A phase II prospective trial of photobiomodulation therapy in limiting oral mucositis in the treatment of locally advanced head and neck cancer patients

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Abstract
Objective: This study aimed to compare the historical incidence rate of severe oral mucositis (OM) in head and neck cancer patients undergoing definitive concurrent chemoradiation therapy (CRT) versus a prospective cohort of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) treated with prophylactic photobiomodulation therapy (PBMT).

Methods: This US-based, institutional, single-arm, phase II prospective clinical trial was initiated in 50 patients (age ≥ 18 years, Karnofsky Performance Scale Index > 60, with locally advanced HNSCC (excluding oral cavity) receiving definitive or adjuvant radiation therapy (RT) with concurrent platinum-based chemotherapy (CT). PBMT was delivered three times per week throughout RT utilizing both an intraoral as well extraoral delivery system. Primary outcome measure was incidence of severe OM utilizing both the National Cancer Institute Common Toxicity Criteria, version 4.0 (NCI-CTCAE) Grade ≥ 3 and the World Health Organization Mucositis Grading Scale (WHO) Grade ≥ 3 versus historical controls; secondary outcome measures included time to onset of severe OM following therapy initiation.

Results: At baseline, all patients included in final analysis (N = 47) had OM Grade 0. Average RT and CT dose was (66.3 ± 5.1) Gy and (486.1 ± 106.8) mg/m², respectively. Severe OM was observed in 11 of 47 patients (23%, confidence interval: 12, 38). OM toxicity grade trended upward during treatment, reaching a maximum at 7 weeks (WHO: 1.8 vs. NCI-CTCAE: 1.7). Subsequently, OM grade returned to baseline 3 months following completion of RT. The mean time to onset of severe OM was (35 ± 12) days. The mean time to resolution of severe OM was (37 ± 37) days.
INTRODUCTION

Oral mucositis (OM) is a major side effect in head and neck cancer (HNC) patients receiving definitive concurrent chemoradiotherapy (CRT) and targeted immunotherapies, particularly when the total dose of radiotherapy exceeds 50 Gy. OM represents an inflammation of the oral cavity in which mucous membranes are damaged leading to mucosal atrophy, erythema, edema, ulceration, and bleeding. Origin and pathobiology of mucosal damage are still unclear. Severe OM often leads to decreased oral intake and impaired nutritional status (and subsequent need for enteral or parental nutrition), intense pain, increased risk of infections, treatment delays and course interruptions, and greater financial toxicity. These factors greatly impact oncologic outcomes (i.e., decreased local control, survival rates) and quality of life (QOL). Previous studies indicate that approximately 40% of HNC patients will experience severe mucositis with radiation and concurrent chemotherapy. Despite multiple clinical trials, no single treatment modality has proven to be effective in substantially reducing incidence or severity of CRT-induced OM. The current standard practice for the management of OM is symptom management and supportive care with narcotic pain medications, anesthetic mouth rinses, and nutritional support with supplementation by mouth or feeding tube.

Photobiomodulation therapy (PBMT), previously termed low-level laser therapy, is an emerging, minimally invasive modality for prevention and management of OM. PBMT utilizes high-density monochromatic narrow band light source with various wavelengths (630–830 nm) to the oral mucosa. Studies suggest that PBMT leads to pain relief, reduces inflammation, and improves tissue repair with no significant in vivo toxicity. Additionally, multiple randomized trials demonstrated reduction in the rates of OM and pain with the use of PBMT. In a systematic review and meta-analysis of 11 randomized placebo-controlled trials published from 1997 until 2009 with a total of 415 HNC patients treated by chemotherapy or radiation therapy (RT), the relative risk for developing OM was significantly reduced after PBMT. This prophylactic effect improved at doses above 1 J, the minimum dose according to World Association for Laser Therapy guidelines for inflammatory conditions (trial dose range: 0.18–6 J). Although several phase III trials demonstrate an improvement in OM with PBMT, no clinical trial within the United States existed before the present study. There is a prospective, multicenter, randomized, double-blind, placebo-controlled, adaptive sample size, two-treatment parallel, pivotal clinical study currently in recruitment to evaluate the MuReva Phototherapy System for use in OM among adult HNC (squamous cell carcinoma of the oral cavity, oropharynx, tonsil and base of tongue) patients receiving CRT (ClinicalTrials.gov Identifier: NCT03972527). Given the global variation in standard baseline characteristics, healthcare environment, treatment, progress in the standard of care and clinical trial regulation, it is essential to perform separate high-quality studies in the United States to further evaluate the safety and efficacy of PBMT for the prevention and management of CRT-induced OM in HNC patients.

Therefore, we performed a single-arm, phase II prospective clinical trial to evaluate the efficacy of prophylactic PBMT to prevent or delay the appearance of severe OM in a cohort of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) receiving CRT. We hypothesize that the addition of PBMT to concurrent CRT will decrease the incidence rate of severe OM to approximately 20% from the historical incidence rate of 40% found among HNC patients undergoing definitive concurrent CRT.

MATERIALS AND METHODS

Study participants, eligibility criteria, and settings

The eligible patients were ≥18 years old, Karnofsky Performance Scale Index (KPS) ≥ 60, with previously untreated, histologically confirmed, locally advanced HNSCC of the nasopharynx, oropharynx, larynx, hypopharynx, or HNC of unknown primary origin. All patients were candidates for definitive or adjuvant RT with concurrent platinum-based chemotherapy. Patients’ clinical treatment plans included a standard fractionation scheme of external beam radiation therapy utilizing intensity-modulated radiation therapy (IMRT) with 6-MV photons and daily image-guided radiation therapy given as a cumulative dose of 50.0–70.0 Gy (1.8–2.0 Gy/fraction, one daily fraction) and concurrent weekly cisplatin 40 mg/m² or every 3-week cisplatin 100 mg/m². The radiation and chemotherapy dose, schedule, modality, technique, and any required adjustments were not influenced by this protocol and followed standard existing institutional practices and evidence-based guidelines.

Exclusion criteria included evidence of current mucositis (Grade > 0; National Cancer Institute Common Toxicity Criteria, version 4.0 [NCI-CTCAE] and World Health Organization Mucositis Grading Scale [WHO]), mucosal ulceration, or unhealed surgical wounds from surgical...
resection or biopsy; prior radiation to the head and neck; gross tumor involvement of the oral cavity or oral mucosa; plan to receive altered fractionation radiotherapy or multiple fractions per day; use of a preexisting feeding tube for nutritional support at the time of study entry; plan to receive concurrent chemotherapy other than the regimens specified in the inclusion criteria; chronic immunosuppression or are on current immunosuppressive therapies; contraindication to RT; enrollment on another investigational trial for OM prevention; or life expectancy of less than 3 months.

The trial was conducted at a single location (UPMC Hillman Cancer Center) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH)/Good Clinical Practice applicable regulatory requirements. All patients provided written informed consent before undergoing any study procedure or receiving any study therapy.

Treatment intervention

All patients received prophylactic PBMT in addition to standard of care measures for OM or other toxicities of therapy. The laser used was a 660-nm, 75-mW aluminum–gallium–indium–phosphorus laser (THOR Photomedicine). At least nine points of contact application for 60 s were used, extra-oraly along the right and left buccal mucosa and intraorally to the dorsal and ventral tongue and soft palate (including lateral and posterior pharyngeal wall). A continuous beam (2.5 Hz pulse frequency) was used. The 1/e² spot size area was 0.260 cm², and 1/e² power density was 0.245 W/cm², yielding total power of 75 mW, total energy of 4.5 J, and fluence of 3.6 J/cm². The patients underwent PBMT applications three times per week concurrently with CRT. PBMT was delivered either immediately before or after the patient’s daily fraction of radiotherapy. During each PBMT treatment session a thorough oral exam was performed to identify any areas of mucositis. If the patient developed intraoral lesions, they were targeted directly with the intraoral probe for 1 min to each site of active mucositis. During the sessions, the patients wore wavelength-specific, dark safety glasses provided by the manufacturer (THOR Photomedicine).

Patients who developed symptomatic mucositis were managed according to the standard of care hospital protocol for OM in addition to PBMT. This includes administration of topical treatments, pain medications, anesthetic mouth rinses, mouth coatings, and nutritional support with supplementation either by mouth or feeding tube, without the use of specific investigational, restricted agents. No standard treatment was denied to a patient on this protocol.

Baseline and follow-up assessments

The primary endpoint was the incidence of severe OM in patients receiving a cumulative radiation dose of at least 50.0 Gy (Grade ≥ 3; NCI-CTCAE or WHO). The secondary endpoints included time to onset of severe OM, mean cumulative radiation dose at the time of OM, duration of OM, the incidence and severity of patient-reported pain (mouth and throat, using a standard 0–10 scale), nutritional status (weight and need for enteral or parental nutrition), dysphagia, xerostomia, dysgeusia, radiodermatitis, and QOL. All non-OM toxicities were evaluated in accordance with the NCI-CTCAE. OM-related QOL and functional impairment were measured by the Karnofsky Performance Scale Index (KPS) stratified into Groups using the following criteria: Group 1 (80%–100%: able to carry on normal activity and to work; no special care needed), Group 2 (50%–70%: unable to work; able to live at home and care for most personal needs; varying amounts of assistance needed), and Group 3 (0–40%: unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly). Patients were evaluated before start of therapy, weekly during therapy, 2 weeks following completion of therapy, and 3 months after the completion of therapy.

Toxicity evaluations were performed independently by formally trained radiation oncologists. Interrater reliability was assessed by the clinical research coordinator.

Statistical methods

To detect a decrease in the incidence of Grade ≥ 3 OM from 40% in the historical controls to 20% in the current study, we planned to enroll 50 patients (45 evaluable patients were required), with a Type I and Type II error of 5% and 20%, respectively. This determination was based on the framework of threshold-crossing. The OM assessment tools were compared using the t-test (p value was two-tailed and considered statistically significant at p < 0.05). Secondary endpoints were summarized with descriptive statistics by visit. The incidences of all-grade and specific grade of OM were summarized with descriptive statistics by visit and for the entire study duration. Time to resolution of severe OM was defined by the number of days from diagnosis of Grade ≥ 3 OM to resolution to baseline grade. All patients who were excluded for analysis of the primary endpoint because of unconfirmed treatment use were included in the sensitivity analysis as having grade 3 or worse OM. SAS version 9.4 (version 9.4; SAS Institute Inc.) was used for statistical analyses of the primary and secondary endpoints.

RESULTS

Patient population

Of 50 subjects enrolled, 47 were eligible for analysis of primary clinical trial endpoints. Two patients dropped out of the trial and one patient did not have complete radiation treatment data available. Clinical and pathological characteristics of the patients, the treatment modalities used, and summary measures are shown in Table 1.
The average age of the total sample was 59.7 ± 7.2 years. Regarding tobacco and alcohol history, 46.8% and 61.7% of patients reported use over study period, respectively. The oropharynx was the most common primary site (n = 33, 70.2%) followed by larynx (n = 8, 17.0%), nasopharynx (n = 3, 6.4%), unknown (n = 2, 4.3%), and hypopharynx (n = 1, 2.1%). Radiotherapy and concurrent chemotherapy specifics are provided in Table 2. Subjects were treated to a mean cumulative RT dose of (66.3 ± 5.1) Gy and (486.1 ± 106.8) mg/m² of platinum-based chemotherapy. All patients received a minimum of 50 Gy to 20% of the oral cavity.

### Severe OM

The mean OM grade and proportion of patients with severe OM over the study period is illustrated in Figure 1. At baseline, all patients had Grade 0 mucositis as determined by WHO Oral Toxicity Scale and NCI-CTCAE assessment. During Week 3 of radiation treatment, the incidence of severe OM was WHO: 2.1% (n = 1/47) versus NCI-CTCAE: 4.3% (n = 2/47). Mean grade at this visit was 0.9 and 0.8 for WHO and NCI-CTCAE, respectively. During Week 6 of radiation treatment, the incidence of severe OM was WHO: 10.3% (n = 4/39) versus NCI-CTCAE: 10.3% (n = 4/39). Mean grade at this visit was 1.5 and 1.3 for WHO and NCI-CTCAE, respectively. At Week 7 of treatment, the incidence of severe OM reached a maximum: WHO: 22.7% (n = 5/22) versus NCI-CTCAE: 22.7% (n = 5/22). Mean grade at this visit was 2.1 and 1.7 for WHO and NCI-CTCAE, respectively. Of 40 patients evaluated 3 months after completion of RT, none reported severe OM by WHO versus 1 (2.5%) by NCI-CTCAE. There was no significant difference between WHO and NCI-CTCAE assessment (t = −0.36, p = 0.7225). Thus, the OM toxicity grade worsened over the course of treatment and returned to baseline (Grade = 0) approximately 3 months following completion of radiation treatment (Table 3).

### TABLE 1  Patient and tumor characteristics, n (%)

| Characteristics                | n = 47 |
|-------------------------------|--------|
| Age (years)                   |        |
| Mean ± SD                     | 59.7 ± 7.2 |
| Median                       | 60.5   |
| Range                        | 44–74  |
| Primary site                  |        |
| Oropharynx                    | 33 (70.2) |
| Larynx                       | 8 (17.0) |
| Nasopharynx                   | 3 (6.4)  |
| Other (unknown primary site)  | 2 (4.3)  |
| Hypopharynx                   | 1 (2.1)  |
| Tobacco history               |        |
| Yes                           | 22 (46.8) |
| No                            | 25 (53.2) |
| Alcohol history               |        |
| Yes                           | 29 (61.7) |
| No                            | 18 (38.3) |

Note: Data presented as numbers, with percentages in parentheses, unless otherwise noted.

### TABLE 2  Radiotherapy and concurrent chemotherapy, n (%)

| Characteristics                                      | n = 47 |
|------------------------------------------------------|--------|
| Delivered radiation-therapy cumulative dose (Gy)     |        |
| Mean ± SD                                           | 66.3 ± 5.1 |
| Median                                              | 70     |
| Range                                               | 54–70  |
| Radiation fractions                                  |        |
| Mean ± SD                                           | 33.1 ± 2.3 |
| Median                                              | 35     |
| Range                                               | 29–35  |
| Irradiated areas in oral cavitya                     |        |
| ≥2                                                   | 47 (100.0) |
| Cisplatin cumulative dose (mg/m²)                    |        |
| Mean ± SD                                           | 486.1 ± 106.8 |
| Median                                              | 482    |
| Range                                               | 270–765 |

Note: Data presented as numbers, with percentages in parentheses, unless otherwise noted.

aDuring each radiation therapy session, at least a portion of two areas in the oral cavity received ≥50 Gy.

and NCI-CTCAE, respectively. Of 40 patients evaluated 3 months after completion of RT, none reported severe OM by WHO versus 1 (2.5%) by NCI-CTCAE. There was no significant difference between WHO and NCI-CTCAE assessment (t = −0.36, p = 0.7225). Thus, the OM toxicity grade worsened over the course of treatment and returned to baseline (Grade = 0) approximately 3 months following completion of radiation treatment (Table 3). Over the entire study period, severe OM was observed in 23.4% (n = 11/47) of patients by WHO assessment and 21.3% (n = 10/47; 95% confidence interval: [12, 28]) of patients by NCI-CTCAE assessment. Thus, the primary objective of the study was statistically significant and achieved. Of the 11 patients with severe OM, the majority (81.8%) received RT for cancer of the oropharynx. The average age among the 11 patients with severe OM was (59.4 ± 7.7) years. Despite the heterogeneity of the patient population experiencing severe OM (oropharynx, nasopharynx, and unknown primary site; differences in RT fields by disease site; weekly or every third-week cisplatin), no subanalyses were conducted due to sample size.

The mean time to onset of severe OM following the initiation of therapy was (35 ± 12) days (Figure 2). The mean time to resolution of severe OM was (37 ± 37) days (Figure 2). Of note, the mean cumulative radiation-therapy dose among patients with severe OM was (65.8 ± 6.6) Gy. Only the primary occurrence of severe OM was utilized in calculation of time to onset and resolution. Likewise, only events occurring from the date of first administration of RT and PBMT until the date of the EOT and within 3 months afterwards are included in both calculations and illustration.
Exploratory endpoints: pain, nutritional status, dysphagia, xerostomia, dysgeusia, radiodermatitis, and QOL

The mean and median NCI-CTCAE grade (in the case of dysphagia, xerostomia, dysgeusia, radiodermatitis) and score (in the case of mouth and throat pain) of these exploratory endpoints over the study period for the entire cohort are illustrated in Figure 3. Mean baseline assessments were as follows: mouth pain (0.1), throat pain (0.5), dysphagia (0.1), xerostomia (0), dysgeusia (0), radiodermatitis (0), weight (88.7 kg). Additionally, 8.5% (n = 4/47) and 19.1% (n = 9/47) of patients reported recent tobacco use and alcohol use, respectively. Furthermore, 100% of patients did not require enteral or parental nutrition and reported KPS ratings between 80% and 100% (Group 1; no significant functional impairment). Similar to what was observed for OM, the grade of all other adverse events peaked at Week 7 of treatment (N = 22): mouth pain (median: 4.0, mean: 3.7), throat pain (median: 6.0, mean: 6.0), dysphagia (median: 2.0, mean: 2.4), xerostomia (median: 2.0, mean: 1.7), dysgeusia (median: 2.0, mean: 1.5). Of note, the proportion of patients reporting tobacco and alcohol use at the Week 7 visit was 4.5% (n = 1). This proportion fell to 2.5% (n = 1) for tobacco use and rose to 7.5% (n = 3) for alcohol use 3 months after completion of RT. Mean weight was downtrending over the course of treatment and reached a low of 78.3 kg 3 months after completion of RT. Mean weight loss was 10.7 kg between the start and end of treatment (EOT). At the EOT, 33.3% (n = 15/45) of patients required enteral or parental nutrition. Three months after completion of therapy, all patients returned to their baseline performance status (Group 1; no significant functional impairment).

Treatment compliance

None of the patients needed to stop or reduce their CRT treatment due to OM. Moreover, 98% of patients completed the prescribed chemotherapy course without delays. Furthermore, no deaths occurred during the study. Generally, patients were evaluated weekly. Depending on their planned radiation treatment plan, patients may have 5-, 6-, or 7-week visits before EOT depending on the time RT dose reached planned maximum. The percentage of patients with 5-, 6-, and 7-week visits before EOT was 17% (n = 8/47), 34% (n = 16/47), and 47% (n = 22/47), respectively. One patient had six visits, but no EOT. There were seven patients (15%) who missed the 3-month post RT visit.

DISCUSSION

This is the first single-arm phase II prospective clinical trial based in the United States to report promising efficacy of PBMT in the prevention and management of OM among locally advanced HNSCC patients treated with concurrent CRT, adding to findings from previous phase III international trials utilizing various forms of phototherapy and warranting further investigation. We demonstrated a severe OM rate of 21%–23% comparable and even lower than prior studies reporting levels of around 40% with PBMT. We also found that severe OM peaked at week 7 of treatment and for the majority of affected patients was non-evident 2 weeks after the completion of treatment. This adds to the limited literature which cites that among HNC patients receiving radiation, OM peaks at
TABLE 3 Oral mucositis characteristics, n (%)  

| Characteristics | n = 47 |  |
|-----------------|--------|---|
| WHO OM Grade 0 at baseline | 47 (100.0) |  |
| NCI-CTCAE OM Grade 0 at baseline | 47 (100.0) |  |
| WHO OM Grade ≥ 3 from initiation to 3 months post-RT | 10 (21.3) |  |
| NCI-CTCAE OM Grade ≥ 3 from initiation to 3 months post-RT* | 11 (23.4) |  |
| Age (years) Mean ± SD | 59.4 ± 7.7 |  |
| Median | 59 |  |
| Range | 50–74 |  |
| Primary site |  |
| Oropharynx | 9 (18.1) |  |
| Nasopharynx | 1 (6.4) |  |
| Other (Unknown primary site) | 1 (2.1) |  |
| Tobacco history |  |
| Yes | 6 (54.5) |  |
| No | 5 (45.5) |  |
| Alcohol history |  |
| Yes | 7 (63.6) |  |
| No | 4 (36.4) |  |
| Cisplatin |  |
| Weekly (40 mg/m²) | 45 |  |
| Every third-week (100 mg/m²) | 2 |  |
| Enteral or parenteral nutrition |  |
| Yes | 7 (63.6) |  |
| No | 4 (36.4) |  |
| Time to onset of severe OM, mean (SD), days | 35 (12) |  |
| Time to resolution of severe OM, mean (SD), days | 37 (37) |  |

Note: Data presented as numbers, with percentages in parentheses, unless otherwise noted.

Abbreviations: NCI-CTCAE, National Cancer Institute—Common Terminology Criteria for Adverse Events, Version 4.0; OM, oral mucositis; WHO, World Health Organization Mucositis Grading Scale.

*95% confidence interval: [12, 28].

Weeks 4–6 of treatment and usually lasts for weeks after completion of radiation. Our findings are set in the context of a major advancement in cancer treatment—IMRT for radiotherapeutic techniques—that does not reduce the incidence of severe OM despite a potential reduction of oral mucosa volume exposed to high dose radiation (≥30 Gy). Contrary to a recent report by Leoute et al., all patients were treated with PBMT without interruption (i.e., no OM grade requirement for treatment initiation and cessation). Evidence of OM at baseline may have led to an over-estimation of PBMT benefit in addition to increasing the risk for treatment interruptions. We also utilized a less stringent light technology, allowing penetration of difficult to reach OM lesions in the oropharynx and hypopharynx and cutaneous and OM concurrent treatment with an extra oral applicator, challenging the potential lack of statistical power reported. Furthermore, we utilized the two most common clinical OM assessment scales, WHO (focuses on mucosal ulceration and feeding capacity) and NCI-CTCAE (relies on the clinician’s observation, patient’s self-reported symptoms, and the effect of OM on feeding capacity and overall safety), to ensure that the severity of mucosal damage was objectively classified. We found no significant difference in classification between assessment scales.

Toxicity outcomes in this trial were favorable. Thirty percent of patients have been reported to stop or reduce their CRT treatment due to OM. In contrast, none of the patients in our cohort required treatment breaks due to OM. Fifteen patients required temporary feeding tubes, and this need dropped by more than one-third by the last follow-up. Prior reports of RT with or without concurrent chemotherapy in HNC have reported 61%–83% patients require feeding tube placement during treatment. One year following treatment, feeding tube dependence up to 41% has been reported. There is variability in reported long-term feeding tube dependence, ranging between 8% and 18%.

Reducing the frequency of these complications is an important step toward mitigation of toxicity in this patient population. Patient-reported QOL outcomes, assessed by the Functional Assessment of Cancer Therapy-Head and Neck Scale (FACT-H&N), were collected as part of this trial and will be analyzed in future reports.

Specifically, prophylactic PBMT was recommended for patients receiving head and neck radiotherapy without concomitant chemotherapy—an upgrade of the 2014 guidelines from a suggestion to a recommendation. A new guideline was issued recommending prophylactic PBMT for patients receiving concurrent chemotherapy and RT for HNC due to new evidence (Level I). In contrast to the MASCC/ISOO recommendations and systematic review, a Cochrane Collaboration systematic review published in 2011 found that there was only weak evidence from two small studies at risk for bias favoring PBMT for the prevention of OM. The authors called for more randomized controlled trials to support the use of PBMT, particularly Laser and LED light sources. There are data showing that there is no difference in the interaction of a laser and a LED with the human tissue. Despite the need for further evaluation, we must acknowledge the advantages of LEDs, which include no laser safety considerations, the ability to irradiate a large area of tissue at once, much lower cost per mW, and the possibility of wearable or take-home devices. Consideration for future trials should include dedicated device self-treatment.

The 2019 novel coronavirus (COVID-19) pandemic has created significant challenges to the delivery of care for patients with advanced HNC requiring multimodality therapy, who harbor a higher risk of infection compared with the overall population and are more susceptible to the need for critical care, respiratory support, and mortality. In addition to changes in clinical practice (particularly within Otolaryngology, Medical Oncology, and Radiation Oncology),
the COVID-19 pandemic has halted or slowed the progression of research designed to improve QOL and symptom management in HNC. However, these international challenges have also highlighted new considerations for future clinical trials designed to characterize the impact of extraoral and intraoral PBMT protocols on OM and survival outcomes of patients with HNSCC. Faria et al. reported use of a closed-mouth extraoral PBMT protocol, delivery by use of a large LED probe, against intraoral devices (often the focus of current treatment protocols) during the pandemic COVID-19 outbreak as a means to control the contact with the saliva of potentially contaminated cancer patients.

Our study has important limitations to consider. First, the trial enrolled a relatively small cohort of patients with relatively short follow-up. Second, although the toxicity outcomes compare favorably to historical controls, the nonrandomized study precludes direct comparison and definitive conclusions regarding comparative toxicity especially since historical cohorts were often not followed with WHO scoring. Third, all patients had treatment at a single institution affiliated with an NCI-designated cancer center and treatment protocols were performed by highly experienced and centralized personnel, which may limit applicability to general practice. Furthermore, the presence of supportive care and other resources may impact the generalizability of the impact of PBMT, particularly in the absence of historical rates of severe OM specifically from the UPMC Hillman Cancer Center. This lack of a historical control is secondary to the recent adoption of WHO scoring which is now common among all patients. Additional limitations included incomplete data (including use of topical creams, pain medications, anesthetic mouth rinses and mouth coatings), possible attrition bias (patients missed follow-up assessments), and no direct comparison of PBMT to local treatments (i.e., honey and oral topicals) though they may have been used in association as a standard of care. Lastly, implicit bias regarding favorability of therapeutic trials (surgery, chemotherapy, radiotherapy, or new antineoplastic treatments) over a supportive care/QOL study for advanced HNC may have impacted
accruals. Nonetheless, the importance of this institutional, phase II trial is that it focuses on evaluating and validating a new therapeutic standard of PBMT in limiting OM. Furthermore, our study characterized the benefits of PBMT through observable OM evolution (using multiple clinical mucositis assessment scales) and the subjective and functional dimensions of OM (nutritional status, dysphagia, xerostomia, dysgeusia, dermatitis, and QOL), many of which are independent emerging applications.

The University of Pittsburgh experience

With mounting positive clinical evidence and practice guideline recommendations from both Cochrane and MASCC in favor of the use of PBMT, the UPMC Hillman Cancer Center Department of Radiation Oncology, in December 2014, initiated a PBMT program to help improve the QOL in patient’s undergoing HNC treatment.

Staff physicians at UPMC Shadyside participate in a Head and Neck Cancer multidisciplinary conference in collaboration with the Department of Otolaryngology, Medical Oncology and Dentistry. Here patients are discussed from not only a disease management standpoint including potential enrollment in clinical protocols, but also in terms of the individual patient’s feasibility in completing therapy based upon their disease state and social circumstances. This is a necessary component of the multidisciplinary management team since prolonging the treatment, whether it is from pain control, weight loss, or other factors, leads to inferior outcomes. As a result, PBMT was a welcomed addition to the tiresome management of OM resulting from CRT.

To date, over 700 patients receiving RT for head and neck carcinoma have been treated with PBMT. The PBMT program has been so successful in the radiation oncology facility at UPMC that currently we have extended use to the inpatient stem cell transplant population for prevention of OM in this extremely high-risk subset of patients.

CONCLUSION

Despite improving medical management and supportive care in HNC patients undergoing concurrent CRT, mucosal damage remains an area of concern for HNC treatment. Compared to historical outcomes, PBMT aides in decreasing severe OM incidence and duration in patients with locally advanced HNSCC. PBMT represents a minimally invasive, prophylactic intervention to decrease OM as a major treatment-related side effect. PBMT was well tolerated with an excellent safety profile that may be used to improve morbidity of CRT and potentially prevent the need for detrimental treatment breaks.

AUTHOR CONTRIBUTIONS

All authors contributed to the design, collection, analysis of data, and manuscript revision.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The trial was conducted at a single location (UPMC Hillman Cancer Center) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH)/Good Clinical Practice applicable regulatory requirements. All patients provided written informed consent before undergoing any study procedure or receiving any study therapy.

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