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Guest Editorial

Current Considerations for Low-Level Laser Therapy/Photobiomodulation Therapy in the Management of Side Effects of Chemoradiation Therapy for Cancer

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Oral mucositis (OM) may develop as a side effect of chemotherapy (CT) in the treatment of cancer patients, hematopoietic stem cell transplantation (HSCT) recipients, and patients with head and neck cancer (HNC) receiving radiation. When severe OM develops in patients undergoing chemoradiotherapy, it is difficult for them to eat and swallow because of pain, and their systemic immunity declines. Therefore, there is no choice but to stop CT or radiotherapy (RT) as cancer treatment.

As measures to deal with OM, keeping the mouth clean, rinsing the mouth, adopting a soft diet, and administering anti-inflammatory analgesics, growth factors, cytokines, antimicrobials, coating agents, anesthetics, and analgesics are recommended. Low-level laser therapy (LLLT), other phototherapies, cryotherapy, natural therapies, and other treatments are also carried out. Despite numerous randomized controlled trials (RCTs) and systematic reviews of LLLT as a noninvasive method for OM, the clinical application of LLLT is still controversial.

Several regimens for care of OM by LLLT or LLLT/photobiomodulation therapy (PBMT) have been presented.[1–3] These regimens or guidelines involve two different approaches on the basis of device characteristics or applications: intraoral application of laser alone[2] or its application in combination with extraoral application of a mixed red and LED cluster.[2,3]

In 2014, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC-ISOO) Clinical Practice Guidelines for Mucositis were updated.[1] In this guideline, LLLT (wavelength 650 nm, power 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2), used to prevent OM in patients receiving HSCT conditioned with high-dose CT, with or without total body irradiation, is recommended as evidence level II, that is, strong evidence supports its effectiveness in the treatment setting listed. In addition, LLLT (wavelength around 632.8 nm), used to prevent OM in patients undergoing RT without concomitant CT for HNC, is also recommended as evidence level III, that is, weaker evidence supports its effectiveness in the treatment setting listed.

In contrast, Bensadoun and Nair[2,3] proposed the photobiomodulation regimen for prevention and/or treatment of a broad range of cancer therapy-induced morbidities in HNC, based on high-quality studies and on expert opinion when considering commercially available devices. This regimen can be used to treat the following complications: OM, radiation dermatitis, dysphagia, hyposalivation and xerostomia, dysgeusia, trismus, osteonecrosis, head and neck lymphedema, and voice/speech alterations because of local inflammation. For the management of OM with this regimen, optimal parameters were proposed for prophylactic and therapeutic purposes.

The treatment protocols for prophylactic use were with CT protocols, start PBMT on the first day of CT or before therapy and continue during all courses of CT and with RT, start PBMT the first day of RT or before RT and continue during all days of RT (no requirement regarding the timing of PB sessions, before or after RT sessions). For therapeutic use, the regimen involved continued treatment at least three times a week until improvement of symptoms. Daily treatment is recommended in cases of severe mucositis.

The PBMT device characteristics and parameters for extraoral application included an infrared (IR) LED cluster or mixed red and IR LED cluster at 20–80 mW/cm^2. The therapeutic PBM dose was 3 J/cm^2 with the IR LED cluster extraorally, 2 J per point intraorally for prophylactic use, and 4 J per point until the whole area involved is covered for therapeutic use.

According to this protocol, to prevent the onset of OM, a mixed red and IR LED cluster is recommended from the outside of the oral cavity of the patient undergoing CT. For RT patients, LLLT/PBMT at 630–830 nm with 20–80 mW output power as the light source from the oral cavity is recommended on the first day of irradiation or before irradiation during radiation therapy. In addition, LLLT/PBMT with 2 J at each point is recommended before OM develops, and 4 J irradiation is recommended as therapy after symptom onset. In contrast, in the updated 2014 MASCC-ISO Clinical Practice Guidelines for mucositis, laser irradiation is recommended as the light source for LLLT/PBMT.

To establish the evidence for the use of LLLT and PBMT for OM, numerous RCTs and systematic reviews have been continuously conducted, but to review this evidence, it is necessary to retrieve the relevant information. However, there

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are documents that are missing in the collected literature because various terms are used as search terms, such as LLLT, low level laser therapy, phototherapy, light therapy, low level light therapy, and soft laser.

To address this problem from another point of view, it was recommended that these terms be unified under ''photobiomodulation therapy,'' which was added to the 2016 version of the MeSH database for the existing record of laser therapy, low level.[4] Universal acceptance and use of this new term, ''photobiomodulation therapy,'' will not only lead to more specific terminology but will also help in the identification of all relevant literature and the establishment of guidelines based firmly on evidence.

Prophylactic LLLT/PBMT reduced severe OM and pain. This holds great benefit for patients' quality of life, as it prevents feeding disorders, immune response reduction, interruption of cancer treatment, and more, before severe OM develops.

The recommended therapeutic LLLT/PBM dose is 2 J per point for intraoral application.[3]

It is important to consider whether LLLT/PBMT is administered prophylactically before the onset of symptoms of OM or it is to be started after the onset of chemoradiotherapy and symptoms of OM are present. There is a big difference in benefit between patients who start chemoradiotherapy when symptoms of OM develop and continue LLLT/PBMT with pain, and those who start when LLLT/PBMT is initiated prophylactically at the beginning of chemoradiotherapy to prevent OM.

No RCTs addressing this issue has been reported.

As another problem, there is concern about use of LLLT/PBMT for severe OM that develops during chemoradiotherapy of cancer patients. When a malignant solid tumor or a potentially malignant region is irradiated with low-dose laser irradiation, it may be stimulated to undergo malignant transformation with negative effects, such as proliferation of tumor cells or promotion of metastasis. To address these concerns, Sonis et al.[5] carried out a review of the literature on the possibility of an impact on tumor growth or proliferation, the risk of local invasion or metastases, a negative effect on a tumor's treatment response (particularly radioresistance in the case of RT in HNC), and whether local application of LLLT could have effects distant from the targeted site.

This investigation showed that the anti-mucositis efficacy of LLLT is independent of its potential to enhance threatening tumor behaviors. However, as conditions such as LLLT parameters, dose, and irradiation time are not unified, it is necessary to conduct clinical studies by unifying these irradiation conditions and use the results for future updating of guidelines or recommendations for LLLT/PBT based on verification of the latest version. Therefore, until it is established that LLLT does not negatively affect established cancers, the North American Association for PBMT states that LLLT is contraindicated.

Although evidence for the efficacy of LLLT/PBMT for the treatment of OM has been established, it is necessary to perform multicenter, clinical studies based on a unified protocol and to clarify that which remains unclear.

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