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PREVENTION OF ORAL MUCOSITIS IN CHILDREN AND ADOLESCENTS UNDERGOING HEMATOPOIETIC CELL TRANSPLANT USING PHOTOBIOMODULATION THERAPY

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Protocol MNEMONIC and Title: Prevention/Treatment of Oral Mucositis in Children and Adolescents undergoing Hematopoietic Cell Transplant (HCT) using Photobiomodulation Therapy (PBM)
Principal Investigator: Belinda Mandrell, PhD, RN
IND Holder: Not Applicable
Brief Overview: Oral mucositis is a significant and common toxicity experienced by patients who receive chemotherapy as a preparatory regimen for a hematopoietic cell transplant (HCT). Furthermore, oral mucositis has been reported as the single most debilitating side effect reported by patients undergoing HCT. The incidence of HCT mucositis among adults is estimated to range between 76% and 89%; however, comparisons are difficult due to variability in patient ages, treatments and criteria for scoring oral mucositis. The use of intra-oral photobiomodulation (PBM) therapy in adult patients after the development of oral mucositis is well documented and now included in the international mucositis guidelines, with limited evidence in pediatrics. This study will build evidence for the incorporation of extra-oral PBM therapy into daily nursing care of children and adolescents undergoing HCT. This intervention has potential in providing evidence for efficacy in the prevention and treatment of oral mucositis, the single most debilitating side effect reported by patients undergoing HCT. Patients admitted for an allogeneic hematopoietic cell transplant (HCT) will be eligible to receive daily extra-oral and intra/oral PBM beginning on the first morning of conditioning chemotherapy and continuing until Day +20 or engraftment (ANC $\geq$ 500 for two consecutive days), at which time treatment will end. Patients admitted for an autologous transplant and determined by the transplant team to be at risk for $\geq$ grade 3 oral mucositis will be eligible to receive daily extra-oral/intra oral PBM beginning on the first morning of conditioning chemotherapy and continuing until engraftment (ANC $\geq$ 500 for two consecutive days) or until patient is without mucositis (grade 1) for two consecutive days.
Intervention: PBM is defined as the application of coherent or non-coherent light to an area of pathology to promote tissue regeneration, reduce inflammation, and relieve pain. The biological mechanism of PBM allows intracellular absorption of energy by intracellular organelles and molecules; however, the amount and specifics of energy absorption is dependent upon the wavelength and rate of energy delivery dependent on the power of the device. PBM is FDA approved for tissue damage, pain and inflammation. There is no age limitation.

Brief Outline of Treatment Plan: Children, adolescents and young adults admitted for an allogeneic HCT and those determined by the transplant team to be at risk for ≥ grade 3 oral mucositis will be eligible to receive PBM (34 x 660 nm 10 mW, 35 x 850 nm 30 mW; 1390 mW total power output at an irradiance of 50mW/cm2).The PBM will be administered by trained research staff beginning on the first morning of the conditioning regimen (plus/minus 2 days) and continue daily until Day +20 or engraftment (event occurring first) and for allogeneic continue daily until engraftment or until the patient is

Protocol MNEMONIC and Title: Prevention/Treatment of Oral Mucositis in Children and Adolescents undergoing Hematopoietic Cell Transplant (HCT) using Photobiomodulation Therapy (PBM)
without grade 1 (no) mucositis for two consecutive days. All patients will receive the standard mouth care regimen prescribed for transplant patients. The nurse, advance nurse practitioner and physician caring for the patient will grade mucositis daily per the Common Toxicity Criteria (version5), and pain will be documented per institutional pain assessment scale (0-10). Patient- reported pain, and oral function will be collected daily.
Study Design: This two-stage design study will assess for development of grade 3 mucositis during daily PBM treatment.
Sample Size: 66
Data Management: Data management and statistical analysis will be provided by the Division of Nursing Research and Biostatistics Department at St. Jude Children's Research Hospital
Human Subjects: The risks to subject are minimal. Retinal irritation is unlikely: however, each patient will be issued glasses for eye protection. Patients will be informed of this during informed consent discussion. Adverse events will be monitored and reported and treated appropriately.

Contents

1.0 OBJECTIVES

The use of intra-oral photobiomodulation therapy (PBM) in adult patients, who develop therapy related mucositis, is included in the international mucositis guidelines, with limited evidence in pediatrics. This intervention has the potential of providing additional evidence within the pediatric literature to the benefits of PBM in the prevention and treatment of oral mucositis in pediatric patients undergoing HCT. The ultimate goal would be incorporation of PBM into daily nursing care guidelines for pediatric patients undergoing HCT, thus improving outcomes and health-related quality of life.

1.1 Primary Objective

To evaluate feasibility and efficacy of photobiomodulation therapy (PBM) in reducing oral mucositis in children and adolescents at risk for grade 3 oral mucositis undergoing an allogeneic hematopoietic cell transplant (HCT).

Hypothesis 1: Children and adolescents will receive 75% of the attempted PMB treatment and will be less likely to develop grade 3 oral mucositis from the 1st day of conditioning to day +20 transplant or engraftment (event occurring first)

1.2 Secondary Objectives

To compare clinical manifestations associated with the development of oral mucositis between those treated with daily PBM and a matched control. Clinical factors to include: grade and duration or oral mucositis.

Hypothesis 2: Children and adolescents treated with extra-oral PBM will develop lower grade mucositis, with shorter mucositis duration (days) than the comparison matched control.

1.3 Exploratory Objective

1. *To evaluate efficacy of photobiomodulation therapy in autologous patients at risk for grade 3 oral mucositis compared to matched control.*

   Hypothesis: Children and adolescents treated with PBM will be less likely to develop grade 3 mucositis than matched control.

2. *To evaluate utilization of play-based procedural preparation and treatment feasibility and parental satisfaction.*

   Hypothesis: Children and adolescents introduced to low level light therapy through play-based procedural preparation will complete treatment at all sites compared to those without play-based preparation.

2.0 BACKGROUND AND RATIONALE

2.1 Background

Oral mucositis is a significant and common toxicity experienced by patients who receive high-dose chemotherapy as a preparatory regimen for a hematopoietic cell transplant (HCT). Furthermore, oral mucositis has been reported as the single most debilitating side effect reported by patients undergoing transplantation.[1] The incidence of HCT conditioning mucositis is estimated to range between 76% and 89%; however, comparisons are difficult due to variability in patient ages, treatments and criteria for scoring oral mucositis.[2, 3]

Oral mucositis is a progressive process that begins shortly after the administration of high-dose chemotherapy and results from DNA strand breaks that result in direct cellular injury of cells in the basal epithelium and within the submucosa resulting in mucosal destruction.[2] Additionally, mucositis represents local tissue reactions including damage from reactive oxygen species, inflammatory cytokines, and damage to submucosa connective tissues and vasculature. Stages of oral mucositis include mucosal burning, erythema, edema with progression to ulceration. Ulceration occurs most commonly on the nonkeratinized mucosa of the mouth floor, tongue, buccal mucosa and soft palate.[3] Oral mucositis is noted several days after completion of chemotherapy with a peak in severity between 6 and 12 days post-transplant.[4]

Oral ulcerations are painful, may become secondarily infected, bleed and impact nutritional intake. Together these factors increase the need for parenteral nutrition, opioid administration for pain and predispose the patient to secondary infection and bacteremia. The cost of oral mucositis can be excessive due to increased utilization of antibiotics, blood products, pain medication and supplemental nutrition thus leading to longer hospitalizations. According to Sonis et al.,[5] a one point increase in peak mucositis grade in HCT has been associated with a 2.1 fold increase in risk of significant infection, 2.7 additional days of parenteral nutrition, 2.6 additional days of hospitalization, additional hospital cost of $25,405 and 3.9 fold increase in risk of mortality with the first 100 days. While reporting benefit, the literature is limited in describing the efficacy of treatment for oral mucositis prevention and treatment among pediatric patients. Most studies have reviewed the efficacy of adult HCT oral mucositis interventions, with the inclusion of laser therapy recommended in adult oral mucositis guidelines.[2] Currently there is insufficient evidence for the application of PBM inclusion into oral mucositis guideline in the pediatric oncology population.[6]

This is a nurse led innovation utilizing a novel therapy for the prevention and treatment of the single most debilitating side effect reported in patients undergoing HCT. This innovative proposal has the potential to change our established Nursing Standard of Oral Care Guidelines for children and

adolescents undergoing a HCT through planned and coordinated application of daily PBM with standard oral care. If the PBM is found to reduce the severity and duration of oral mucositis, the change in nursing routine with the inclusion of nurse delivered PBM will have a direct impact on improving health outcomes specifically patient reported pain, decrease in positive blood and oral cultures and less days of nutritional support. A decrease in the severity and duration of oral mucositis will also have a potential impact on health care cost with a decrease in supportive care measures, which may subsequently decrease days of hospitalization.

2.2 Rationale for Photobiomodulation Therapy

PBM is defined as the application of coherent light to an area of pathology to promote tissue regeneration, reduce inflammation, and relieve pain. The biological mechanism of PBM allows intracellular absorption of energy by intracellular organelles and molecules; however, the amount and specifics of energy absorption is dependent upon laser wavelength and rate of energy delivery dependent on the power of the laser.[7] Mitochondria in stressed or ischemic tissues produces excessive mitochondrial nitric oxide (mtNO) which binds to cytochrome c oxidase, competitively displacing oxygen and consequently reducing ATP, but this inhibition of mitochondrial respiration significantly increases production of ROS (free radicals). These excess ROS trigger the process of inflammation, cell death and subsequently oral mucositis. Light of the correct wavelength (generated by low intensity lasers and LED's), when applied to stressed tissues, is absorbed by cytochrome c oxidase. The light displaces the mtNO thereby reducing oxidative stress and increasing ATP production; this reduces inflammation and increases cell metabolism. A recent comprehensive review described the mechanisms of action for light therapy and molecular interactions and the implication of cytochrome c oxidase as the photo acceptor modulating light therapy.[8]

Figure 1 demonstrates the stages of wound healing and the benefit of light stimulation.[8]

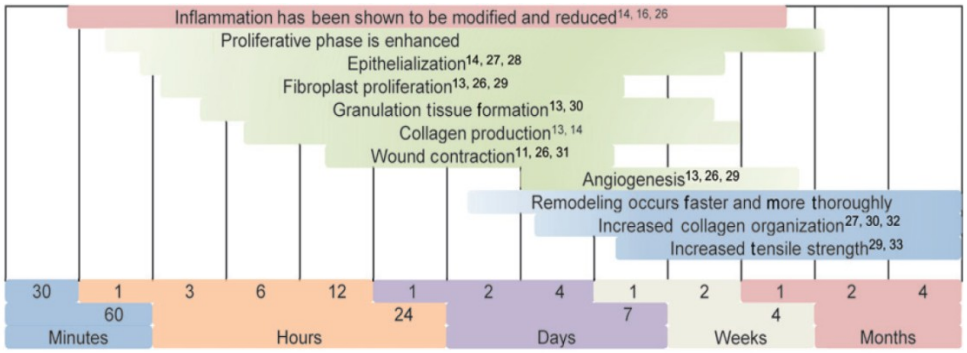

Figure1 Wound healing stages light therapy is cited to act upon

Figure 2 illustrates possible excitatory pathway by which light stimulates the electron transport chain to higher functionality[8]

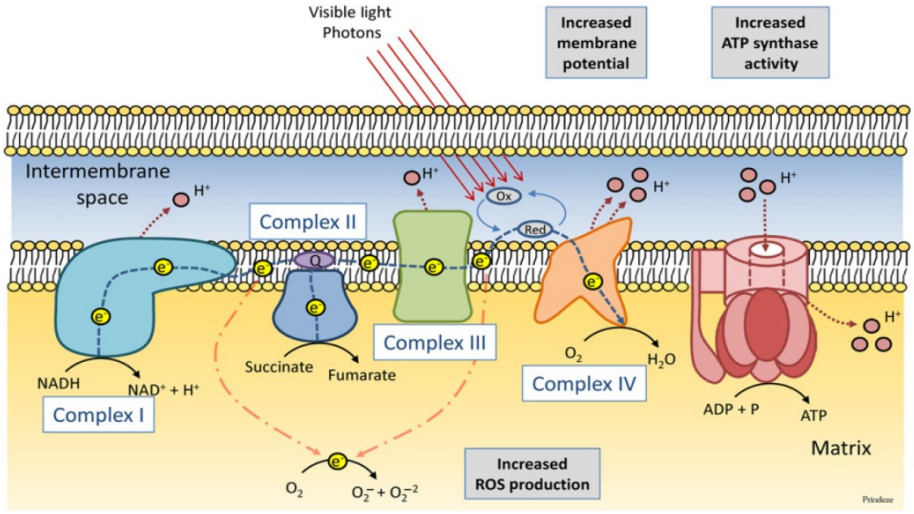

Figure 2 Effects of light therapy on the mitochondrial electron transport chain. Cytochrome *c* is stimulated to switch redox states, transferring electrons to cytochrome *c* oxidase at a higher rate, increasing proton transport and subsequently the mitochondrial membrane potential. Increase in hydrogen ion gradient drives ATP synthase to increase ATP catalysis. Electron transport follows decreased energy states (▪ ▪ ▪), while electron leakage reduces oxygen to reactive oxygen species(▬ ▪ ▬)

Several studies have evaluated the effect of PBM on prevention and treatment of oral mucositis among adult patients undergoing HCT, with encouraging results. [9-11] These results prompted a change in the latest update of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) mucositis guidelines and now include a new recommendation for the use of PBM (34 x 660 nm 10 mW, 35 x 850 nm 30 mW; 1390 mW total power output at an irradiance of 50mW/cm2), in prevention of adult

patients receiving HCT conditioned with high-dose chemotherapy, with or without total body irradiation .[12] The guideline also suggested the use of PBM in the prevention of oral mucositis in head & neck cancer patients treated with radiation therapy without concomitant chemotherapy.

Pediatric Evidence

A recent guideline was published by The Pediatric Oncology Group of Ontario (POGO) Mucositis Prevention Guideline Development Group specific to PBM. After review of the literature, the group placed high value on the possible reduction in mucositis with such intervention with a low risk of harm. While the evidence was adequate for potential benefit, the recommendation was weak due to the need for specialized equipment, expertise and unknown feasibility to deliver the therapy in routine clinical care.[13] This recommendation was taken from a systematic review by Oberoi et al, [14] of 18 prophylactic PBM studies. The meta-analysis reported PBM significantly reduced the incidence of severe mucositis, overall grade of oral mucositis, the incidence of severe pain, overall mean pain scores and use of opioid analgesia.

PBM has been evaluated in two small sample studies, as a device to prevent oral mucositis in pediatric patients undergoing HCT.[6, 15] The first study treated 9 patients with PBM directly to the mucositis lesion and 12 control who had received a HCT or chemotherapy. The patients were treated for 5 days. Patients were evaluated by mucositis duration, with PBM OM duration 5.8 ± 2 days and the control 8.9 ± 2.4 days. [15] The second study treated 12 patients four times a week with a protocol of combined intraoral and extraoral PBM for an average of 22 days and matched to a retrospective group. Mucositis severity was significantly less than the control group, and higher (non-significant) oral function than the control. [6] Another study reviewed 51 HCT pediatric patients treated with daily PBM and found good clinical outcomes with control of mucositis severity and pain reduction.[16] This technique was further evaluated with the objective of controlling pain associated with oral mucositis in a pediatric transplant population with successful outcomes.[17]

Many of the cited studies have delivered PBM intraoral as individual small “spots” via a laser probe, specific to oral mucositis sites from the lips to soft palate in a time consuming manner and one which may be challenging in pediatric use.[18] A more recent approach is use of a larger light-emitting diode (LED) through an extra oral approach, treating the oral, oropharyngeal, and esophageal mucosa, with improved patient corporation. [19] A recent study evaluated the feasibility of extraoral PBM by trained nurses for the prevention of oral mucositis in HCT patients.[20] The study enrolled 13 HCT patients 4 years and older. The study did not evaluate

efficacy but found the treatment delivery to feasible and well tolerated.

The timing of PBM during therapy is inconsistent across studies. An adult study began treatment at day 1 of conditioning and continued until day 2 post progenitor cell infusion.[7] Three pediatric studies were reviewed for initiation of PBM, with two studies beginning PBM at day 1 of conditioning, [6, 20] and the third study initiating PBM after the completion of conditioning.[16] Two studies continued PBM until engraftment[6, 16] and the third continued until day 20 after cell infusion.[20]

HCT Patient Experience at St. Jude

To better understand our patient experience, we conducted a retrospective review of the HCT patient experience and reviewed the medical records of 45 patients. [21] Patients were divided into two groups based on mucositis severity (mucositis defined as ≥ grade 3 on the Common Terminology Criteria of Adverse Events). Demographic and clinical data were obtained via electronic medical record review and compared between groups.

This retrospective study reviewed transplant admissions between June 2015 and May 2016.[21] During this period, 75% of the allogenic transplant patients had ≥ grade 3 mucositis with median mucositis onset at Day 3 (range -3 to 9) after progenitor cell infusion, median mucositis duration of 11 days, median of 9 days from (range 3 to 26) mucositis onset to engraftment and a median of 2 days (range -21 to 26) from engraftment to the end of mucositis. All of the 25 patients received parenteral nutrition and 96% received pain medications for oral pain. Patients with ≥ grade 3 mucositis were more likely than those with grade 1/2 mucositis to have positive blood or oral cultures (p=0.018), to have undergone an allogeneic transplant [17 of 21 patients (p=0.008)] and had significantly longer hospitalizations (p=0.002). However, our review did find a subset of patients receiving auto transplant, such as neuroblastoma, to be at risk for high grade mucositis.

Our retrospective data revealed the onset of mucositis can be as early as Day -3 with continuation until engraftment. While studies have variability in timing of PBM, these findings support our proposed initiation of therapy to begin on the first morning of conditioning until engraftment with an ANC ≥500 for two consecutive days. Seventy-five percent of the those with grade 3 mucositis had undergone an allogenic transplant and 33% autologous. Therefore, patients undergoing autologous transplant and at risk for grade 3 mucositis, as identified by the bone marrow transplant clinicians will be included in the exploratory objective.

To determine sample size, we extended our review of allogenic transplant recipients from May 2015 to June 2019. Our review identified 93 first allogeneic transplant patients, with 66 (71%) developing grade 3 mucositis during transplant.

Play-Based Procedural Preparation

Child life specialists are psychosocial providers who focus on improving coping skills and reducing stress among children and families in medical environments. These developmental experts implement play-based interventions to promote feelings of control, familiarity, understanding, and predictability in otherwise stressful and unfamiliar hospital settings. One such intervention is play-based preparation, in which child life specialists use age appropriate language and medical play to assess children's and families' understanding, to teach new concepts, and to determine coping plans that are implemented during procedures (Burns-Nader & Hernandez-Reif, 2016). This style of preparation incorporates a familiar concept, play, with unfamiliar medical concepts and materials to increase predictability, understanding, and expectations to assist children and families' abilities to cope with their hospitalization.[22]

Child life interventions are useful for preparing children in developmentally appropriate ways, and they also have an impact on parental satisfaction associated with medical experiences. When child life specialists provide psychosocial services prior to and during children's procedures, parents are more satisfied with their child's care and find the child to be more cooperative (Sanchez Cristal, et. al., 2018). Parents also report a strong appreciation for the respect and compassion associated with interventions supported by child life specialists.

Preparing children and families for procedures reduces preprocedural anxiety and improves postprocedural emotions of children and families. [23] Although several studies demonstrate the positive impact of child life preparation on children's responses to invasive procedures such as needle sticks and surgeries less is known about the role of play-based preparation for non-invasive procedures. These non-invasive procedures, such as routine physical examinations of blood pressure or temperature, can also be unfamiliar and scary for children in the hospital. Low-level light therapy (LLLT) for mucositis is a non-invasive and unfamiliar intervention for children. Using play to prepare children for this procedure may help clarify its importance and their role while also creating space to develop a coping plan. The following child life aims will explore the impact of a play-based preparation for LLLT on parent satisfaction and feasibility of patient participation.

3.0 **RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT**

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria

3.1.1 No age limitation
3.1.2 To be admitted for an allogeneic hematopoietic cell transplant,
3.1.3 All eligible autologous hematopoietic cell transplant, at risk for grade 3 mucositis per transplant service secondary to conditioning regimen or previous history of grade 3 mucositis
3.1.4 Dental exam prior to admission, as per preadmission criteria
3.1.5 Willingness of research participant to provide assent/consent and parent/ legal guardian/representative to give written informed consent.

3.2 Exclusion Criteria

3.2.1 Deemed by transplant team as unable to participate
3.2.2 Known sensitivity to light therapy
3.2.3 Inability or unwillingness of research participant or legal guardian/representative to give written informed consent.
3.2.4 CAR-Tcell Protocol

3.3 Research Participant Recruitment and Screening

Potential participants undergoing HCT will be identified in the weekly bone marrow pre-admission conference. Each participant being admitted for an allogenic transplant and meeting inclusion criteria will be offered PBM therapy. The bone marrow transplant clinicians may identify autologous recipient at risk for grade 3 mucositis per conditioning regimen or history of high-grade mucositis. These participants will be included for the exploratory objective. For all patients meeting inclusion criteria, an appointment will be made with the participant and family during the HCT evaluation period. The potential participant and parents will be approached by a member of the study team who will briefly explain the

study and respond to any patient/family questions. An educational slide show presentation delivered by an ipad will describe the PBM process and mechanism (see attached). At that time, the patient and parents will be asked if they wish to participate in the study. If they agree, the informed consent/assent document will be reviewed and signed. This meeting will take place approximately one week to day of admission to in-patient Transplant Service. All patients who meet the study criteria will be approached for enrollment.

After low level light therapy consent, participants will be offered the opportunity to receive a play-based preparation by a certified child life specialist (CCLS). Those who elect to receive this child life preparation will be scheduled to meet with a trained CCLS prior to admission. The play-based preparation will incorporate age and developmentally appropriate explanations of the non-invasive procedure and will be adapted to each patient's psychosocial and cognitive developmental needs. To standardize the child life preparation, the following components will be included in each of the interventions: hands on manipulation of the LLLT equipment (ie. Glasses and light tool), demonstration and return demonstration of procedure on a medical doll, and discussion and development of coping plan for procedure. The play-based preparation intervention will last approximately 30 minutes.

3.4 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the 'Participant Eligibility Checklist'. The Study Team will enter the Eligibility Checklist information into the Central enrollment system. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The signed consent/assent form must be faxed or emailed to the Clinical Trials Operations (CTO) [redacted] or emailed to [redacted] in order to complete the enrollment. If you have a prospective research enrollment and need assistance releasing your consent on a weekend or holiday, please call the Milli helpline ([redacted]).

3.5 Procedures for Study Staff

Prior to initiating the study, nursing research staff attended a photobiomodulation therapy workshop, under the direction of the Thor laser manufacture. All staff have been trained and assessed in extraoral PBM application during the workshop. Additionally, the protocol has been written in consultation with Dr. Migliorati, who has been instrumental in the study of PBM for the prevention of

mucositis in adults and was co-author of the international mucositis guidelines published in Supportive Care in Cancer.[24] Light therapy is commonly administered by dental technicians and a small (n=13) feasibility study found that trained staff (nursing) were adequate in administration of PBM. [20] Study staff will also be trained in consent processes, data transfer, and plans to monitor intervention integrity and data quality.

4. DESIGN AND METHODS

4.1 Design and Study Overview

This study will enroll children and adolescents prior to admission for an allogeneic HCT, and those undergoing an autologous transplant at deemed at risk for grade 3 oral mucositis. Light therapy will be administered by trained persons within Nursing Research Division: Belinda Mandrell, Judy Bosi, Susan Ogg and Michele Pritchard. The parent may hold the device in place with assistance from the trained persons. Patients will receive extra-oral and intra-oral PBM on the first day of conditioning, those undergoing an allogeneic HCT will have treatment daily until engraftment or +Day 20 (event occurring first). For those undergoing an autologous transplant treatment will continue until engraftment or until the patient is without mucositis for two consecutive days. If the patient becomes acutely ill during therapy and misses 4 consecutive days of PBM, the data will not be evaluated. These patients will be replaced to give 66 evaluable patients for the primary objective. Patients in isolation will continue to receive PBM with the device covered in plastic and cleaned prior to leaving the isolation holding area.

The PBM will be delivered through application of the LED Cluster Probe externally to the right external buccal, left external buccal, mid face with mouth open and submandibular and left/right cervical. Patients who develop an oral lesion, intra-oral directed therapy will be administered with the dental light probe. For patients that can tolerate, an intraoral probe will deliver light directly onto the oral mucosa, this will then replace the mid face application with mouth open. Each laser application will be timed at 60 seconds. [8] The PBM treatment will be administered via the THOR Model LX2M unit. All participants will receive the standard mouth care regimen prescribed for HCT patients. Observation and treatment will begin the first day of conditioning and continue daily until engraftment (2 consecutive days of ANC $\geq$ 500) or Day +20 (which comes first) and until mucositis resolution for two consecutive days for the autologous transplant.

Feasibility will be assessed similar to Treister et al [20] through the number of successful treatments administered by the total number of attempted treatments, providing the percentage of successful treatment administered. Daily treatment will include 6 sites of PBM application, with application documented as receiving all 6 applications, in part treatment (at least one to five sites) or no treatment. A successful treatment is defined as the treatment is successfully administered to 4 or more sites. Reasons for partial or no treatment will be documented. Criteria for feasibility is that the percentage of successful treatments administered exceeds 75%. The collected data will be summarized for total days on protocol, days treatment is received, cumulative dose and the number of treatments received at each site.

Table Summary of Photobiomodulation Therapy Delivered

Case number	*Days on protocol* [a]	*Days received treatment* [b]	*Total cumulative dose (J/cm^2)* [c]	*Treatment site = right face*	*Treatment site = midline face*	*Treatment site = left face*	*Treatment site = left neck*	*Treatment site = midline neck*	*Treatment site = right neck*

[a]Days on protocol defined as from the first day of hematopoietic cell transplantation conditioning through engraftment

[b]Days received treatment defined as days with treatment during any of the on-protocol days

[c]Cummulative dose define as single treatment dose multiplied by the number of treatment sites (up to 6 in total) for each treatment session

Efficacy will be assessed with assessment of grade 3 mucositis development from day 1 of conditioning to Day +20 of transplant or engraftment as a binary outcome (yes/no)

Daily observation: The observation of oral mucositis will be conducted by non-study staff and conducted as clinical care by the nurse, advanced practice provider and/or physician.

Assessment: Each patient or parent proxy will complete the Children's Mucositis Assessment via ipad along with documentation of mucositis grade, duration, days of nutrition support, use of narcotics, positive oral and blood cultures.

Each patient will be matched and compared to a previously treated patient. The comparison will be matched on primary disease, conditioning regimen, age and sex, with comparison of treatment variables of mucositis grade, duration, pain medications, days of nutritional support, blood and oral cultures, to day +20 or engraftment (depending upon which occurs first).

5.0 DRUG/DEVICE/BIOLOGIC AGENT INFORMATION

The PBM treatment will be administered via the Food and Drug Administration (FDA) approved THOR Model LX2M unit (THOR Photomedicine Ltd, Chesham, UK). The THOR LX2M is a red and near infrared light emitting diode (LED) licensed for management and treatment of inflammation and tissue repair. The THOR Model LX2M has a 69 Diode LED Cluster Probe (34 X 660nm 10mW, 35 X 850nm 30mW: 1390mW total power output) at an irradiance of $50mW/cm^2$. The unit is portable and can be carried to each patient room. Cleaning will be according to hospital equipment policy.

Safety

The PBM poses less risk than that associated with the class IV surgical laser used in dentistry. While the potential hazards are ocular, the PBM are class 3B lasers and emit divergent beams with the ocular risk diminishing with distance.[25] Recommendations include avoiding direct aim of the laser into the eye and the use of safety spectacles for use with laser therapy. The safety spectacles will be prescribed according to age, with the adjustable Ibis Infant eye protection for patients less than 1 year of age and the adjustable kids laser safety googles for the young child. Patients, staff, and observers must wear laser safety glasses while

PBM is in use. Specific contraindications are listed below:

Contraindications to PBM

Eyes
THOR lasers have divergent beams but are potentially harmful if viewed directly from a distance of less than 1.1 meters. Patient, practitioner and observers should wear THOR laser safety glasses when the laser is in use.

Relative contraindications / precautions

Cancer
Do not use PBM over any known malignant lesions unless:
1. for pain relief during the terminal stages of the illness, but only with their physicians permission.
2. For cancer therapy side effects (e.g. oral mucositis, radiation dermatitis, etc.),

Pregnancy
There is no evidence of harm to an unborn baby however there are no safety tests either, so for medical legal reasons we recommend not treating directly over the developing fetus. It may be used on the pregnant woman for the treatment of back pain etc.

Thyroid
There is no evidence of harm and there is some evidence of benefit for treating Hashimoto's thyroiditis with PBM. It is conceivable that a high intensity laser treatment direct to the thyroid might (temporarily) stimulate (or inhibit) some thyroid activity. The THOR LED treatments are however relatively low intensity and far less likely to trigger any adverse events when treating that region of the neck.

Tattoo
Treatment over a tattoo with higher irradiance laser may cause pain as the dye absorbs the laser energy and gets hot. If treatment is painful remove treatment probe from contact and treat ~15mm from surface of skin.

Hair on the head
Treatment on the head and neck with high irradiance laser may cause pain as the melanin in the fine superficial hair follicle absorbs a lot of the laser energy. If treatment is painful remove treatment probe from contact and treat ~15mm from surface of skin.
Very dark skin

Occasionally some people with very dark skin feel an unpleasant amount of heating. If treatment is painful remove treatment probe from contact and treat ~15mm from surface of skin.

Cleaning of Laser Between Patients

All laser heads will be covered with clear disposable dental sleeves that are approved for use with the LLLT and in dentistry. At treatment completion the sleeves will be discarded and all laser heads, laser box and all cords will be cleaned with disinfectant wipes (Sani-Cloth) and allowed to air dry in between each patient, per discussion with infectious disease.

6.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

6.1 Pre-Study Evaluations

Each participant will have a pre-transplant dental assessment to assess for caries, periodontal disease and mouth ulcerations, as well as pre-transplant oral and nasal cultures as per protocol.

6.2 Response Evaluations During Therapy

Parent Satisfaction

After the initial LLLT treatment, a parent-reported satisfaction survey will be administered via paper questionnaire. Parent satisfaction will be reported by parents on a 5-point Likert scale to questions adapted from a parent satisfaction survey used in a study regarding child life services in pediatric imaging [26] Parents will be asked to rate their level of satisfaction on 10 items, with 1 = Strongly Disagree to 5 = Strongly Agree. An additional marker of "not applicable (N/A)" will be available as a response option for parents who respond to the survey and did not receive a child life play-based preparation. Higher scores indicate higher satisfaction.

Parent Satisfaction Survey Items

1. The procedure was explained using language my child could understand.
2. My child's emotional needs were met.
3. Staff showed concern for my child's comfort.
4. I knew what to do to help my child.
5. Staff showed concern for my questions and worries.
6. Staff respected my knowledge of my child.

7. I am satisfied with the care provided to my child.
8. The child life intervention was helpful for my child's understanding in the procedure.
9. Staff were friendly and helpful.
10. Staff worked together well to care for my child.

Pain and Oral Function Assessment

After the 6-minute laser/ treatment session the child or parent proxy will complete the mucositis evaluation scale which includes self-report oral function specific to ability to swallow, eat and drink, as well as the patient's self-reported need for medication specific to mouth pain. The evaluation of mucositis can be completed in less than 5 minutes and is a validated inventory, Children's International Mucositis Evaluation Scale which has been used for mucositis in pediatric HCT. [27] The scale has test-retest reliability with $r>0.8$ for all respondent types. See attached. The scale is available in English, Spanish and Portuguese.

The study staff will maintain a treatment log for each participant. Data collected will include: days on PBM protocol, days treatment received, total cumulative dose defined as single treatment dose multiplied by the number of treatment sites (up to 6 in total) for each treatment session.

Mucositis will be graded according to the Common Toxicity Criteria for Adverse Events version 5: Grade I patient is asymptomatic or with mild symptoms, no intervention, Grade II patient has moderate pain, no interference with oral intake and a modified diet, Grade III patient has severe pain, interfering with oral intake, Grade IV life-threatening, Grade V death.

In addition to the study staff assessment, the clinical assessment of mucositis and pain from the daily APN and physician physical assessment will be collected.

Chart Abstraction

The patient's age, sex, primary diagnosis, transplant type, conditioning regimen, radiation dose, time to engraftment, days of nutritional support, utilization of pain medication, and results of positive oral, nasal and blood cultures during transplant.

6.3 Off-Study Evaluations

1. Patients are off-study on last day (Day +20 or engraftment or absence of mucositis)

of PBM administration except for patients undergoing autologous tandem transplant will discontinue treatment with mucositis resolution and then resume light therapy with second transplant. Thus, these patients will remain on study until resolution of mucositis after second transplant. Therefore, will not reconsent with the second transplant, parents and patient may refuse if desired

7. CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

7.1Off-study criteria

7.1.1 Death
7.1.2 Request of the Patient/Parent
7.1.3 Discretion of the Study PI, such as the following

- The researcher decides that continuing in the study would be harmful
- A treatment is needed that is not allowed on this study
- The participant misses > 3 consecutive days of PBM the data cannot be used in the study
- The participant's condition gets worse
- New information is learned that a better treatment is available, or that the study is not in the participant's best interest
- Study evaluations are complete

8. SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

8.1. **Adverse Events (AEs)**

Adverse events will be monitored from the time of first study intervention, Day 1 of conditioning until Day +20 or engraftment. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study.

8.2. **Definitions**

Adverse Event (AE): Any untoward medical occurrence associated in a study participant after the first intervention on study. Adverse Events grade 1-4 will be graded by the NCI CTC AE version 5.0.

Serious Adverse Event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

* results in death; * is life-threatening (places the subject at immediate risk of death from the event as it occurred); * requires inpatient hospitalization or prolongation of existing hospitalization; * results in a persistent or significant disability/incapacity; * results in a congenital anomaly/birth defect; or * any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

8.3. Handling of Adverse Events (AEs) and Deaths

Recording of Adverse Events and Serious Adverse Events: Skin will be assessed and recorded daily for erythema or breakdown prior to light application.

Reporting Adverse Events and Serious Adverse Events: The St. Jude PI, upon awareness of an event, will determine the seriousness of AEs and ensure that all UPs are entered into the electronic submission system (iRIS) within 10 days. All (pertinent, as in recording above) AEs, serious or not, will be recorded in a log, spreadsheet, or report and submitted to the St. Jude IRB at the time of continuing review.

Reporting of Unanticipated Problems (UPs): The St. Jude PI will refer to St. Jude Human Research Protection Program (HRPP) Policy 01.720 for specifics on the reporting of unanticipated problems to the St. Jude IRB. The St. Jude IRB reports UPs to BIMO as per 21 CFR 56. The UP link follows: [redacted]

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

9. DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

9.1 Data Collection and Confidentiality

All data will be kept confidential and will be maintained in a secure, password protected database accessible only by study personnel. Study numbers will be assigned to each patient so that the patient's medical record number will not be used as the identifying number. All data will be kept confidential and stored in locked files inside locked offices. The site PI, study team, and staff of the

CPDMO at SJCRH will have access to the original data forms. Participants may decline without any negative repercussions whatsoever. Those refusals will be documented in the research record and examined for any possible patterns in patient/parent demographic variables.

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9.2 Study Monitoring

This study is considered low risk for monitoring purposes. The Principal Investigator (PI) and study team are responsible for ensuring participant eligibility and protocol compliance. The study team will hold meetings as needed to review case histories or quality summaries on participants and will generate minutes which are signed by the PI.

A quality review for form completeness will be performed on the informed consent forms of 100% of St. Jude participants by Clinical Trials Operations (CTO) personnel.

CTO will review up to 10% of the study participants annually for life status, status on study, and the appropriateness of the informed consent and eligibility processes. The monitor will annually verify regulatory documentation pertinent to the study, all Serious Adverse Event reports, and Age of Majority consenting on all study participants. The plan for monitoring may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended). The Monitor will generate a formal report which is shared with the Principal Investigator, study team, and the Internal Monitoring Committee (IMC).

Protocol continuing reviews by the Institutional Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, Unanticipated Problems and/or Serious Adverse Event reports are reviewed by the IRB.

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size

A review from June 2015 to May 2019, identified 93 first allogeneic transplant patients with similar conditions, and 66 (71%) of them developed grade 3 or above oral mucositis. With an estimated clinically meaningful effect size of 20% for PBM, the estimated percentage of patients who will receive PBM and develop grade 3 oral mucositis is 51%.

We will use the two-stage one-arm design with historical controls to monitor both efficacy and futility. The complete historical control sample will be used in both the interim analysis and final analysis. The test statistic in Chang et al [28] treats the historical control sample as if they are the control arm in a two-arm design. Given the relatively small sample size, we did not use the asymptotic distribution of the test statistic. Instead, we used Monte Carlo methods to estimate the sampling distribution of the test statistic under null and alternative hypotheses by 100,000 Monte Carlo data sets. The simulation program is written in R.

The rules of which accommodate both efficacy and futility**.** The null hypothesis is p_0=0.71; the alternative hypothesis is p_1=0.51; The type-I error rate = 0.05 and power 0.8 are used.. The detailed information about the two-stage design is shown in the following table. The attained type-I error rate and power are 0.048 and 0.813, respectively.

Look #	n	Boundaries		Boundary Crossing Probability (Incremental)			
				Under H0		Under H1	
		Efficacy	Futility	Efficacy	Futility	Efficacy	Futility
1	40	20	29	0.015	0.508	0.526	0.015
2	66	38	39	0.033	0.444	0.288	0.172
Total				0.048	0.952	0.813	0.187

The expected sample size under null and alternative hypotheses is 56 and 51, respectively. In the historical data between July 2015 and May 2016, 24 patients received allogeneic HCT. We estimate that study accrual of 66 transplant patients will be completed in 31 months after study activation.

10.2 Statistical Analyses

10.2.1 Statistical analysis for the primary objective

To evaluate the feasibility and efficacy of photobiomodulation therapy (PBM) in reducing oral mucositis in children and adolescents at risk for grade 3 oral mucositis undergoing an allogeneic hematopoietic cell transplant (HCT).

Hypothesis 1: Children and adolescents will receive 75% of the attempted PMB treatment and will be less likely to develop grade 3 oral mucositis from the 1st day of conditioning to day +20 of transplant or engraftment.

Descriptive statistics (counts, percentages, mean, median, standard deviation and interquartile range) and confidence interval will be calculated for the percentage of successful treatment administered, total days on the protocol, days treatment is received, cumulative dose and the number of treatments received at each site.

The count, percentage and confidence interval will be calculated for allogeneic HCT patients who receive PBM and develop Grade 3 mucositis. Whether the percentage of the prospective sample is significantly different from the historical rate is accessed by the monitoring rule in Section 10.1.

10.2.2 Statistical analysis for the secondary objective

To compare clinical manifestations associated with the development of oral mucositis between those treated with daily PBM and a matched control. Clinical factors to include: mucositis grade, duration, and days to engraftment.

Hypothesis 2: Children and adolescents treated with extra-oral PBM will develop lower grade mucositis, with shorter mucositis duration (days) than the comparison matched control.

Patients enrolled in the PBM study will be matched to a transplant control that did not receive PBM by age, sex, primary disease and transplant regimen. For a patient receiving PBM, the patients with the same sex, primary disease and transplant regime will be used as the candidate pool. The patient in the pool with the smallest difference of age is selected as matching. If there is more than one patient in the pool that satisfies the smallest difference of age, a reproducible random number generator will be used to randomly select one patient out of the multiple candidates.

The patient identifier, age, sex, primary disease and transplant regime for the patients without PBM in the historical data will be sent to the Biostatisticians without the outcome of development of grade 3 mucositis. The patient identifier for the selected patients in the historical data will be determined. Then other information for these patients will be obtained for analysis.

The two groups will be compared from day 1 of conditioning regimen until engraftment (2 consecutive days of an ANC>500) or Day+20.

The PBM group and the historical group without PBM will be compared on mucositis grade, duration of mucositis (number of days) and days from cell infusion to engraftment. We will compute the descriptive statistics (mean, standard deviation, median, and range) of the duration of mucositis and days to engraftment. We will also compute the descriptive statistics (count and percentage) of mucositis grade. To compare the clinical variables between the PBB and matched control groups, we will use generalized linear model with the variables for matching as covariates. The difference will be assessed by two-sided Wald tests with type I error rate < 0.05. For the duration of mucositis, the subset of patients who developed Grade 3 mucositis will be compared with their match control patients with similar methods described above.

10.2.3 Statistical analysis for the exploratory objective

To evaluate efficacy of photobimodulation therapy in autologous patients at risk for ≥ grade 3 oral mucositis compared to matched control.

The count, percentage of developing Grade 3 mucositis and its confidence interval will be calculated for autologous HCT patients who receive PBM. In the historical data between July 2015 and May 2016, 8 neuroblastoma patients who received autologous HCT were at risk for grade 3 mucositis. It is expected that – 22 autologous HCT patients will be treated with PBM. Fisher's exact test or two-sided Wilcoxon rank-sum test with type I error rate < 0.05 is used to compare these patients with the patients in the historical data. The matching is based on age, sex, primary disease, and conditioning regimen.

To evaluate utilization of play-based procedural preparation and treatment feasibility and parental satisfaction.
Descriptive statistics (counts, percentages, mean, median, standard deviation and interquartile range) and confidence interval will be calculated for the percentage of successful treatment administered, total days on the protocol, days treatment is received, cumulative dose and the number of treatments received at each site between those who had procedural based preparation and those that did not. Descriptive statistics (counts, percentages, mean, median,) will describe parental satisfaction.

10.4 Anticipated Completion Dates

Anticipated Primary Completion Date : 35 months after activation
Anticipated Study Analysis Completion Date: 1 year after completion
Anticipated date of reporting: 2 years after completion

11. OBTAINING INFORMED CONSENT

The process of informed consent will follow institutional policy. Informed consent should be obtained by the principal investigator, Belinda Mandrell, PhD, RN, Susan Ogg MSN, RN, Judy Bosi, CRA or Mary Caples CRA, in the presence of at least one non-physician witness. Eligible parents will first be approached by a member of the study team regarding the study purpose, methods and design details. Only with parental permission will the eligible patients be approached regarding participating in the study. Both verbal and written assent and consent procedures will be completed in a private room and following our institutional guidelines. The consent/assent process will be documented in the medical record per institutional guidelines. Patients and parents may decline participation without any negative repercussions whatsoever. Refusals will be documented in the research records and examined for any possible patterns. All patients who meet eligibility criteria regardless of gender or minority status are fully eligible to participate in this study. Any adverse effects experienced by participating patients during their enrollment on this protocol will be reported to the IRB at both sites within 48 hours. At the time of consent, documentation will be made in the medical record specific to patient and parental information regarding COVID-19 risk and distribution of COVID information sheet.

11.1 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants will be reconsented should they become 18 during the study period. must be consented at the next clinic visit after their 18th birthday.

11.2 Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CPDMO websites.

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