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ORIGINAL ARTICLE

Photobiomodulation therapy in the management of chronic oral graft-versus-host disease

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Abstract
Aim Patients treated with allogeneic hematopoietic stem cell transplantation (HSCT) may experience oral complications associated with chronic graft-versus-host disease (cGVHD). These complications may significantly affect quality of life, even many years post-HSCT. Current treatment options for oral cGVHD are limited and often include steroid or other immunomodulatory medications, which may not adequately control the oral condition. A non-immunosuppressive intervention for symptomatic relief in oral cGVHD would thus be a welcome addition to the treatment paradigm.
Materials and methods We report seven cases of oral cGVHD that were treated with photobiomodulation therapy (PBM), previously known as low-level laser therapy (LLLT). Patients underwent at least two PBM treatments per week in addition to local treatment with steroids, and if on systemic therapies, these were either unchanged or dosage was reduced during the period of PBM therapy. Follow-up data is presented for 4 weeks of treatment.
Results Oral pain, sensitivity, and dry mouth improved in most patients. These findings suggest PBM therapy may represent an additional approach for management of oral cGVHD, and suggest that controlled studies should be conducted to confirm the efficacy and safety of PBM therapy in oral cGVHD and to determine optimal PBM therapy protocols.

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Introduction

The oral cavity may represent the primary site of chronic graft-versus-host disease (cGVHD) in recipients of allogeneic hematopoietic stem cell transplantation (HSCT), which may not respond satisfactorily to systemic and/or local treatment with steroids or other immunomodulatory medications or may persist despite control or resolution of cGVHD at other sites of involvement. When present, oral symptoms may affect oral function and have negative impact on quality of life.

Typical mucosal lesions are lichenoid in appearance with white and red changes that may progress to ulcerations. Mucosal pain and tissue sensitivity may be present and may result in food avoidance that may lead to weight loss and nutritional compromise. The microscopic appearance of oral mucosal cGVHD is similar to that of oral lichen planus, with a heavy immune cell infiltration and epithelial cell and epidermal basement membrane destruction [1]. On the dorsal tongue, the lesions may present with patchy loss of papillae, and with lichenoid or plaque-like changes. Patients with cGVHD involving the salivary glands may have hyposalivation and are at risk for developing complications due to diminished salivary defense mechanisms, including antifungal and anti-cariogenic activities [2]. In addition, dry mouth may compromise swallowing, speech, and sleep. Salivary gland cGVHD mimics Sjögren syndrome and is characterized by histopathological changes, consisting of mononuclear infiltration with periductal infiltration, and/or atrophy of salivary gland lobules and peri-glandular fibrosis [2]. Sclerodermatous changes are less common, but when present, oral manifestations may include limited lip opening, limited jaw opening, and limited mobility of the tongue, and is associated with dysphagia.

Treatment of oral cGVHD consists of immunomodulatory medications that may be administered systemically, but patients with local oropharyngeal symptoms may respond to topical therapy [3, 4]. There are significant limitations to cGVHD treatment, including limited effect in some cases, additional immune suppression of the host, hyperglycemia, osteoporosis and Cushingoid changes, and increased risk of opportunistic infections [1, 4]. A non-immunosuppressive intervention for symptomatic relief in oral cGVHD would thus be a welcome addition to the treatment paradigm.

Photobiomodulation (PBM) therapy, previously known as low-level laser therapy (LLLT), has been examined in a number of painful, inflammatory, and non-healing conditions, including prevention and treatment of oral mucositis in cancer patients, wound healing, and pain management, and is supported in the literature [5–7]. Although the complex biological mechanisms underlying the therapeutic effects of PBM therapy have not been completely elucidated and may vary among different cell types and tissue states, laboratory and clinical studies suggest that PBM therapy significantly reduces inflammation, promotes repair, and prevents fibrosis [8–10].

Materials and methods

We report seven cases of oral cGVHD that were treated with PBM therapy with therapeutic protocol as recently described [9]. Briefly, light was applied to all sites of mucosal involvement, using a 660-nm intraoral laser probe via a light guide, power 75 milliwatt (mW), pulsed 2.5 Herz (Hz), illuminated area 2.5 centimeter $(cm)^2$, irradiance 30 mW/cm^2, irradiation time 60 s per point, energy 4.5 Joules (J) per point, and energy density 1.8 J/cm^2. Extra-orally, a cluster of 69 light-emitting diodes (LEDs) containing 660 nanometer (nm) and 850-nm LEDs, total power 1400 mW, pulsed 2.5 Hz, illuminated area 28 cm^2, irradiance 50 mW/cm^2, irradiation time 60 s, energy 84 J, and energy density 3 J/cm^2 was applied to the salivary glands and cervical lymph node chain bilaterally. The device was manufactured by THOR Photomedicine Ltd., Chesham, Buckinghamshire, UK.

Signs and symptoms of oral cGVHD were assessed prior to PBM therapy. Pain was assessed on a 0–10-point scale, and reported as worst pain in the prior 24 h. All patients underwent at least two PBM treatments per week, and cGVHD and related symptoms were reassessed following 4 weeks of treatment. The patients were treated in Los Angeles, CA, USA, and the Academic Medical Center of the University of Amsterdam, the Netherlands. All the patients provided informed consent for being included in this publication.

Case reports

Case 1

An 18-year-old male had received a matched related donor HSCT from a sister 5 years earlier for the treatment of acute myeloid leukemia (AML). He was diagnosed with cGVHD 9 months post-HSCT and presented with oral, skin, ocular, and lung involvement and manifestations of systemic sclerosis. The oral cavity was the most symptomatic site. He had initial improvement with photopheresis, but this was discontinued 1 month before the PBM therapy visit due to lack of continuing benefit. At the time of the visit, medications included prednisone (7.5 milligram/day (mg/day)), sirolimus (1 mg/day),

budesonide oral rinse (6 mg/5 milliliter (ml) three times a day (tid)) for the prior 9 months, chlorhexidine rinse, antimicrobial prophylaxis (fluconazole, sulfamethoxazole/trimethoprim, and acyclovir), famotidine, and morphine suspension (10 mg/5 ml; 10–15 ml every (q) 2–4 h for mouth pain). Oral symptoms included sensitivity to spicy and acidic foods (9/10 on a visual analog scale, (VAS)), mucosal pain with eating and with oral care (VAS 10/10), and taste loss (VAS 5/10). The morphine rinse provided limited pain relief (VAS 8/10). He had limited rotation and flexion in the neck, dysphagia, and limited mouth opening (inter-incisal opening 12 mm), suggestive of sclerosis. Due to the oral condition, oral intake was limited, and the majority of nutrition was obtained by gastrostomy (G)-tube. Saliva production was within normal limits (whole resting saliva (WRS) 1.33 mg/min, whole stimulated saliva (WSS) 2.00 mg/min), and there were no complaints of dry mouth. Clinical findings of mucosal GVHD included ulceration of the lateral borders of the tongue bilaterally, with erythema involving the tongue and cheeks, and lichenoid striations in approximately 50 % of the soft palate, cheeks, and lips. The National Institutes of Health (NIH) Oral Mucosal Score (OMS) cGVHD total score at presentation was 10 (Table 1).

Following 1 month of PBM therapy twice weekly, pain with eating was reported as 2/10 VAS; sensitivity to spicy and acidic foods was 5/10. Ulceration remained on the right and left lateral tongue but was reduced in size, and erythema was less severe throughout the involved mucosal sites. Inter-incisal mouth opening was increased (18 mm) with combined PBM therapy and physiotherapy. NIH OMS cGVHD total score following PBM therapy decreased to 5 (Table 2). No changes in systemic immunosuppressive medications were made during this period.

Following initial improvement, PBM therapy was reduced to once weekly, and signs and symptoms remained stable, but when weekly treatment was not provided, signs and symptoms increased.

Case 2

A 25-year-old female was treated with myeloablative chemotherapy and HSCT from a 10/10 human leukocyte antigen (HLA)-matched unrelated donor for Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). The transplantation was performed in 2014. She developed rapid onset acute GVHD with skin, oral, and liver involvement and was initially treated with prednisone (80 mg/day). As liver function improved, prednisone was tapered. Despite the systemic management, oral GVHD persisted, and she presented with cGVHD and associated oropharyngeal pain.

When seen for oral management 8 months post-HSCT, the patient's medications included prednisone (60 mg/day), cyclosporine A (50 mg twice daily (bid)), prednisone eye drops (1 %), lubricant eye drops, sertraline, insulin, antimicrobial prophylaxis (acyclovir, sulfamethoxazole/trimethoprim, voriconazole), esomeprazole, ursodiol, zolpidem, morphine (15 mg q 8 h), lorazepam, ondansetron, and metoclopramide. Dietary supplements included calcium and vitamins B and D.

She had severe hyposalivation (WRS 0.49 mg/min, WSS 0.16 mg/min) and mouth pain requiring morphine (15 mg; taken 30 min prior to eating) and used "Magic mouth wash" prior to mouth care and eating. Dexamethasone rinse was prescribed, but was discontinued due to stinging with use. The patient had a marked Cushingoid appearance.

NIH OMS cGVHD total score prior to PBM therapy was 13. Lichenoid changes involved 80 % of oral mucosal surfaces, the dorsal tongue was atrophic with patchy lichenoid changes, and there was ulceration of the lateral borders of the

Table 1 Main oral findings prior to PBM therapy

Pat. Nr.	Ulcers	Erythema	Lichenoid	Mucoceles	Oral GVHD OMS score	Mouth pain (VAS)	Dry mouth (VAS)	Inter-incisal opening (mm)
1	6	2	2	0	10	8	0	12
2	6	3	3	1	13	7	8	–
3	6	3	3	0	12	5	0	–
4	6	3	3	3	15	5	0	–
5	3	3	1	0	7	6–7	0	8
6	3	3	3	0	9	8	8	24
7	6	3	3	0	12	8	7	16

Ulcers, erythema, lichenoid, and mucoceles were scored using the NIH OMS score (Bassim CW et al. Validation of the National Institutes of Health chronic GVHD Oral Mucosal Score NIH OMS using component-specific measures. Bone marrow transplant 2014; 49: 116–121), *VAS* Visual Analog Scale (0–10); representing the maximal 24-h score. Mouth opening was only recorded if reduced opening was suspected

Table 2 Main oral findings following 4 weeks of PBM therapy

Pat. Nr.	Ulcers	Erythema	Lichenoid	Mucoceles	Oral GVHD OMS score	Mouth pain (VAS)	Dry mouth (VAS)	Inter-incisal opening (mm)
1	3	1	1	0	5	2	0	18
2	3	1	1	1	6	0	3	–
3	3	1	2	0	6	2	0	–
4	3	2	3	2	10	3	0	–
5	3	1	1	0	5	3	0	18
6	3	1	2	0	6	2	0	36
7	3	2	2	0	7	3	3	19

Ulcers, erythema, lichenoid, and mucoceles were scored using the NIH OMS score (Bassim CW et al. Validation of the National Institutes of Health chronic GVHD Oral Mucosal Score using component-specific measures. Bone marrow transplant 2014; 49: 116–121), *VAS* Visual Analog Scale (0–10); representing the maximal 24-h score. Mouth opening was only recorded if reduced opening was suspected

tongue and gingival atrophy. Reported oral symptoms were dryness (VAS 8/10), pain (VAS 7/10), and mucosal sensitivity (VAS 10/10).

Following 2 weeks of PBM therapy twice weekly, saliva production improved (WRS 0.54 mg/min, WSS 0.76 mg/min), and mucosal GVHD was clinically improved, while prednisone was decreased to 50 mg/day. Symptoms consisted of dry mouth (VAS 7/10), pain (VAS 3/10), and sensitivity (VAS 4/10). After 4 weeks of PBM therapy, saliva function was further improved (WRS 0.68 mg/min, WSS 1.11 mg/min). Symptoms consisted of no pain, mucosal sensitivity (VAS 3/10) and dry mouth (VAS 3/10); the NIH OMS cGVHD total score was 6.

Case 3

A 47-year-old female with diffuse B cell lymphoma received an autologous HSCT in 2004. She subsequently developed treatment-related myelodysplastic syndrome (MDS), which lead to an allogeneic HSCT from a matched unrelated donor 8 years later.

Post-transplant, she developed cGVHD with skin, eye, and mouth involvement together with onset of bronchiolitis obliterans. She also developed osteoporosis with femoral head fracture and compression fractures despite a history of bisphosphonate use. She was also diagnosed with bone exposure on the lingual aspect on the left mandibular region (4 × 6 mm), which was consistent with medication-related osteonecrosis of the jaw (MRONJ). Treatment for osteonecrosis included pentoxifylline (400 mg tid), vitamin E (400 mg tid), and chlorhexidine rinse (0.12 %; rinse and spit 15 ml four times a day (qid)) and concurrent PBM therapy. A sequestrum developed at the site of mandibular bone exposure, and gentle sequestrectomy was possible after 4 weeks of treatment with resolution of necrosis and full mucosal cover. She also had a history of basal cell carcinoma of the skin post-HSCT.

Seventeen months post-HSCT, her medications included prednisone (up to 60 mg/day), mycophenolate mofitil, cyclosporine eye drops, microbial prophylaxis (acyclovir, fluconazole, azithromycin), teriparatide (since osteonecrosis of the jaw), atovaquone, calcium and vitamin D, omeprazole, tacrolimus ointment for local skin lesions, and compounded oral budesonide mouth rinse (3 mg/5 ml).

She experienced increased severity of skin cGVHD that was treated with an increase in prednisone (40 mg/day) and rituximab. The treatment resulted in decreased dermatitis, but oral and ocular symptoms continued, leading to prescription of mycophenolate mofetil (1000 mg bid). At this time, oral cGVHD involved all mucosal surfaces, and the NIH cGVHD total score was 12. She denied dry mouth and reported oral pain (VAS 5/10) and mucosal sensitivity (VAS 8/10). She was treated with PBM therapy twice weekly. She reported pain reduction for up to 24 h after each PBM treatment.

Prednisone was decreased after 2 weeks on PBM therapy to 30 mg/day, due to improvement. One month following initiation of PBM therapy, her NIH OMS cGVHD total score was 6. Prior symptoms were reported as improved (i.e., mouth pain (VAS 2/10) and mucosal sensitivity (VAS 3/10)). She also reported increased taste sensitivity. Thus, oral symptoms had improved while decreasing systemic steroids.

Case 4

A 54-year-old female diagnosed with MDS progressed to AML received a 10/10 HLA-matched related donor allogeneic HSCT. She was diagnosed with relapsed MDS while presenting with acute GVHD. She was placed on azacitidine for relapsed MDS, and donor chimerism had increased from 91 to 99.7 %. She developed a skin rash together with onset of oral cGVHD.

When the patient presented, her medications included furosemide, docusate, senna, esomeprazole, ranitidine, miralax, ondansetron, vitamins B12 and D, folic acid, calcium, magnesium, antimicrobial prophylaxis (acyclovir, sulfamethoxazole/trimethoprim), clonazepam and tramadol as needed, prednisone (40 mg/day), and dexamethasone (0.5 mg/5 ml) plus budesonide oral rinses (3 mg/5 ml TID). After 1 month of prednisone, the skin rash improved, and prednisone was reduced to 30 mg/day. However, oral involvement continued. Symptoms included mouth pain (VAS 5/10), mucosal sensitivity (VAS 8/10), and dysgeusia. The NIH OMS cGVHD total score was 15 with ulceration and erythema on the cheeks and extensive striations on all oral mucosal surfaces.

Dysgeusia and peripheral neuropathy were treated with topical clonazepam (1 mg tid), and PBM was initiated. After 4 weeks of PBM therapy twice weekly, NIH cGVHD score was 10, and mouth pain was rated VAS 3/10 and mucosal sensitivity VAS 4/10.

Case 5

A 13-year-old male with AML received an allogeneic matched unrelated donor HSCT with total body irradiation (TBI)/cyclophosphamide conditioning. He developed acute GVHD (grade 4) and asthma. He was seen 3½ years post-HSCT with the following diagnoses: cGVHD with scleroderma-like features, bronchiolitis obliterans, dysphagia, oral bleeding, and cataracts. Due to oral involvement and sclerodermatous changes, he was G-tube-dependent. His medications included prednisone (20 mg/day), sirolimus (0.5 mg), megestrol, atovaquone, morphine (10 mg/5 ml; 7.5 ml qid), methadone (5 mg/5 ml solution-3 ml, as needed), dexamethasone rinse (0.5 mg/5 ml), omeprazole, lisinopril, lorazepam, tacrolimus 0.05 % ointment, and ondansetron. Opioid analgesics were used due to oropharyngeal pain.

Prior to PBM therapy, the NIH OMS cGVHD total score was 7, and pain was reported as VAS 6–7/10. Due to oral pain, morphine and methadone were each used twice daily. Ulceration was present on the buccal mucosae with severe erythema of the maxillary and mandibular attached gingiva. Maximum inter-incisal opening was severely limited at 8 mm.

After 4 weeks of PBM therapy twice weekly, the NIH cGVHD score was 5. Oral pain (VAS 3/10) was improved and allowed reduced use of methadone 2.5 mg/day and morphine 5 ml/day before sleep. Also, the patient reported that oral pain decreased for up to 8 h following PBM therapy. He reported increased oral intake due to reduced oral pain, decreased dysphagia, and choking on food, and that he was able to complete small meals more quickly. Due to reduced oral pain, his oral hygiene improved with decreased intensity of gingival erythema. He also had increased inter-incisal opening of 18 mm that occurred with combined PBM and physiotherapy, and improvement in oral mucosal erythema.

Case 6

A 67-year-old female with relapsed chronic lymphocytic leukemia (CLL) underwent a non-myeloablative allogeneic HSCT from an unrelated 10/10 HLA-matched donor in 2013. The conditioning regimen consisted of fludarabine and TBI. Complete donor chimerism was reached promptly. She developed acute GVHD of the liver and skin following tapering of cyclosporine. Her symptoms responded well to systemic steroid treatment.

She was diagnosed with cGVHD involving the skin, liver, and oropharynx 11 months post-HSCT due to oropharyngeal complaints that did not respond satisfactorily to cyclosporine, dexamethasone, or budesonide oral rinses. At presentation, her medications consisted of prednisolone 15 mg qd, ursodiol 300 mg qd, esomeprazole 20 mg bid, cyclosporine 100 mg bid, cotrimoxazol 480 mg/day, valacyclovir 500 mg tid, metformin 850 mg tid, calcium/D3 500/800 IE/day, alendronic acid 70 mg once weekly, mirtazapine 15 mg/day, fluconazole 50 mg/day, and dexamethasone rinse (0.5 mg/5 ml). Oral pain while eating was VAS 8/10; oral mucosa sensitivity 6/10 and dry mouth VAS 8/10 were her main complaints. The oral mucosa and gingiva were erythematous with lichenoid striae, the dorsum of the tongue showed hyperkeratotic lesions (Fig. 1), and on the buccal and labial mucosa, there were large ulcerations covered with pseudomembranes (Fig. 2). In addition, she had a painful ulceration on the lower vermillion border of the lip that was treated with tacrolimus ointment 0.1 % tid. She had complaints of stiffened and swollen cheeks and limited jaw opening (inter-incisal opening 24 mm). Prior to PBM, the NIH OMS cGVHD total score was 9, and WRS and WSS were 0.6 and 1.6 mg/min, respectively.

After 1.5 weeks of PBM administered 2–3 times a week, oral ulcers had expanded (now involving >20 %). This may have been due to discontinuation of oral dexamethasone rinses. However, pain and sensitivity, as well as xerostomia,

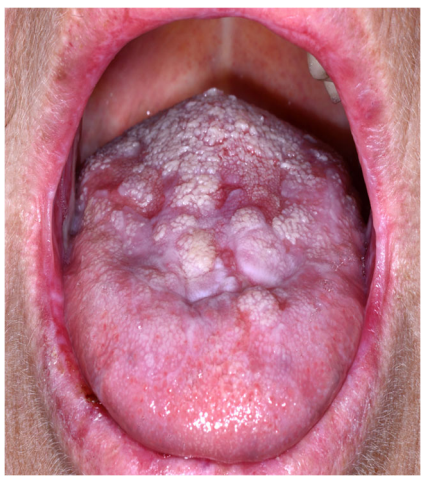

Fig. 1 Dorsal tongue of patient 6, before the start of PBM therapy

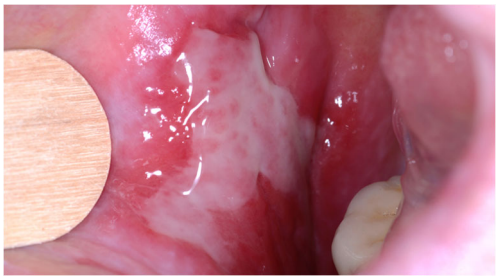

Fig. 2 Buccal mucosa of (same) patient 6 before PBM therapy

had markedly improved. After 4 weeks of PBM therapy there was markedly less buccal erythema (Fig. 3), and reduced hyperkeratosis of the tongue (Fig. 4). The NIH OMS cGVHD total score was 6 (mouth pain VAS 2/10, mucosal sensitivity VAS 4/10). Her cheeks felt less stiff and swollen, and her mouth opening had improved (36 mm). Stimulated whole salivary flow had improved (WRS 0.4 mg/min, WSS 2 mg/min). She had no longer complaints of xerostomia and was able to sing in a chorus again.

Following 4 weeks of PBM therapy, PBM was reduced to once weekly, and signs and symptoms remained stable. After 4 months, PBM was discontinued, and oral ulcerations and associated pain and sensitivity flared despite the use of dexamethasone rinse (0.5 mg/5 ml) and tacrolimus ointment 0.1 % tid. Again, signs and symptoms of oral cGVHD improved with PBM therapy twice weekly.

Case 7

A 65-year-old male with AML-M2 underwent allogeneic HSCT with peripheral stem cells from his HLA-identical sister. Conditioning consisted of fludarabine and TBI. During myelosuppression, he suffered from severe oral mucositis. One year post-HSCT, he developed cGVHD affecting the oral cavity, gastrointestinal tract, and skin, which was treated with prednisolone 10 mg and cyclosporine. When he was referred for oral complaints, his medications included hydrocobamine 1000 μg/3 months, triamcinolone cream, fluticasone propionate cream, diprolene gel, metformin 500 mg tid,

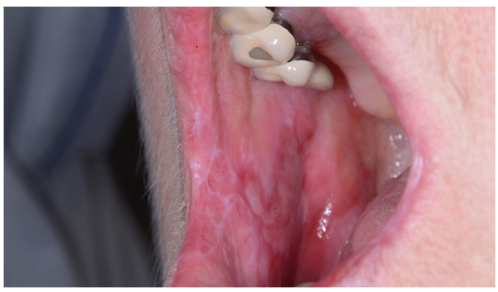

Fig. 3 Buccal mucosa of patient 6 after 4 weeks of PBM therapy. Less inflammation present and less sensitivity and pain reported

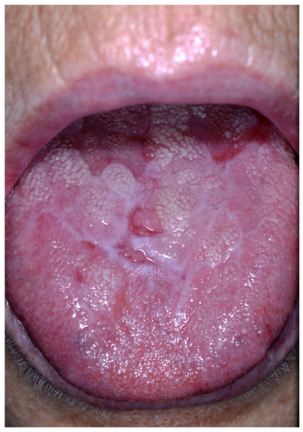

Fig. 4 Dorsal aspect of the tongue following 4 weeks of PBM therapy

levothyroxine 50 mg once daily, fluconazole 50 mg once daily, and valacyclovir 500 mg tid. Despite dexamethasone oral rinses (0.5 mg/5 ml qid) and lidocaine gel application, mouth pain was severe (VAS 8/10) and oral sensitivity continued (VAS 6/10). The NIH OMS cGVHD total score was 12. The patient was unable to tolerate oral intake and had difficulty performing oral hygiene measures. The patient also suffered from xerostomia and dry eyes, and reported taste alteration. WRS and WSS were 0.1 and 0.5 mg/min, respectively, and mouth opening was reduced (16 mm).

He had a PBM therapy device for home use available (wavelength 650 nm, energy 1 mW), which he applied to the oral ulcerations with total treatment time between 30 and 60 min daily. Self-treatment with this PBM therapy device alleviated symptoms of sensitivity and pain, but other symptoms remained unchanged; the patient was therefore treated with PBM therapy as described in the "Materials and methods" section. He stopped using dexamethasone rinses and lidocaine gel. After 4 weeks of PBM therapy twice weekly, he reported marked improvement. Oral pain was reduced (VAS 3/10), oral sensitivity (VAS 3/10), xerostomia complaints improved, and salivary production increased (WRS 0.3 mg/min, WSS 0.7 mg/min). He experienced less mouth stiffness and had increased inter-incisal opening (19 mm). Eating and speaking improved. The NIH OMS cGVHD total score decreased to 7. However, dysgeusia persisted.

Discussion

In the cases presented above, the addition of PBM therapy combined with systemic and/or local immunosuppressive therapy resulted in significant clinical improvements in oral signs and related symptoms of oral GVHD. In this case series in addition to mucosal GVHD, we also report improvement of dry mouth, mucosal sensitivity/mouth pain, taste, and range of jaw opening. The NIH OMS cGVHD total score showed an overall reduction in mucosal lesions in these patients by

45 %. Symptoms were also significantly improved. Furthermore, in four of the seven cases, oral cGVHD improved while systemic immunosuppressant medications were reduced. This clinical course suggests that PBM therapy may be an effective adjunct for controlling mucosal cGVHD and associated pain. This suggests increased effect of PBM therapy in these cases, and the potential to reduce systemic immunosuppression due to improved management of oral GVHD. In addition, these cases suggest that PBM therapy may be effective in stimulating salivary glands and to reduce mucosal stifness and/or tissue fibrosis leading to improved mouth opening. No adverse events associated with PBM therapy were noted.

These findings are consistent with results of isolated case reports of oral mucosal cGVHD treated with PBM therapy [11–14]. Consistent pain relief of mucosal cGVHD lesions has also been obtained with using a high-intensity CO_2 laser [15]. We are not aware of any clinical trials or any other reports of PBM therapy for cGVHD. However, a cohort of 30 patients with oral lichen planus (which is clinically and histologically similar to mucosal cGVHD) was treated with PBM therapy in patients who were non-responders to topical corticosteroid therapy. The authors reported significant reductions in clinical scores as well as symptomatic relief [16]. None of these reports noted any adverse effects of PBM therapy.

Systematic reviews have suggested efficacy of PBM therapy for the management of oral mucositis and associated pain in HSCT recipients and in head and neck cancer (HNC) patients [6, 17–20]. Furthermore, there is evidence suggesting that PBM therapy may reduce fibrosis [21].

The literature on PBM for the management of xerostomia and hyposalivation is limited. Some studies suggest an increased salivary flow following PBM therapy in non-cancer patients [22, 23]. Animal studies have shown an increase in the number of duct epithelial cell mitoses, and stimulation to protein synthesis in submandibular glands following PBM therapy [24, 25]. Less severe xerostomia was reported following prophylactic PBM therapy in HSCT recipients [26] and in a small randomized controlled trial in HNC patients treated with radiotherapy [27]. Increased salivary flow was observed following PBM therapy in HNC patients when compared to controls [28].

PBM therapy of symptomatic oral cGVHD may improve local management allowing a decrease of systemic immunosuppressive therapy. This is an attractive approach to management of oropharyngeal GVHD, which may be the worst or only site of cGVHD involvement. Other indications for the use of PBM therapy in cGVHD such as taste disorders and dysphagia may evolve. Decreasing symptoms associated with oral cGVHD will contribute to a better overall quality of life for these patients and also decrease the risk for long-term adverse effects on oral health. Moreover, there may be a potential use for PBM therapy at other mucocutaneous tissues affected by cGVHD (e.g., ocular, skin, vaginal).

Although PBM therapy has plausible safety in this setting, some vigilance is warranted as oral cGVHD can lead to an increased risk for oral squamous cell cancer [29]. In vitro studies assessing the effect of PBM on tumor cells report conflicting results, likely to be specific to PBM therapy power and dose; studies on these topics are ongoing. However, no clinical studies to date have reported enhanced tumor growth as a result of PBM therapy exposure.

Our findings suggest that oropharyngeal involvement by cGVHD that persists despite systemic therapy and topical steroids may be managed with PBM. A randomized double-blinded clinical trial on efficacy PBM therapy for a minimum of two treatments per week for 4 weeks should be considered. In addition, future investigations to better define optimal PBM therapy wavelengths, power density, fluence, pulse structure, and treatment intervals should be conducted, and other potential indications for the use of PBM therapy in cGVHD should be explored.

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Compliance with ethical standards

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

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