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ORIGINAL ARTICLE

Chronic oral graft-versus-host disease: induction and maintenance therapy with photobiomodulation therapy

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Abstract

This study presents follow-up of a prior study of patients with chronic symptomatic oral chronic graft-versus-host-disease (cGVHD) managed with photobiomodulation therapy (PBM therapy for 1 month. Here, we report long-term follow-up of a series of patients where PBM therapy in patients with oral cGVHD for maintenance follows the initial period of PBM therapy for continuing management.

Patients and methods We report continuing follow-up of 7 cases of oral cGVHD that were treated with PBM therapy. PBM therapy was continued in these patients with the goal of determining the best management schedule of PBM to maintain or improve control of each patient's symptoms and signs of oral cGVHD.

Results Oral sensitivity and mucosal changes of cGVHD were controlled with a continuing schedule of PBM therapy of up to 6–8-week treatment intervals in patients with continuing GVHD. These findings suggest that PBM therapy represents an additional approach for continuing management of oral cGVHD and that the frequency of treatment should be individualized for each patient to provide best control of oral findings. In one case weekly PBM treatment was continued, while in others, management on a monthly or bimonthly basis was associated with control of the oral condition. PBM may be individualized and provided based upon best control of the symptoms and signs of oral GVHD.

Keywords Photobiomodulation therapy · Low level laser therapy · Induction therapy · Maintenance therapy · Oral graft-versus-host disease

Introduction

Oral involvement by chronic graft-versus-host-disease (cGVHD) in recipients of allogeneic hematopoietic stem cell transplantation (allo-SCT) may be a highly impactful site of persisting symptoms despite systemic and/or local treatment with steroids or other immunomodulatory medications.

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Oral mucosal cGVHD commonly presents with lichenoid lesions with white and red changes and mucosal atrophy and may include mucosal ulceration involving nonkeratinized oral mucosa of the cheek, lips, lateral border of the tongue, floor of mouth, and palate. Keratinized oral mucosa may also be affected. On the dorsal tongue, GVHD may present with loss of papillae and lichenoid or plaque-like changes with ulceration. Gingival involvement may include atrophy, striations, erythema, and ulceration. Mucosal sensitivity and oral pain may be present often requiring pain management and impacting oral function and quality of life [1, 2].

Patients with cGVHD may have salivary gland involvement leading to hyposalivation which may compromise swallowing, speech, and sleep. Minor salivary gland mucous retention may be seen. Further, in a subset of cases, sclerotic changes may occur resembling systemic sclerosis with oral findings of limited oral aperture, limited range of jaw opening and tongue movement, and fibrosis of the buccal mucosa [1–3].

Patients with local oropharyngeal symptoms may respond to topical therapies [4, 5]. However, there are limitations to current management of cGVHD [1, 5]. GVHD even when manifesting primarily oropharyngeal symptoms represents a chronic condition, local oral management does not address the underlying immune host response, and therefore, chronic management may be needed for control of oropharyngeal manifestations.

Photobiomodulation (PBM) therapy has been examined in a number of painful, inflammatory conditions, including oropharyngeal mucositis in cancer patients, [6–11] and in oral lichen planus [12–15]. PBM has anti-inflammatory and analgesic activity. PBM anti-inflammatory effects are attributed to increased ATP production in mitochondria, decreased reactive oxygen species, and reduction in proinflammatory cytokines including TNF [9]. In a prior paper, we presented 7 cases of oral cGVHD treated with PBM for 4 weeks, which showed patient response to the addition of PBM therapy [2]. We hypothesized that the initial response in these cases may be considered "induction therapy" to assess initial response of oral findings to PBM therapy. In this report, we describe 7 patients treated on a continuing basis with PBM to control oral cGVHD after the "induction" period of 4 weeks PBM as maintenance therapy.

Patients and methods

Seven patients with oral cGVHD that were treated with induction PBM therapy, twice weekly for 4 weeks, in addition to systemic and local therapies for GVHD who were treated for a minimum of 6 months were included in this report. These patients had a response to induction PBM and continued to receive PBM due to continuing signs/symptoms of oral cGVHD. Two of these seven patients were included in our prior study of induction PBM as previously reported [2]. We sought to determine the frequency of PBM therapy necessary to maintain control or further improve findings of oral cGVHD.

PBM therapy (formerly called low level laser therapy) was applied to sites of mucosal involvement (660-nm intraoral laser probe, 75 milliwatt (mW), pulsed 2.5 Herz (Hz), 2.5-cm-diameter area, irradiance 30 mW/cm^2, 60 s per point, at energy 4.5 J per point, with energy density 1.8 J/cm^2). Extraorally, a cluster probe of light-emitting diodes (LEDs) (660- and 850-nm LEDs), total 1400 mW, pulsed Illuminated area 28 cm^2, irradiance 50 mW/cm^2, 60 s, energy 84 J, and energy density 3 J/cm^2) was applied opposite to the area of buccal mucosa involvement and the first echelon cervical lymph nodes. A THOR low level laser device (THOR Photomedicine Ltd., Chesham, Buckinghamshire, UK) was used in these cases. Patients wore safety glasses during PBM treatments. Signs and symptoms of oral cGVHD were assessed, including mucosal erythema and ulceration; pain was scored on a 0–10 point visual analogue scale (VAS) and reported as pain in the prior 24 h. GVHD was scored using NIH criteria for clinical trials in chronic GVHD, as summarized by Lee [16].

All patients provided informed consent prior to therapy and for inclusion in this publication.

Case reports

All cases had severe GVHD according to NIH criteria for clinical trials in cGVHD, as summarized by Lee [16]. Two of the patients (cases 1 and 2) have been included in a prior report of oral GVHD following 4 weeks of induction PBM therapy [2], with additional follow-up in the current report.

Case 1

An 18-year-old male was seen 5 years post allo-SCT from his sister for treatment of acute myeloid leukemia (AML). He developed cGVHD at 9 months post-SCT with oral, skin, ocular, and lung involvement and systemic sclerosis. He had short-term improvement with photopheresis, but this treatment was discontinued due to recurrence of cGVHD 1 month before PBM was initiated. At the pre-PBM visit, GVHD was severe. Medications included prednisone (7.5 mg/d), sirolimus (1 mg/d), budesonide oral rinse [6 mg/5 ml, tid] for the prior 9 months, chlorhexidine rinse, antimicrobial prophylaxis (fluconazole, sulfamethoxazole/trimethoprim, and acyclovir), famotidine, and morphine suspension [rinse and swallow; 10 mg/5 ml; 10–15 ml every (q) 2–4 h for mouth pain]. He reported oral pain with spicy and acidic foods and with oral care (VAS 10/10) and taste loss (VAS 5/10).

Morphine rinse provided some pain relief (VAS 8/10) with eating. He had limited neck rotation and flexion, dysphagia, and limited mouth opening (inter-incisal opening 12 mm). The majority of his nutrition was obtained via gastrostomy (G)-tube. Unstimulated and stimulated whole saliva production was within normal limits. Oral cGVHD included ulceration of the lateral borders of the tongue, erythema involving the tongue, and cheeks (Table 1).

Clinical findings following 4 weeks of PBM therapy twice weekly are shown in Table 1. Ulceration remained on the lateral borders of the tongue but was reduced in size, and erythema was reduced. No changes in systemic immunosuppressive medications were made during this period.

Following initial improvement with PBM therapy, treatment was reduced to once weekly, and he remained stable; however, when weekly treatment was not provided, signs and symptoms increased. Follow-up was continued with once weekly PBM treatment for 6 months, when he returned home and was not seen after that date. At his last visit, inter-incisal jaw opening was 23 mm, and diet was advanced as dysphagia had improved. Budesonide oral rinse (6 mg/5 ml tid) continued.

Case 2

A 13-year-old male with AML received a matched unrelated donor (MUD) allo-SCT and developed acute GVHD (grade IV). He was seen for oral cGVHD 3.5 years post-SCT. He had cataracts and scleroderma-like features of bronchiolitis obliterans, dysphagia, and limited jaw opening. He was G-tube dependent. Medications included prednisone (20 mg/day), sirolimus (0.5 mg), megestrol, atovaquone, morphine suspension (10 mg/5 ml; 7.5 ml qid), methadone (5 mg/5 ml solution-3 ml BID), dexamethasone rinse (0.5 mg/5 ml), omeprazole, lisinopril, lorazepam, tacrolimus 0.05% ointment, and ondansetron. He had used Plaquenil for 6 months, but this was discontinued. Opioid analgesics were used due to oral pain.

Table 1 shows oropharyngeal findings prior to PBM and following initial PBM treatment. Oral pain was 6–7/10. Ulceration was present on buccal mucosa bilaterally, severe erythema on maxillary, and mandibular attached gingiva. Inter-incisal opening was 8 mm. Following 1 month of PBM twice weekly, pain with eating was decreased to 2/10 VAS, and sensitivity to spicy and acidic foods was 5/10. Ulcerations of the lateral borders of the tongue were reduced in size, and erythema was reduced throughout the mouth. Inter-incisal mouth opening was increased. 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. After 6 months, PBM was reduced to biweekly and finally once every 3–4 weeks with maintained improvement. If time exceeded 4 weeks between treatments, oral GVHD symptoms and signs increased.

Table 1 Oral findings prior to Induction photobiomodulation therapy

Patient no.	Ulcers	Erythema	Lichenoid	Mucoceles	Total oral GVHD score	Mouth pain (VAS)	Dry mouth (VAS)	Inter-incisal opening (mm)
Pre-photobiomodulation therapy								
1	6	2	1	0	9	8	0	12
2	2	7	1	0	10	6–7	0	8
3	4	9	2	0	15	8	8	35
4	2	10	6	3	21	8	0	38
5	3	8	4	0	15	6	8	40
6	4	9	4	0	17	5	0	43
7	6	3	3	0	12	8	7	16
Post induction photobiomodulation therapy								
1	3	1	1	0	5	2	0	18
2	1	6	1	0	8	3	0	14
3	2	5	2	0	9	3	8	35
4*	2	10	4	3	19	6	0	37
5	2	6	4	0	12	4	2	40
6	3	4	3	0	10	5	0	41
7	3	2	2	0	7	3	3	19

*2 months post PBM

Ulcers, erythema, lichenoid, and mucoceles were scored using the NIH OMS score (16) and VAS (visual analogue scale) (0–10), representing the maximum 24-h score

After 3 years of follow-up with ongoing PBM treatments provided on a 3–4-week schedule, he had no oral pain, patchy mild erythema on the lateral borders of the tongue and cheeks bilaterally, and moderate erythema of maxillary anterior attached and marginal gingiva. Inter-incisal opening and cheek mobility with increased space allowing oral hygiene in the molar region was seen.

Case 3

A 60-year-old male with a diagnosis of AML received a MUD SCT in January 2013. He developed cGVHD around day +100 with oral mucosal change, dry mouth, dry eyes, and nail involvement. He was maintained on prednisone (10 mg/d) and mycophenolate mofetil (2000 mg/day), which remained his primary immunosuppression with attempts at gradual dose reduction over time post-SCT. Prednisone was very gradual tapered to 7 mg/day with periods of increase to 10 mg/day when symptoms increased during attempted tapering. Mycophenolate mofetil was also gradually reduced to 1500 mg/day. Dry mouth and eyes was managed with topical therapies. He also had trials of ruxolitinib and ibrutinib with no improvement.

When seen for oral care in May 2016, he had severe cGVHD with oral symptoms resulting in major limitation in oral intake. He was begun on topical budesonide rinse (9 mg/5 ml tid), bethanechol (25 mg tid), and topical tacrolimus (0.03%) to local ulcers when present. Oral cGVHD improved from prior to PBM therapy to 4 weeks follow-up (Table 1). PBM was gradually reduced to once weekly, with twice weekly treatments provided when oral symptoms increased. Over time, after 12 months of PBM, treatment was reduced to every 1–3 weeks. Over continuing months of follow-up, stability was achieved with fluctuation in pain and oral ulcerations on the cheek or tongue when increasing weeks between PBM visits and when associated with viral infection and potentially associated with spicy/acidic food in diet. Bethanechol was changed to cevimeline (30 mg tid) with gradual increase in saliva while continuing PBM therapy. He used lidocaine topical when oral pain was experienced in order to facilitate diet. If PBM therapy was not provided every 2 weeks, oral symptoms, tissue erythema, and ulceration recurred, but when PBM was provided on a weekly basis, he returned to baseline after 2–4 weeks of increased frequency of treatment while continuing all topicals (Table 2). Intermittent topical antifungals were used when clinical evidence of candidiasis was seen. Last follow-up was 3.5 years after the first visit for PBM therapy and approximately 6 years post-SCT. Saliva production was increased, and cevimeline was discontinued. PBM was continued on a 2-week basis.

Case 4

A 38-year-old female completed SCT from a 9 of 10 matched MUD for myelodysplastic syndrome (MDS)/AML in December 2014. She had onset of cGVHD in July 2015. GVHD was graded as severe. She was referred for oral cGVHD in December 2015. Immunosuppression at that time included prednisone (20 mg/day), tacrolimus (1.5 mg BID), sirolimus (1 mg/d), ruxolitinib, and oral budesonide (3 mg/5 ml) compound oral rinse. Plasmapheresis did not improve oral changes. Oral pain was rated 8/10; oral GVHD with ulceration and moderate erythema affected mucosa of the lips, cheeks, tongue, and gingival tissues (Table 1). She improved after 4 weeks of PBM (Table 1). Posttreatment oral pain remained improved to 4/10 for 6 weeks following PBM visits, with gradual increase and exacerbation associated with occasional upper respiratory infection, bronchitis, and pneumonia. Repeated visits over 2 years followed, each with 6–8 weeks of symptomatic improvement following each PBM treatment series of 3 treatments. Due to travel distance and medical management with intermittent admissions to hospital, more frequent visits were not possible, and she was treated on a 2–3-month schedule with 3 consecutive days of treatment. Prior to the last follow-up visit, she was begun on ibrutinib (480 mg/day).

Case 5

A 57-year-old male, with chronic lymphocytic leukemia, received MUD-SCT in 2006, donor lymphocyte infusion in 2015, and second SCT in 2016 from a different 10/10 HLA-matched MUD. He recalled oral mucositis during the SCT admissions. When seen, he had severe GVHD with mouth pain; dry mouth; and lung, liver, skin, and gastrointestinal involvement. He had a history of fungal sinusitis, recurring bronchitis and pneumonia in the prior year. Current medical management included management of hypertension, diabetes type 2, and ongoing treatment for recurring lung infection and fungal sinusitis. He was treated with hip replacement surgery in 2017 and surgery for penile squamous cell carcinoma in 2018.

When seen in September 2016, immunosuppression included prednisone (10 mg/day) and tacrolimus (1500 mg/day). He had not have responded to ruxolitinib. He had mouth pain and dry mouth affecting diet. For oral cGVHD management, he was provided budesonide (6 mg/5 ml rinse TID), tacrolimus ointment (0.03%) to apply to local ulcers, and intralesional dexamethasone injections for chronic ulceration on the dorsal tongue. Whole saliva was increased with bethanechol (25 mg TID) from pretreatment resting 0.2 mg/min and stimulated 0.08 mg/min to 0.4 mg/min and 0.43 mg/min, respectively. PBM therapy was provided twice weekly, and after 4 weeks, pain was resolved, and overall estimate of

mucosal GVHD was reduced (Table 1). PBM therapy was continued along with topicals, and he continued to improve with reduction in frequency of PBM to monthly treatments. He did have episodes of oral sensitivity and mucosal lesions with intercurrent infections, including upper respiratory infection and bronchitis which improved with increased frequency of PBM therapy to twice weekly for 3 weeks. His last visit was in November 2018, when he had minimal residual mucosal changes of GVHD (Table 2) and occasional oral sensitivity with highest VAS pain 2/10. Dry mouth remained improved.

Case 6

A 49-year-old female was treated for lymphoma in 2004 and developed MDS treated with allo-SCT from her sister in June 2012. She developed cGVHD of the skin, eyes, and mouth. When seen for oral changes, she was on prednisone (10 mg/day), but with episodic increased skin GVHD, prednisone was increased (20 mg/day), followed by taper back to 10 mg/day. She had been treated for basal cell carcinoma of the left lower eyelid. She had hip replacement surgery.

Oral cGVHD included a painful ulcer on right lateral tongue, which was confirmed as GVHD on biopsy. Budesonide (5 mg/5 ml) rinse was provided for local treatment. PBM therapy was started in November 2014 and continued for 4 weeks twice weekly PBM and no changes in medications (Table 1). She had intermittent flares of skin, ocular, and lung GVHD, often accompanied with oral changes, and prednisone was increased up to 40 mg/day with gradual tapering after flare of symptoms improved.

She had continuing treatment with gradual reduction in PBM therapy to once monthly while experiencing occasional episodes of flare with psychological stress and following hip surgery. Oral signs and symptoms remained controlled for most of the follow-up period, although flares did occur with increased stress, viral infection, and when PBM therapy was not provided monthly. With flare of oral symptoms, additional PBM visits weekly were provided until it improved after 1–2 weeks of increased frequency of PBM. Last follow-up was 18 months after first seen for PBM therapy, with control of oral changes and related symptoms (Table 2).

Case 7

A 69-year-old male with AML-M2 underwent allo-SCT with peripheral stem cells from his HLA-identical sister in 2007. One year post-HSCT, he developed cGVHD affecting the eyes, oral cavity, gastrointestinal tract, and skin.

He was referred for oral complaints in 2016. Despite treatment with dexamethasone rinses (0.1 mg/ml 4 times daily) and lidocaine gel, the oral cavity remained very painful (VAS 8/10), sensitivity score (VAS 6/10). The NIH cGVHD score was 12 (Table 1). The patient was unable to tolerate oral intake and had difficulty performing oral hygiene. He also suffered from xerostomia, dry eyes, and taste alteration. His mouth opening was reduced.

He was offered induction PBM therapy. He stopped using dexamethasone rinses and lidocaine gel. After induction PBM therapy twice weekly, he reported marked improvement (Table 1). Oral pain was reduced (VAS 3/10), xerostomia improved, and salivary production increased, and inter-incisal opening increased. Eating and speaking improved. The NIH cGVHD score decreased to 7.

Because of these improvements, PBM therapy provided at the hospital twice weekly was continued. After 3 months, PBM was reduced to once weekly with satisfying results. Oral GVHD flared when PBM therapy was completely stopped. In addition to oral symptoms, the patient developed bronchiolitis obliterans (treated with azithromycin, beclomethasone/formoterol aerosol, and montelukast). PBM was restarted once weekly, and clobetasol gel 0.25 mg/g (applied to oral lesions) and

Table 2 Oral findings following continuing photobiomodulation therapy

Patient no.	Ulcers	Erythema	Lichenoid	Mucoceles	Total oral GVHD score	Mouth pain (VAS)	Dry mouth (VAS)	Inter-incisal opening (mm)
1	0	5	1	0	6	2	0	23
2	0	4	0	0	4	0	0	33
3	1	4	2	0	7	2	3	35
4*	4	10	5	2	21	6	0	28
5	1	3	2	0	6	2	2	39
6	1	2	4	0	7	1	0	–
7	2	1	0	0	3	3	0	35

*improved × 2 months then recurred followed by weekly photobiomodulation therapy to last follow-up visit

Ulcers, erythema, lichenoid, and mucoceles were scored using the NIH OMS score (16) and VAS (visual analogue scale) (0–10), representing the maximal 24-h score. Mouth opening was only recorded if reduced opening was suspected

tacrolimus 1 mg/g ointment (lips) were prescribed. In addition, he started using extraoral PBM with a home device every other day (Photopuncture Torch, 660-nm LED approximately 700 mW/cm^2 for 4–5 min in total). Current other medications include esomeprazole 20 mg, valacyclovir 500 mg tid, and imatinib 100 mg once daily. At two occasions, the patient developed oral pseudomembranous candidiasis successfully treated with fluconazole.

Over the last 3 years, this regimen controlled oral GVHD symptoms, while at times, PBM could not be provided, or with a trial of discontinuing treatment while using clobetasol or tacrolimus, oral pain increased. Xerostomia, salivation, and inter-incisal mouth opening continued to improve to normal values.

In 2019, a lesion suspect for SCC developed at the lower lip, but histologic evaluation concluded this to be a "reactive inflammatory lesion."

Discussion

In this current report, patients managed with follow-up PBM treatments because of continuing signs/symptoms of oral cGVHD after induction treatment with PBM are described. All patients met criteria for severe cGVHD [16]. This report examines the frequency of PBM therapy necessary to maintain control and to provide additional improvement of oral cGVHD following improvement with induction of 4 weeks of twice weekly PBM.

PBM therapy has been recommended by the Mucositis Study Group of the Multinational Association for Supportive Care in Cancer for preventive management of oral mucositis in head and neck cancer (HNC) patients treated with chemoradiation therapy and in SCT recipients [17, 18]. The robust biologic effects, specifically anti-inflammatory and analgesic effects, suggest potential use of PBM therapy in T cell–mediated inflammatory mucosal conditions such as lichen planus. Studies of PBM therapy in lichen planus have shown significant reduction in clinical scores as well as providing symptomatic relief [13–15, 19].

In our prior report, we found that the addition of PBM to ongoing systemic and/or local immunosuppressive therapy resulted in clinical improvements in oral cGVHD in the first 4 weeks of twice weekly PBM treatment [2]. The NIH oral cGVHD score showed an overall reduction in mucosal lesions by 53% [2]. These findings were consistent with results of isolated case reports of oral mucosal cGVHD treated with PBM therapy [20–23].

Our current case series had a median follow-up at 25.1 months. Total GVHD score decreased approximately 28% at 4 weeks and was maintained at last visit with a further 20% improvement in total score following continuing PBM at last follow-up. Pain was reduced from a median of 6.9 prior to induction PBM to 3.7 after induction and was 2.0 at last follow-up. These findings suggest that PBM therapy may be an effective adjunct for controlling mucosal cGVHD and associated mucosal pain, in patients with initial response to PBM. Continuing PBM therapy resulted in maintenance with reduced frequency of treatments which was seen to further suppress oral cGVHD with continuing treatment. If oral cGVHD is the primary driver of systemic immunosuppressive therapy, PBM may provide additional improvement and allow an opportunity to modify systemic therapy.

Limited jaw opening was present in 3 patients (patients 1, 2, and 7) and improved in all patients at 4 weeks and with continuing treatment further improved, likely related to reduced ulcerative mucosal change and possible due to reduced regional tissue fibrosis. In another report, we identified increase in range of motion of the jaw in a subset of patients with fibrotic changes and reported alleviation of fibrotic changes in oral cGVHD [24].

We noted that PBM therapy resulted in improvement in salivary gland function where dry mouth was reported in 3 patients. In these cases, the severity was reduced from patient reported 8/10 to 5/10, whereas one patient did not experience improvement in xerostomia after continuing PBM treatment. The literature on PBM for the management of hyposalivation/xerostomia shows variable results in non-cancer patients [25, 26]. Animal studies have shown an increase in the number of ductal epithelial cell mitoses and stimulation of protein synthesis in submandibular glands following PBM therapy [27, 28]. Improvement in xerostomia was reported following prophylactic PBM in SCT recipients [29] and in a small randomized controlled trial in HNC patients treated with radiotherapy [30, 31].

Although PBM therapy has plausible safety in this setting, vigilance is warranted as oral cGVHD is associated with increased risk for oral squamous cell cancer [32].

Limitations of this case series includes variability in progress of cGVHD and changes in therapy over the long-term follow-up period. In addition, the number of cases in the report is small, although resistant and persisting oral cGVHD is not common in patients who have had systemic therapy and topical treatments prior to and throughout follow-up. This report suggests that PBM may provide maintenance of improvement and may yield additional benefit in management with continuing PBM for management of persisting and symptomatic oral cGVHD. The frequency of treatment should be individualized for each patient based upon control of symptoms and signs of oral cGVHD to provide best patient management. Further study is warranted.

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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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