem cell transplant patients receiving a high-dose CT conditioning regimen [7, 9, 14]. However, the median maximal OM severity (assessed using the WHO oral toxicity scale ranging from grade 0-4), experienced in our cohort was 1, which is lower than data from previous studies [1].

Although PBM has been shown to be effective and safe in several randomized clinical trials and meta-analyses [4, 5, 8, 15, 16], it is rarely used in routine practice. This is because the treatment is time-consuming, the equipment heavy and unwieldy, and the lasers need to be tuned by multiple parameters (wavelength, irradiance, pulse structure, coherence, polarization, energy, fluence), generating a lack of standardization. The procedure, which depends on the operator, is not entirely reproducible because the distance to the mucosa is difficult to evaluate and the amount of energy delivered cannot be determined

with precision. In contrast, the CareMin650 is a small and handy device that delivers reproducible and precisely controlled light through the direct application of fabric made of woven optic fibers in contact with the mucosa [3].

In this study, PBM therapy delivered by the CareMin650 device was feasible, and was simple to use: the operator needs only to select a dose, and the light box automatically calculates the application time needed for correct dose delivery. Therefore, the application can be performed by any trained health professional (doctor, nurse, or resident). Most patients feel able to comply with this treatment by themselves after initial medical assistance.

Moreover, the local tolerance was very good as no device-related AEs (local pain, irritation, or unpleasant sensations) were reported. In terms of efficacy, only two patients discontinued treatment because of painful OM. Finally, in addition to safety and efficacy, the patient and user satisfaction questionnaire data showed that the CareMin650 device is acceptable to patients and health care professionals for use in clinical practice.

This single-center study has some limitations; it was conducted on a limited number of patients receiving a high-dose CT conditioning regimen before autologous HCT, without randomization, which does not allow us to formally conclude on the effectiveness of the system.

In conclusion, PBM by the CareMin650 device was safe and easy to perform. It seems to be effective since few patients developed a grade 3-4 OM. These promising results pave the way to developing a larger, randomized study.

Statements And Declarations

Funding and Acknowledgements

The authors acknowledge NeoMedLight, 90 rue Frédéric Fays, 69100 Villeurbanne, France and Cell Therapies Research & Services (CTRS), 63 rue de l'Est, 92100 Boulogne-Billancourt, France for their generous and continuous support of this research work. The authors also thank the clinical teams who cared for the study patients and for their dedication to this study.

Competing Interests

The authors declare no competing financial interests.

Author Contributions

NS and EB designed the study, NS collected the data, and all authors recruited patients. NS and EB prepared the manuscript for publication. All authors analyzed the data, reviewed the manuscript, and agreed to its submission for publication.

Ethics approval

All study procedures complied with ethical standards and the guidelines of the 1964 Declaration of Helsinki. There were no invasive procedures planned for human beings during the study period.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable.

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Tables

Table 1. Patient characteristics at baseline

Characteristic	N = 25
Age (years), median (range)	58 (39-74)
Gender, n (%)	
Male	14 (56)
Female	11 (44)
BMI (kg/m ²), median (range)	25.6 (16.4-34.0)
Conditioning regimen, n (%)	
High dose melphalan	21 (84)
BEAM	4 (16)
Number of photobiomodulation sessions	
Per patient, median (range)	7 (4-12)
Total, n (%)	178 (100)
Device-related adverse events	0

Abbreviations: BMI: body mass index; BEAM: BCNU, Etoposide, Ara-C and Melphalan.

Table 2. Characteristics of OM lesions and analgesia

OM-related features	N = 25
Mucositis grade, median (range)	
NCI-CTACE v5.0	1 (0-4)
OAG	10 (8-12)
OM severity, maximal grade of any lesion	
Grade 0	7 (28)
Grade 1	12 (48)
Grade 2	5 (20)
Grade 3	0
Grade 4	1 (4)
OM-related intravenous analgesia, n (%)	
Patients requiring level 2 analgesics, n (%)	6 (24)
Duration of level 2 analgesia (days), median (range)	2 (1-4)
Patients requiring level 3 analgesics, n (%)	13 (52)
Duration of level 3 analgesia (days), median (range)	7 (4-14)

Abbreviations: NCI-CTACE v5.0, The National Cancer-Institute Common Terminology Criteria for Adverse Events version 5.0; OAG, Oral Assessment Guide; OM, Oral Mucositis.

Table 3. Patient satisfaction questionnaire

Question	N = 21
How do you rate the insertion of the applicator into the single-use pads?	
Very easy	3 (14)
Pretty easy	16 (76)
Difficult	2 (10)
Very difficult	0
Have you experienced disconnections while using the CareMin650 device?	
Never	21 (100)
Rarely	0
Occasionally	0
Often	0
Was the application of the device on the areas to be treated painful?	
Absolutely not painful	19 (90)
Slightly painful but tolerable	2 (10)
Quite painful	0
Very painful	0
How do you consider the length of the treatment sessions?	
Short	5 (24)
Quite short	13 (62)
Quite long	3 (14)
Very long	0
In general, during the sessions, who kept the device in contact with the mucosa?	
Myself	20 (95)
The caregiver	1 (5)
During the session, did the presence of the device on the areas to be treated cause any discomfort?	
No discomfort	9 (43)

A slight but bearable discomfort	10 (48)
Discomfort requiring repositioning of the device	2 (9)
An important gene requiring the removal of the device	0
Based on your experience, do you think that a patient can follow this treatment alone or is medical assistance essential?	
A patient can apply it alone	11 (52)
Help is needed during the first sessions	9 (43)
Another person must always be present	1 (5)
Are you satisfied overall with your use of the CareMin650 device?	
Completely satisfied	15 (71)
Quite satisfied	6 (29)
Mostly dissatisfied	0
Not at all satisfied	0

Figures



Figure 1

CareMin650.

Pictures showing light box and oral pads (**1A**) and oral pads placed in the mouth (**1B**).