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REVIEW

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Management of oral mucositis: a systematic review

Joey DANWIEK, Rahmi AMTHA *, Indrayadi GUNARDI

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REVIEW

Management of oral mucositis: a systematic review

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ABSTRACT

INTRODUCTION: Oral mucositis is one of the most common complications following chemotherapy and/or head and neck radiotherapy. Various treatments for oral mucositis have been proposed. However, there has still been no review of the most frequent and most effective type of therapy to treat oral mucositis. This systematic review aims to determine the most frequent and effective types of therapy to treat and reduce the severity of oral mucositis.

EVIDENCE ACQUISITION: The literature search was carried out using PRISMA guidelines. Publications included from 2010 to June 2021 with a clinical trial, prospective, and retrospective observational research design. The following databases were used: PubMed, Cochrane Library, and Wiley Online Library. The search was for limited articles published in English, which were screened and analyzed by three authors. The risk of bias of each study was also assessed by three authors simultaneously, using different types of instruments depending on its study design.

EVIDENCE SYNTHESIS: Forty-seven of 1274 journals were included. From 3577 subjects, oral mucositis was more common in males than females (2.12: 1), with a mean age of 56.39 (18-90 years). The most commonly used types of therapy are low-level laser therapy (396 subjects) and lysozyme-based compounds (314 subjects). Meanwhile, the most effective type of therapy is low-level laser therapy.

CONCLUSIONS: Low-level laser therapy is the most commonly used oral mucositis therapy and is also the most effective in reducing the degree of oral mucositis and associated pain.

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KEY WORDS: Mucositis; Therapy; Systematic review.

Introduction

Cancer is a disease caused by abnormal and malignant cell growth.[1] The cancer cells are easily detached from the primary site; thus, spreading neoplastic cells to other organs known as metastasis may occur. Metastasis was often being the leading cause of death.[2] In 2020, 19.3 million new cases have been detected, and approximately 10 million deaths resulted from cancer worldwide.[3] Globally, about 1 in 6 deaths were caused by cancer.[2] The Global Burden of Disease (GBD) study revealed that head and neck cancers represent 5.3% of all cancer types (excluding non-melanoma skin cancers) and estimated that there were 890,000 new cases of head and neck cancer in 2017.[4]

Cancer can be fatal; thus, cancer patients usually receive special treatment. Generally, cancer treatment could be categorized into three major types, namely surgery, chemotherapy, radiotherapy, or a combination of those therapies.[5] The mechanism of chemotherapy and radiotherapy were different from surgery. Apart from acting specifically on cancer tissues, chemotherapy and radiotherapy acted by inhibiting the growth of rapidly dividing cells, thereby interfering with the mechanism of cell division. Aside from inhibiting the cancer cell growth, chemotherapy and radiotherapy may cause various side effects

because normal cells are also affected by ionizing or chemotherapeutic agents released by these therapies.[6] Oral mucositis (OM) was one of the most common chemotherapy and/ or radiotherapy complications for head and neck cancer.[5, 7, 8]

According to most studies, this complication occurred in up to 80% of patients receiving high-dose chemotherapy, 20-40% of patients receiving conventional chemotherapy, and up to 100% of patients receiving head and neck cancer radiotherapy.[9, 10] According to MASCC/ISOO, it presented as an ulcerative lesion surrounded by erythematous areas on various parts of oral mucosa and usually associated with significant pain.[10] Severe oral mucositis may affect the oral functional status, including impaired food and drugs intake and speech function. In advanced stages, oral mucositis may lead to malnutrition, an increase in the duration of hospitalization and the risk of infections prior to ulceration in the oral cavity, and ultimately reducing the patient's quality of life. These symptoms may cause delays in cancer treatment and have a potential impact on cancer treatment itself to affect the possibility of optimal healing.[10, 11]

Various methods of prevention and treatment of oral mucositis have been proposed. In 2020, The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ ISOO) published a revision of evidence-based clinical practice guidelines for mucositis. Treatment methods were categorized into eight groups: 1) basic oral care; 2) anti-inflammatory agents; 3) photobiomodulation (laser and other light therapy); 4) cryotherapy; 5) antimicrobials, coating agents, anesthetics, and analgesics; 6) growth factors and cytokines; 7) natural and miscellaneous agents; 8) all interventions for gastrointestinal mucositis.[12]

The rationale of this study was that there were limited systematic review of the most frequent and most effective type of therapy to treat oral mucositis. Therefore, it is necessary to do further research to be a source of information to determine the effectiveness of different types of therapy against oral mucositis.

Evidence acquisition

The literature searching and the selection process was carried out using the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines on three databases, namely PubMed, Wiley and Cochrane Library. Searching the sources was done systematically by determining the Population, Intervention, Comparison, Outcome, and Time (PICO(T)); continued by stating the inclusion and exclusion criteria(s), then composing the phrase of the Boolean search for each database. Studies that met the inclusion criteria and fitted the research question and outcome of this review were included and analyzed. The process of collecting data was also done by three investigators independently (JD, IG, and RA). Two investigators (JD and IG) sought and extracted data that matched the outcomes stated in PICO(T).

The data synthesis according to PRISMA are follow: 1) data for the most commonly used and most effective types of therapy were reported in charts and tables; 2) this systematic review was carried out by preparing data tabulations and graphs for each therapy from the collected studies. No data conversion or statistical calculation was needed for this study; 3) the method to tabulate the results of individual studies was done by grouping the same therapy from each study; 4) there was no measurement of the therapy's size effect as it was impossible due to incomparable data; 5) the meta-analysis could not be analyzed as the data were not comparable; 6) this study was limited to a systematic review; therefore, no sensitivity analysis was conducted.

This systematic review has been registered in Open Science Framework (OSF), OSF registration number: 10.17605/OSF.IO/PV5AN (2021) with https://osf.io/cf3zk/.

Determining PICO-T

Population

Cancer patients (at least 18 years of age) underwent head and neck radiotherapy or chemotherapy or chemoradiotherapy and were diagnosed with oral mucositis.

Intervention

Any therapy was given to treat oral mucositis. According to The Multinational Association of

Supportive Care in Cancer and International Society of Oral Oncology (MASCC / ISOO), types of oral mucositis therapy may include basic oral care; anti-inflammatory; photobiomodulation (laser and other light therapy); cryotherapy; antimicrobials, coating agents, anesthetics, and analgesics; growth factors and cytokines; natural and miscellaneous agents.

Comparison

A non-exposed controlled group or placebo.

Outcome

- Epidemiological data:
  - Patient data: age and gender.
  - The severity of oral mucositis at the first and last observation.
- The most common types of therapy that was used to treat oral mucositis.
- The most effective therapy in reducing the severity of oral mucositis.
- Additional outcome: the most frequently used chemotherapy/chemoradiotherapy regimens that induced oral mucositis.

Time

Included studies were all of those published before June 2021.

Inclusion and exclusion criteria(s)

The inclusion criteria(s) for this systematic review are English based journals with Randomized Controlled Trial (RCT), clinical trial, retrospective observational (case report or case series), prospective observational (cohort, case-control, cross-sectional) study design. Meanwhile, the exclusion criteria(s) for this review are other systematic reviews, in vivo studies in animals, studies focusing on preventive therapy of oral mucositis, studies on other primary oral lesions with a specific background that coincidence with oral mucositis, and studies that include patients with no previous history of radio/chemo/chemoradiotherapy.

Boolean search

Boolean words for database searching was tabulated in Supplementary Digital Materials.

Risk of bias assessment

The risk of bias assessment was carried out by three investigators independently (JD, IG, and RA). A different type of study quality assessment tool was used, depending on the study's design as follow:

- randomized controlled trial (RCT): Cochrane Collaboration Modified Tool for Assessing Risk of Bias for Rct's, Part I&2;
- randomized uncontrolled clinical trial: The Cochrane RoB 2.0 Tool;
- non-randomized experimental studies: The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies);
- prospective observational studies (cohort): Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort Studies;
- prospective observational studies (case-control): Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-control Studies;
- prospective observational studies (cross-sectional): Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cross-sectional Studies;
- retrospective observational studies (case reports): Joanna Briggs Institute (JBI Critical Appraisal Checklist for Case Reports.

Evidence synthesis

Results

The search strings that were used for the literature search can be seen in Supplementary Digital Material 1 (Supplementary Table I). The number of records obtained from 3 databases using Boolean sentences was 460 PubMed journals, 809 Cochrane journals, and 5 Wiley journals. From a total of 1274 journals obtained, 197 similar articles were found, so these articles were not included. Then, 1077 journals underwent the screening process. 948 out of 1077 journals had to be excluded because 668 journals had irrelevant titles, 202 journals had inappropriate abstract, and 78 journals did not have a full-text version or a full-text other than English language. Furthermore, from 129 full-text journals, 82 were excluded because they did not fit the research problem, such as prophylaxis and preventive therapy for

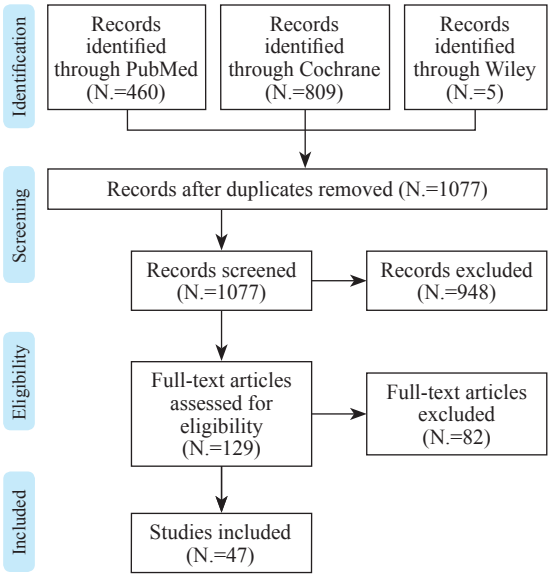

Figure 1.—PRISMA diagram.

oral mucositis, subjects reported under 18 years old, there was no data on age or a specific population, and the intervention agents were proved to be no more beneficial than the control. In the end, 47 full-text journals were included and analyzed. The selection process can be seen in the PRISMA diagram (Figure 1).

Risk of bias assessment

Thirty-one studies with RCT study design were assessed using the Cochrane collaboration modified tool for Assessing Risk of Bias for Rct's, Part I&2. All RCT studies mainly were low and moderate; only two studies presented a high risk of bias (Oton-Leite *et al.*[13] and Leppla *et al.*[14]). One study with a randomized uncontrolled clinical trial design was assessed using the Cochrane RoB 2.0 tool and resulted in a high risk of bias which favours the experimental group. In addition, nine quasi-experimental studies, two cohort studies, one case-control study, one cross-sectional study, and two case reports were assessed using the Joanna Briggs Institute (JBI) instrument. Only one study with quasi-experimental showed a high risk of bias (Guo *et al.*).[15] The detailed results can be seen in Supplementary Digital Material 2 (Supplementary Table II, Supplementary III, Supplementary IV).[13-34, 36, 39-57]

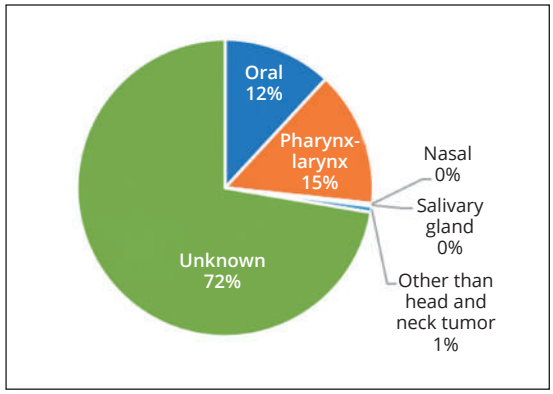

Figure 2.—Distribution of subjects according to the location of tumor.

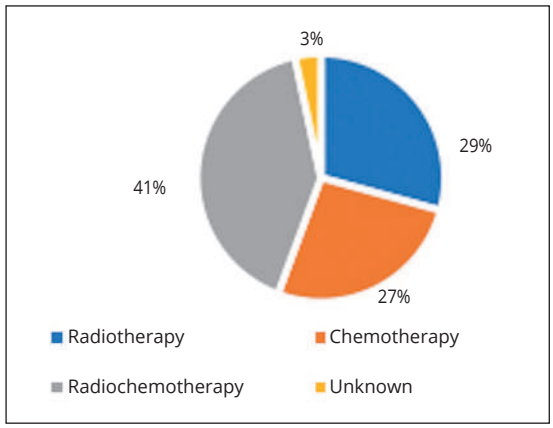

Figure 3.—Distribution of subjects according to types of cancer treatment.

Subject characteristics

Of the total 3577 subjects included in this systematic review, oral mucositis was more common in males than females (2.12 *vs.* 1), with a mean age of 56.39 (range 18-90 years). The most common tumor site was the pharynx-larynx (15%), followed by the oral cavity (12%) and other sites (1%), respectively (Figure 2). Moreover, radiochemotherapy (41%) was the most reported treatment for cancer, followed by radiotherapy (29%) and chemotherapy (27%) (Figure 3).

The most frequent oral mucositis therapy

Data related to the types of oral mucositis therapy received by the research subjects can be seen

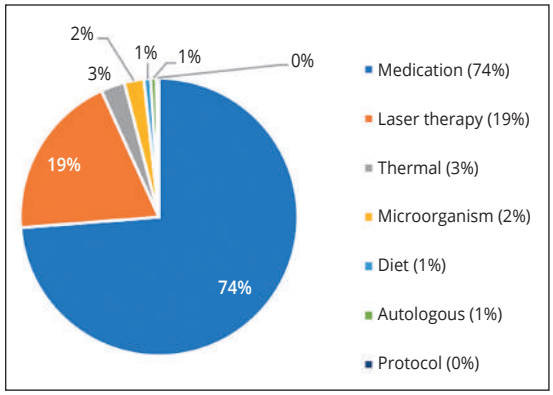

Figure 4.—Distribution of subjects according to types of therapy received.

in Figure 4. The further distribution of the types of medication and light therapy received by the research subjects can be seen in Figure 5, 6, respectively.

The most effective oral mucositis therapy

The data collected were types of therapy that can significantly reduce the severity of oral mucositis at the beginning and end of therapy, and those compared with the control group. The severity of oral mucositis was determined by the degree of oral mucositis and its associated pain. Types of therapy that significantly reduce the severity of oral mucositis can be seen in Table I, II.[13, 15-20, 22-26, 28, 30, 35, 36, 39, 40, 42, 44-50, 52, 54-58]

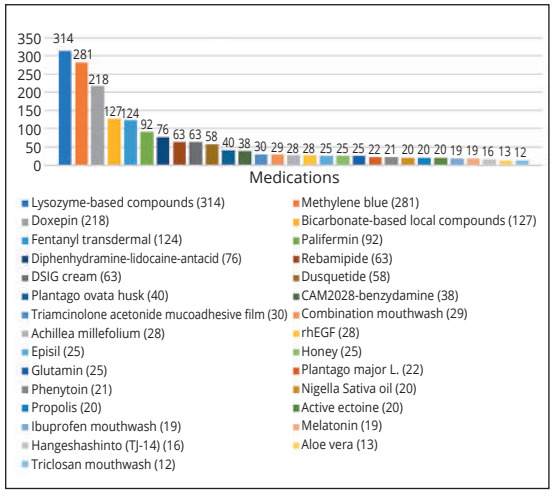

Figure 5.—Distribution of subjects according to types of medication received.

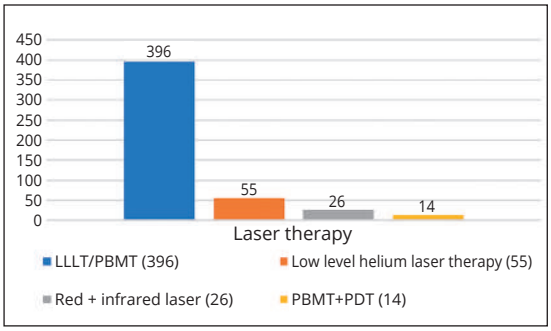

Figure 6.—Distribution of subjects according to types of laser therapy received.

The most frequently used chemotherapy/chemoradiotherapy regimens that induced oral mucositis

As shown in Figure 7, the most commonly used cancer treatment regimen for chemotherapy and radiochemotherapy that induced oral mucositis is cisplatin, followed by melphalan. However, several publications did not report the chemotherapy regimen used. Therefore, this distribution may change based on the completeness of the data obtained.

Discussion

Subject characteristics

Oral mucositis was more common in males than females, with a ratio of 2.12:1, and a mean age

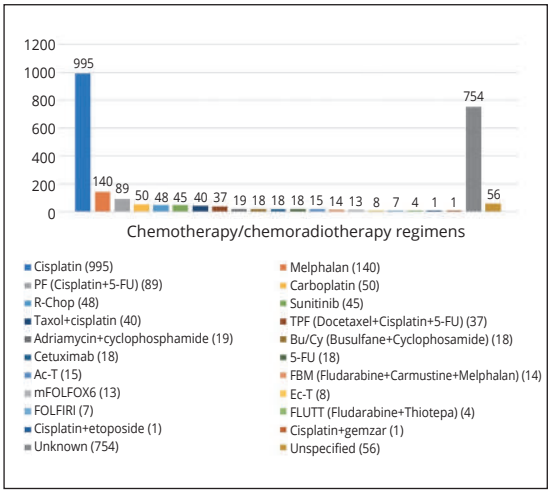

Figure 7.—Distribution of subjects according to types of chemotherapy/chemoradiotherapy regimens received.

TABLE I.—*Oral mucositis therapy that significantly decrease the severity of OM degree.*

Studies	Study design	Types of oral mucositis therapy	Oral mucositis assessment tools	Significant reduction in OM degree (WHO)	
				Intervention group	Control group
Satheeshkumar *et al.*[16]	RCT	Triclosan Mouthwash	WHO	1 patient (8%) developed grade 4 OM**	10 patients (83%) developed grade 4 OM
Carvalho *et al.*[17]	RCT	Low-level laser therapy (InGaAlP diode laser)	WHO	Week 2: 0.78±0.93* Week 3: 1.59±0.97** Week 4: 1.52±0.85**	Week 2: 1.41±0.93 Week 3: 2.30±0.47 Week 4: 2.30±0.87
Henke *et al.*[18]	RCT	Palifermin	WHO	Severe OM (grade 3/4) was found in 47 patients (51%)*	Severe OM (grade 3/4) was found in 63 patients (67%)
Oton-Leite *et al.*[13]	RCT	Low-level laser therapy (InGaAlP diode laser)	WHO	Follow-up: 2.12 (2.00)**	Follow-up: 2.95 (3.00)
Ghalayani *et al.*[22]	RCT	TA mucoadhesive film Licorice mucoadhesive film	WHO	Initial: 2.40±0.49 Week 4: 0.96±0.81**	Initial: 2.36±0.49 Week 4: 0.93±0.78
Miranzadeh *et al.*[24]	RCT	Achillea millefolium	WHO	Initial: 2.39±0.875 Day 7: 1.07±0.85** Day 14: 0.32±0.54**	Initial: 2.39±0.875 Day 7: 2.75±0.87 Day 14: 2.89±0.956
Akhavan-Karbassi *et al.*[30]	RCT	Propolis Mouthwash	WHO	Initial: 1.85±0.813 Day 3: 1.60±1.05** Day 7: 0.550±0.945**	Initial: 2.50±1.54 Day 3: 2.00±0.725 Day 7: 1.75±0.851
Soares *et al.*[36]	RCT	Red + infrared low-level laser therapy	WHO	After treatment: 1.70±1.08*	After Treatment: 1.77±0.752
Martins *et al.*[40]	RCT	Photobiomodulation therapy (PBMT)	WHO	Initial: 0 14th RT: 1.88±0.83 30th RT: 1.68±0.85**	Initial: 0 30th RT: 2.65±0.93
Soltani *et al.*[58]	RCT	*Plantago major L.*	WHO	Initial: 0.00±0.00 Week 5: 1.36±0.10** Week 7: 0.14±0.07**	Initial: 0.68±0.10 Week 5: 2.23±0.09 Week 7: 0.95±0.08
Agha-Hosseini *et al.*[42]	RCT	Mouthwash containing vitamin E, triamcinolone, and hyaluronic acid	WHO	Initial: 4.00±0.00 Week 4: 2.03±0.186**	Initial: 4.00±0.00 Week 4: 2.97±0.183
Bonfili *et al.*[46]	Quasi	Platelet gel supernatant (PGS)	WHO	After treatment: 1.69±0.946*	After treatment: 2.52±0.704
Pinheiro *et al.*[49]	Quasi	Photobiomodulation therapy (PBMT), photodynamic therapy (PDT)	WHO	PBMT (intervention) Initial: 2.00(2.00) After 4 weeks: 0.00(0.00)**	PBMT + PDT (intervention) Initial: 2.00(2.00) After 4 weeks: 0.00(0.00)
Rezk-Allah *et al.*[48]	Quasi	Low level laser therapy	WHO	Initial: 2.35±0.695 End of chemotherapy: 1.13±0.333**	
Dao *et al.*[52]	Cohort	Active ectoine	WHO	Initial: 1.75±0.716 Day 21: 0.962±1.34*	Initial: 1.93±0.703 Day 21: 0.643±0.633
Chen *et al.*[54]	Case control	Cryotherapy	WHO	After cryotherapy (median): 2*	Without cryotherapy: 2.5
Lino *et al.*[56]	Case report	Laser phototherapy (LPT or LLLT)	WHO	Initial: grade 3 OM (difficulty in eating solid foods) After 1 LPT session: reduction in pain After 4 LPT sessions: more symptom improvement After 10 LPT sessions: OM lesions healed	
Mobadder *et al.*[57]	Case report	Photobiomodulation therapy (PBMT)	WHO	Initial: 2 After 5 PBMT sessions: 0	
Carvalho *et al.*[17]	RCT	Low-level laser therapy (InGaAlP diode laser)	NCI	Week 2: 0.78±0.93** Week 4: 1.56±1.09*	Week 2: 1.56±1.09 Week 4: 2.33±0.88
Oton-Leite *et al.*[13]	RCT	Low-level laser therapy (InGaAlP diode laser)	NCI	Follow-up: 1.50(1.00)**	Follow-up: 2.95 (3.00)
Gautam *et al.*[19]	RCT	Low-level helium neon laser therapy	RTOG	Last week of chemoradiotherapy: incidence of grade >2 OM is 29%**	Last week of chemoradiotherapy: incidence of grade >2 OM is 89%
Gautam *et al.*[20]	RCT	Low-level laser therapy	RTOG	End of RT: the number of patients that developed severe OM is 18.2%*	End of RT: the number of patients that developed severe OM is 58.3%
Oton-Leite *et al.*[28]	RCT	Low-level laser therapy (InGaAlP diode laser)	NCI	7th RT: incidence of grade 2 OM is 25% (3 of 12 patients)* 21th RT: 6 patients (50%) with grade 3 OM* 35th RT: 25% patients developed grade 3 OM (3 of 12) *	7th RT: incidence of grade 2 OM is 76.9% (10 of 13 patients) 21th RT: 12 patients (92.3%) with grade 3 OM 35th RT: 53.8% patients developed grade 3 OM (7 of 13)

(To be continued)

TABLE I.—*Oral mucositis therapy that significantly decrease the severity of OM degree (continues).*

Studies	Study design	Types of oral mucositis therapy	Oral mucositis assessment tools	Significant reduction in OM degree (WHO)	
				Intervention group	Control group
Jiang *et al.*[35]	RCT	Probiotics	NCI	After treatment: 1.42±0.887**	After treatment: 2.46±0.505
Martins *et al.*[40]	RCT	Photobiomodulation therapy (PBMT)	NCI	Initial: 0 30th RT: 1.80±0.96**	Initial: 0 30th RT: 2.61±0.94
Tanaka *et al.*[47]	Quasi	Elemental diet (ED)	NCI	Incidence of grade >2 OM in ED completion group:15.4% (2 of 13 patients)* Incidence of grade >2 OM in ED non-completion group: 66.7% (4 of 6 patients)	
Cunha *et al.*[44]	Quasi	Red laser and red + infrared laser	Monopoli index	Red+infrared laser After treatment: 0.667±0.516*	After treatment: 1.33±1.86
Lin *et al.*[26]	RCT	DSIG cream	OAG	Day 2: 12.1±1.1* Day 3: 12.0±1.2* Day 4: 11.3±1.3* Day 5: 10.4±1.3*	Day 2: 10.2±1.0 Day 3: 9.3±0.9 Day 4: 8.5±0.6 Day 5: 8.0±0.2

*P<0.05; **P<0.01.
WHO: World Health Organization; NCI: National Cancer Institute; RTOG: Radiation Therapy Oncology Group; OAG: Oral Assessment Guide.

TABLE II.—*Oral mucositis therapy that significantly decrease OM associated pain.*

Studies	Design	Types of oral mucositis therapy	Pain assessment tools	Significant reduction in pain (VAS)	
				Intervention group	Control group
Gautam *et al.*[19]	RCT	Low-level helium neon laser therapy	VAS	Initial: 0.11 Week 6: 4.36** Incidence of pain in the end of chemoradiotherapy is 18%**	Initial: 0.65 Week 6: 6.76 Incidence of pain in the end of chemoradiotherapy is 71%
Oton-Leite *et al.*[13]	RCT	Low-level laser therapy (InGaAlP diode laser)	VAS	Follow-up: 2.88(3.00)**	Follow-up: 7.64(8.00)
Gautam *et al.*[20]	RCT	Low-level laser therapy	VAS	End of RT: the number of patients with severe mouth pain (VAS>7) is 8,3%*	End of RT: the number of patients with severe mouth pain (VAS>7) is 50%
Hasheminasab *et al.*[39]	RCT	*Plantago ovata* husk	VAS	Day 7: 2 (1-3)**	Day 7: 3 (2-4)
Soltani *et al.*[58]	RCT	*Plantago major L.*	VAS	Initial: 0.14±0.07 Week 5: 2.18±0.14* Week 7: 0.50±0.10*	Initial: 2.14±0.22 Week 5: 5.41±0.17 Week 7: 2.95±0.18
Ioroi *et al.*[50]	Quasi	Ibuprofen mouthwash	VAS	Day 3 Initial: 4.11 15 minutes after gargle: 2,83 (95% CI: -1,62, -4,04)	
Hadjieva *et al.*[25]	RCT	Bioadhesive barrier-forming lipid solution (CAM2028)	NRS	Initial: 6.5 5 minutes after treatment: 4.6*	Initial: 6.4 5 minutes after treatment: 4.6
Leenstra *et al.*[23]	RCT	Doxepin mouthwash	NRS	After treatment: Area under curve (AUC) for mouth and throat pain reduction -9.1**	After treatment: Area under curve (AUC) for mouth and throat pain reduction -4.7
Guo *et al.*[15]	Quasi	Fentanyl transdermal (patch)	NRS	Initial: 5.54±0.86 Day 10: 2.82±0.68**	
Xing *et al.*[45]	Quasi	Fentanyl transdermal (patch)	NRS	Initial: 6 (range 3-9) Day 15: 0 (0–4)**	
Roldan *et al.*[55]	Cross-sectional	Methylene blue (MB)	NRS	Initial: 7.7±1.83 After treatment: 2.51±2.76**	

*P<0.05; **P<0.01.
VAS: Visual Analog Scale; NRS: Numerical Rating Scale.

of 56.39 (18-90 years). Epidemiological data regarding the mean age and prevalence of oral mucositis in men and women obtained in this systematic review showed similar results to another study by Trotti *et al.*[59] This study assessed the incidence of oral mucositis in 6181 subjects and

found that the mean age of the 4217 subjects was 56 (range 14-87 years).[59] This indicates that oral mucositis was commonly found in the elderly population. Regression analysis by Çakmak *et al.* showed that older adults may have increased the risk of oral mucositis by 1.03 times (P<0.05).[60] It was suggested that older adults tend to experience oral mucositis more often due to less effective DNA repair, and it would take a prolonged period of healing time.[14]

The study conducted by Trotti *et al.*[59] also showed that the prevalence of oral mucositis in men was higher than that in women, 81% *vs.* 29% in 5421 subjects. Although the percentage is quite far from this review, the results showed that men are more dominant in experiencing oral mucositis.[59] However, there has been no scientific explanation regarding the difference in the prevalence of oral mucositis by sex until now. The higher prevalence of oral mucositis in men was related to other risk factors that contribute to the emergence of oral mucositis, such as genetics, nutritional status, comorbidities, poor oral health, type and dose of cancer therapy, and others.[61, 62] According to the researcher's analysis, the higher prevalence of oral mucositis in males may also be due to the higher prevalence of smoking and alcohol consumption in males than females. WHO showed that the prevalence of smoking in men compared to women was 36.7% *vs.* 7.8%.[63] In addition, the Centers for Disease Prevention and Control also reported that the prevalence of alcohol consumption was higher in men (58%) compared to women (47%).[64]

This study found that the tumor predilection in the pharynx-larynx (54.5%) was higher than in the oral cavity (44.3%). According to Global Cancer Observatory (GLOBOCAN), Indonesia's percentage of cancers in the pharynx-larynx and oral cavity was 75% *vs.* 17.1% in 2020.[65] Both of these results showed that head and neck cancers are more commonly occur in the pharynx-larynx rather than the oral cavity.

This systematic review also assessed the predilection of a tumor. Almost 72% of subjects were presented with no data about the primary tumor location. Moreover, the tumor's location may not be from the head and neck in patients receiving chemotherapy or chemoradiotherapy. Most of the publications regarding oral mucositis in patients receiving head and neck radiotherapy would usually describe the type and location of the tumor. In contrast to publications on oral mucositis induced by chemotherapy or chemoradiotherapy, the tumor site was seldom described.

In addition, from this review, it was found that most oral mucositis subjects underwent cancer therapy in the form of chemoradiotherapy, followed by radiotherapy and chemotherapy. Concomitant use of chemotherapy and radiation was also suggested as a risk factor that promotes the incidence and severity of oral mucositis.[62] One study suggested that patients receiving chemoradiotherapy (coef. 0.145; P<0.05) were at high risk for developing severe oral mucositis.[66]

The most frequent oral mucositis therapy

Out of 47 studies, 28 studies reported oral mucositis therapy in the form of medications. Fourteen studies reported the use of laser, and one study each reported thermal, microorganism, diet, autologous, and protocol as oral mucositis therapy. The most commonly used type of therapy was determined by the number of respondents who received the therapy.

Figure 4-6 represents the number of subjects receiving oral mucositis therapy. Based on the number of subjects, medication (1866 subjects) consisted of lysozyme-based compounds (314 subjects), methylene blue (281 subjects), doxepin (218 subjects), bicarbonate-based local compounds (127 subjects), transdermal fentanyl (124 subjects), palifermin (92 subjects), diphenhydramine-lidocaine-antacid (76 subjects), rebamipide (63 subjects), DSIG cream (63 subjects), dusquetide (58 subjects), *Plantago ovata* husk (herbs) (40 subjects), CAM2028- benzydamine (38 subjects), triamcinolone acetonide mucoadhesive film (30 subjects), combination mouthwash of vitamin E, triamcinolone, and hyaluronic acid (29 subjects), *Achillea millefolium* (28 subjects), rhEGF (28 subjects), episil (25 subjects), honey (25 subjects), glutamine (25 subjects), *Plantago major L.* (22 subjects), phenytoin: 11 (gargle) + 10 (tablets) (21 subjects), *Nigella sativa* oil (20 subjects), propolis (20 subjects), active ectoine (20 subjects), ibuprofen mouthwash (19 subjects), melatonin (19 subjects), hangeshash-

into (tj-14) (16 subjects), *Aloe vera* (13 subjects), and triclosan gargle (12 subjects).

In addition, photobiomodulation therapy (491 subjects) consisted of low-level laser therapy (396 subjects), low-level helium laser therapy (55 subjects), red + infrared laser (26 subjects), and photobiomodulation therapy + photodynamic therapy (PBMT + PDT) (14 subjects). Moreover, oral mucositis therapies in the form of thermal (cryotherapy) consisted of 70 subjects, probiotics (*Bifidobacterium longum*, *Lactobacillus lactis*, and *Enterococcus faecium*) 58 subjects, diet (elemental diet) 20 subjects, autologous (platelet gel supernatant) 16 subjects, and protocol using Oral Care Self-management Support protocol (OrCaSS) 8 subjects.

It can be denoted that the most frequent type of oral mucositis therapy in the form of medication was lysozyme-based compound (314 subjects). However, the lysozyme-based compound was not necessarily the most effective therapy because this study had only been reported by one publication, and there was no in-depth research on its effectiveness.

Meanwhile, the low-level laser therapy (LLLT) (396 subjects) was the most often used type of photobiomodulation therapy for oral mucositis. It was suggested that LLLT might be a promising treatment for oral mucositis with low side effects and a shorter duration of ulceration.

The most effective oral mucositis therapy

In the data extraction process, various oral mucositis therapy has been reported. Moreover, the data collection on the subject was also diverse between each publication. Thus, the effect size of each therapy was not possible to be calculated to determine the most effective type of therapy. Therefore, the most effective therapy was determined by reducing in the degree of oral mucositis, both objective and subjectively. The reduction in oral mucositis by the quality of life assessment was not reported. The publications on the quality of life in oral mucositis were very limited. Also, the domains of each quality of life assessment instrument were varied between studies, making it difficult to compare one instrument with another.

As in Table II, some publications reported limited data about the degree of oral mucositis at baseline and after therapy, while several publications only described data at the end of therapy (Hasheminasab *et al.*,[39] Chen *et al.*,[54] Bonfili *et al.*,[46] Soares *et al.*,[36] Jiang *et al.*,[35] and Cunha *et al.*[44]). In addition, some publications only reported the incidence of a certain degree of oral mucositis at a specific time during the study (Satheeshkumar *et al.*,[16] Henke *et al.*,[18] Oton-Leite *et al.*,[13] and Tanaka *et al.*[47]). Moreover, one publication only focused on comparing with the control group, and no analysis showed between before and after intervention therapy (Carvalho *et al.*[17]). Two publications stated the results were significant but did not provide information about the value of reduction of oral mucositis severity (Wei *et al.*[51] and Ameen *et al.*[37]), thus excluded from the table. There were three publications (Carvalho *et al.*,[17] Martins *et al.*,[40] and Oton-Leite *et al.*[13]) that reviewed the reduction in the degree of oral mucositis using two types of instruments simultaneously (WHO and National Cancer Institute [NCI] Scale).

There was a publication that showed the most considerable decrease in the degree of oral mucositis from the beginning to the end of the study, as well as from the comparison with the control group using *Achillea millefolium*.[67] *Achillea millefolium* reduced the degree of oral mucositis (using WHO instrument) from 2.39±0.875 to 0.32±0.54 within 14 days compared from 2.39±0.875 to 2.89±0.956 in the control group.[24] This agent was given as an antibacterial herbal mouthwash that affects various pathogens and has excellent anti-inflammatory properties.[68, 69] Although the results showed the most significant reduction in oral mucositis; this publication has several drawbacks. This study did not mention the specific chemotherapy regimens and doses received by study participants. Then, it was only focused on chemotherapy-induced oral mucositis, so its effect on radiotherapy-induced or chemoradiotherapy-induced oral mucositis was unknown.

In addition, the types of therapy in the form of medication that can also drastically reduce the degree of oral mucositis from the beginning to the end as well as from the comparison with the control group with a shorter duration were Dioctahedral Smectite Iodine Glycerin (DSIG) cream (five

days) and propolis mouthwash (7 days). DSIG cream reduced the degree of oral mucositis (using Oral Assessment Guide (OAG) instrument) from 12.1±1.1 to 10.4±1.3 within 5 days compared from 10.2±1.0 to 8.0±0.2 in the control group.[26] However, DSIG cream was shown to be effective only for chemotherapy-induced oral mucositis. Its long-term use also has not been proved to be effective. In addition, publications regarding propolis mouthwash did not mention the demographic characteristics of the subjects and chemotherapy regimens used. Therefore, propolis mouthwash was not highly recommended considering these limitations, compared to commercial mouthwash.[70]

The medication therapy has been shown to significantly reduce the severity of oral mucositis in the intervention group; and compared to the control. However, these medication required a longer time to heal epithelial breakdown. Several publications have reported four type regimes, such as active ectoine (3 weeks), a combination mouthwash containing vitamin E, triamcinolone, and hyaluronic acid (4 weeks), *Plantago major L*. (4 weeks), and triamcinolone acetonide mucoadhesive film and licorice mucoadhesive film (4 weeks). Out of four types of treatment, the most significant reduction in the degree of oral mucositis (WHO) was found in the combination mouthwash, from 4.00±0.00 to 2.03±0.186, compared to 4.00±0.00 to 2.97±0.183 in the control group.[42] However, combination mouthwash was shown to be only effective for radiotherapy-induced oral mucositis.

Moreover, the types of oral mucositis medication only proven to reduce the degree of oral mucositis compared to the control group were triclosan mouthwash and palifermin. Triclosan showed a lower incidence of severe oral mucositis (using WHO instrument) than palifermin, 8% *vs.* 51%.[16, 18] Triclosan was a broad-spectrum antibiotic agent that effectively reduced the degree of radiotherapy-induced oral mucositis and the duration of oral mucositis (23.6 days).[16]

Many types of photobiomodulation therapy were presented in the systematic review, such as PBMT (LLLT), PBMT+PDT, and red + infrared LLLT. Light therapy with PBMT could significantly reduce the degree of oral mucositis, both when compared from the beginning of the study and the control group. Publication by Pinheiro *et al.* showed that PBMT and PBMT+PDT reduced the degree of oral mucositis (using WHO instrument) from 2.00(2.00) to 0.00(0.00) in 4 weeks.[49] This was also supported by the case report by Mobadder *et al.*,[57] which stated that the degree of oral mucositis (using WHO instrument) decreased from 2 to 0 after five sessions of PBMT therapy and Lino *et al.*,[56] which stated that the degree of oral mucositis (using WHO instrument) decreased from 3 to 0 after ten sessions. In addition, publications by Carvalho *et al.*,[17] Martins *et al.*,[40] Oton-Leite *et al.*[13] suggested that PBMT reduced the degree of oral mucositis (using WHO and NCI instruments) significantly compared to the control group. A decrease in the degree of oral mucositis (Radiation Therapy Oncology Group [RTOG] Scale) was also found in the publication by Gautam *et al.*[20] The writer revealed that at the end of radiotherapy, the incidence of severe oral mucositis (3 and 4) was only 18.2%, compared to 58.3% in the control group.[20]

PBMT was effectively reduced the severity of oral mucositis induced by radiotherapy, chemotherapy, and chemoradiotherapy. PBMT (LLLT) itself could be a red laser or infrared laser with varying energy density and irradiation time. The laser may penetrate tissues, help in repair oral mucosal tissue, and provide an analgesic effect when pain occurs.[71] Meanwhile, PDT was a therapy that uses photosensitizing agents that could be used as cancer therapy. The agents had a high degree of selectivity in killing microorganisms and showed minimal toxicity to host cells.[72] The combination of PBMT+PDT had shown to require a shorter time to heal oral mucositis, which was only 12 days (17 days in the PBMT group).[49]

Research by Gautam *et al.*[19] suggested a different type of laser for LLLT namely, the helium-neon laser. The study also showed promising results, namely a lower incidence of grade >2 oral mucositis (RTOG) (29% *vs.* 89% in the control group). Another study by Soares *et al.*[36] proposed a new combination of red + infrared LLLT. The study showed that the severity of oral mucositis (WHO) decreased significantly compared to the red laser group alone (1.70±1.08 *vs.* 1.77±0.752).[40] This study was in line with Cunha *et al.*[44] that stated

that the degree of oral mucositis also decreased significantly after treatment with red + infrared laser, 0.667±0.516 compared to 1.33±1.86 in the control group.

Besides medication and photobiomodulation therapy, oral mucositis therapy could also be in the form of thermal (cryotherapy), autologous (platelet gel supernatant), microorganisms (probiotics), and diet (elemental diet). Cryotherapy and platelet gel supernatant showed a significant reduction in the degree of oral mucositis (WHO) compared to the control group, namely 2 *vs.* 2.5 and 1.69±0.946 *vs.* 2.52±0.704, respectively.[46, 54] Aside from reducing the degree of oral mucositis, cryotherapy was shown to shorten the duration of oral mucositis, which was only 7.8 days, compared to 10.1 days in those who did not receive cryotherapy.[54] In addition, platelet gel supernatant also delayed the onset of grades 3 and 4 oral mucositis. The severe oral mucositis appeared on day 28 in subjects given platelet gel supernatant and appeared on day 21 in the control group.[46]

Probiotics also showed a significant reduction in the degree of oral mucositis (NCI) compared to the control, namely 1.42±0.887 *vs.* 2.46±0.505.[35] Moreover, the elemental diet also showed a lower incidence of grade >2 oral mucositis (NCI), which was 15.4% *vs.* 66.7% in patients who did not complete the therapy.[47] However, these four types of therapy require further research as they do not show the reduction in the degree of oral mucositis compared to the initial study and are also limited to a specific type of oral mucositis. Cryotherapy and elemental diet were only effective for chemotherapy-induced oral mucositis, whereas probiotics were only effective for chemoradiotherapy-induced oral mucositis, and platelet gel supernatant was only effective for radiotherapy/chemoradiotherapy-induced oral mucositis.

In terms of decreasing oral mucositis associated pain, as seen in Table II, not all publications stated the pain level at baseline and after therapy. Several publications only reported the level of pain at the end of therapy, namely those by Oton-Leite *et al.*,[13] Hasheminasab *et al.*,[39] and Leenstra *et al.*[23] One publication only presented the incidence of a particular pain level at a specific time during the study, such as the publication by Gautam *et al.*[20] Several publications stated the results were significant but did not provide information about the pain reduction value, namely the publication by Rezazadeh *et al.*,[43] Carvalho *et al.*,[17] and Wei *et al.*,[51] so they are not included in the table.

Low-level laser therapy showed the most considerable decrease in pain compared to the control. Publication by Oton-Leite *et al.*[13] showed a significant difference in the median Visual Analog Scale (VAS) value at the end of the study, namely 2.88(3.00) *vs.* 7.64(8.00) in the control group. This was in line with the study by Gautam *et al.*,[19] which stated that the incidence of patients with severe oral pain (VAS>7) was 8.3% at the end of radiotherapy compared to 50% in the control group and the duration of the pain was 10.0 *vs.* 16.5 days. In addition, LLLT using a helium-neon laser also successfully reduced pain (using VAS instrument), but the reduction was not as significant as a regular LLLT.

Various mouthwashes also showed a significant reduction in pain, including ibuprofen, *Plantago ovata* husk, doxepin, methylene blue (MB), and Bioadhesive barrier-forming lipid solution (CAM2028). The mouthwash with the most significant pain reduction from beginning to the end is MB. MB mouthwash was proven to reduce pain (Numerial Rating Scale [NRS]) of radio/chemo/chemoradiotherapy-induced oral mucositis from 7.7±1.83 to 2.51±2.76 in just a few minutes after gargling.[55] However, the publication did not specify the exact time needed for gargling. Besides that, the publication also did not mention data on radiotherapy techniques and chemotherapy regimens received by subjects.

Moreover, the mouthwash that significantly reduces pain compared to the control group was *Plantago ovata* husk. This herbal mouthwash took one week to reduce pain (VAS) to 2 (1-3) compared to 3(2-4) in the control group.[39] This mouthwash was only effective for chemotherapy-induced oral mucositis, and its effectiveness in a shorter duration was not yet known. Furthermore, doxepin mouthwash also decreased pain compared to the control group. However, the results of this study were very limited because the data obtained were only in the form of the Area Under Curve (AUC) for mouth and throat pain reduc-

tion. Essential data such as the mean or median was also not available.

Besides mouthwash, oral mucositis medication could also be taken orally. *Plantago major L*. was taken three times a day from three days before radiotherapy until the end. This drug could reduce pain in radiotherapy-induced oral mucositis compared to control. In 7 weeks, pain (VAS) was reduced to only 0.50±0.10 *vs*. 2.95±0.18 in control group.[58] In addition, oral mucositis medication can also be administered through a patch. Transdermal fentanyl (patch) was administered at a rate of 25 g/hour and changed every 72 hours. Transdermal fentanyl was an opioid drug proven to reduce pain (using NRS instrument) in chemoradiotherapy-induced oral mucositis from 5.54±0.86 to 2.82±0.68 in 10 days.[15] The results of this study were also in line with research by Xing *et al.*[45] that showed a decrease in pain (NRS) from 6 (range 3-9) to 0 (0-4) after 15 days.

According to the researcher's analysis, low-level laser therapy (photobiomodulation therapy) is the most effective type of oral mucositis therapy because it has been discussed by many publications and has been proven to decrease the severity of oral mucositis in terms of the degree of radio/ chemo/ chemoradiotherapy-induced oral mucositis and its associated pain.

The most frequently used chemotherapy/chemoradiotherapy regimens that induced oral mucositis

Cisplatin was the most frequently used chemotherapy/chemoradiotherapy regimen that induced oral mucositis. This antineoplastic agent was in the class of alkylating agents. Alkylating agents were the first and most commonly used anticancer drugs in chemotherapy. Alkylating agents acted directly on DNA, causing cross-linking of the DNA strands, abnormal base pairing, or breaking of DNA strands, thereby preventing cell division. Although it could be used for most types of cancer, it was beneficial in treating slow-growing cancers. The effectiveness of alkylating agents on rapidly growing cells was not very promising.[5]

Cisplatin, cisplatinum, or *cis*-diamminedichloroplatinum (II), was a well-known chemotherapeutic agent. It has been used for various treatments of human cancers, such as bladder, head and neck, lung, ovarian, and testicular cancers. It has been proven effective against various types of cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas. Its mechanism of action has been linked to its ability to crosslink with the purine bases on the DNA, interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells.[73]

This systematic review found that melphalan is the second most used chemotherapy/ chemoradiotherapy regimen that induced oral mucositis. Melphalan was also in a class of anti-cancer drugs of alkylating agents used to treat multiple myeloma (a type of cancer of the bone marrow). Melphalan was also used to treat a specific type of ovarian cancer, early and advanced breast cancer, childhood neuroblastoma, polycythaemia vera, and amyloidosis (a disease in which abnormal proteins build up in tissues and organs in the body). Moreover, this agent was also used for regional arterial perfusion in localized malignant melanoma and localized soft-tissue sarcoma of the extremities.[74]

Melphalan could inhibit tumor growth by chemically altering the DNA nucleotide guanine through alkylation and causes linkages between strands of DNA. This chemical alteration inhibits DNA replication and transcription of RNA and ultimately disrupts nucleic acid function. These changes caused cytotoxicity in both dividing and non-dividing tumor cells. In addition, melphalan also possessed some immunosuppressive activity.[74]

A study conducted by Bensinger *et al.*[75] stated that cisplatin and melphalan were associated with a greater risk of developing oral mucositis. Other than that, doxorubicin, 5-fluorouracil (5-FU; bolus more than infusional), methotrexate, and cyclophosphamide also carried high risks of developing oral ulceration.[75] Moreau *et al.* revealed that there is a 31% to 36% risk in patients receiving high-dose melphalan.[76] Furthermore, the study conducted by Curra *et al.*[77] reported the patients who received cisplatin experienced more severe oral mucositis.

Limitations of the study

There were several limitations of this systematic review:

• meta-analysis was challenging because the effectiveness of each therapy differed from one to another, and the data displayed in several publications was only in the form of graphs or images, using median, not the mean value. In addition, the time of data collection varies between publications, making it challenging to be homogenized;

• several publications do not clearly present the data needed for the risk of bias assessment, but these publications are still included in this systematic review;

• there were several promising therapies but only discussed in one publication. Therefore, it was difficult to determine the exact potential of these therapies in reducing the degree of oral mucositis and pain;

• this systematic review did not discuss the decrease in oral mucositis severity in terms of quality of life. The publications on the quality of life in oral mucositis were very limited. Also, the domains of each quality of life assessment instrument were varied, making it difficult to compare one instrument with another.

The limitation of the review process was that the scope of research was too broad. In the future, it is expected that further research that focuses explicitly on low-level laser therapy (photobiomodulation therapy) will be conducted because this therapy has been proven to be the most effective in reducing the severity of oral mucositis.

Conclusions

Low-level laser therapy (photobiomodulation therapy) was the most reported type of therapy by many publications and recommended for the treatment of oral mucositis. This therapy has been proven to reduce the degree of radio/ chemo/ chemoradiotherapy-induced oral mucositis and its associated pain.

References

1. NIH National Cancer Institute. What Is Cancer? – NCI; 2019 [Internet]. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer [cited 2023, Mar 1].

2. WHO. Cancer; 2021 [Internet]. Available from: https://www.who.int/health-topics/cancer#tab=tab_1 [cited 2023, Mar 1].

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209–49.

4. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, *et al.*; Global Burden of Disease Cancer Collaboration. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2019;5:1749–68.

5. NIH National Cancer Institute. Cancer Registration & Surveillance Modules | SEER Training; 2018 [Internet]. Available from: https://training.seer.cancer.gov/modules_reg_surv.html [cited 2023, Mar 1].

6. Volpato LE, Silva TC, Oliveira TM, Sakai VT, Machado MA. Radiation therapy and chemotherapy-induced oral mucositis. Rev Bras Otorrinolaringol (Engl Ed) 2007;73:562–8.

7. NIH National Cancer Institute. Radiation Therapy Side Effects - NCI; 2018 [Internet]. Available from: https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/side-effects [cited 2023, Mar 8].

8. Amtha R, Gunardi I, Ching Cheong S, *et al.* Oral Mucosal Lesion Detection Accuracy Post Lectures and Tests in Clinical Dental Students. J Int Dent Med Res 2018;11:101–6.

9. Kashiwazaki H, Matsushita T, Sugita J, Shigematsu A, Kasashi K, Yamazaki Y, *et al.* Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. Support Care Cancer 2012;20:367–73.

10. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, *et al.*; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453–61.

11. Münstedt K, Männle H. Using Bee Products for the Prevention and Treatment of Oral Mucositis Induced by Cancer Treatment. Molecules 2019;24:3023.

12. Elad S, Cheng KK, Lalla RV, Yarom N, Hong C, Logan RM, *et al.*; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2020;126:4423–31.

13. Oton-Leite AF, Elias LS, Morais MO, Pinezi JC, Leles CR, Silva MA, *et al.* Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy. Spec Care Dentist 2013;33:294–300.

14. Leppla L, De Geest S, Fierz K, Deschler-Baier B, Koller A. An oral care self-management support protocol (OrCaSS) to reduce oral mucositis in hospitalized patients with acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation: a randomized controlled pilot study. Support Care Cancer 2016;24:773–82.

15. Guo SP, Wu SG, Zhou J, Feng HX, Li FY, Wu YJ, *et al.* Transdermal fentanyl for pain due to chemoradiotherapy-induced oral mucositis in nasopharyngeal cancer patients: evaluating efficacy, safety, and improvement in quality of life. Drug Des Devel Ther 2014;8:497–503.

16. Satheeshkumar PS, Chamba MS, Balan A, Sreelatha KT, Bhatathiri VN, Bose T. Effectiveness of triclosan in the man-

agement of radiation-induced oral mucositis: a randomized clinical trial. J Cancer Res Ther 2010;6:466–72.

17. Carvalho PA, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA. Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral Oncol 2011;47:1176–81.

18. Henke M, Alfonsi M, Foa P, Giralt J, Bardet E, Cerezo L, *et al.* Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. J Clin Oncol 2011;29:2815–20.

19. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya GA. Low level helium neon laser therapy for chemoradiotherapy induced oral mucositis in oral cancer patients - a randomized controlled trial. Oral Oncol 2012;48:893–7.

20. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Guddattu V. Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. J Photochem Photobiol B 2015;144:51–6.

21. Kim KI, Kim JW, Lee HJ, Kim BS, Bang SM, Kim I, *et al.* Recombinant human epidermal growth factor on oral mucositis induced by intensive chemotherapy with stem cell transplantation. Am J Hematol 2013;88:107–12.

22. Ghalayani P, Emami H, Pakravan F, Nasr Isfahani M. Comparison of triamcinolone acetonide mucoadhesive film with licorice mucoadhesive film on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial. Asia Pac J Clin Oncol 2017;13:e48–56.

23. Leenstra JL, Miller RC, Qin R, Martenson JA, Dornfeld KJ, Bearden JD, *et al.* Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32:1571–7.

24. Miranzadeh S, Adib-Hajbaghery M, Soleymanpoor L, Ehsani M. Effect of adding the herb Achillea millefolium on mouthwash on chemotherapy induced oral mucositis in cancer patients: A double-blind randomized controlled trial. Eur J Oncol Nurs 2015;19:207–13.

25. Hadjieva T, Cavallin-Ståhl E, Linden M, Tiberg F. Treatment of oral mucositis pain following radiation therapy for head-and-neck cancer using a bioadhesive barrier-forming lipid solution. Support Care Cancer 2014;22:1557–62.

26. Lin JX, Fan ZY, Lin Q, Wu DH, Wu XY, Chen YR, *et al.* A comparison of dioctahedral smectite and iodine glycerin cream with topical mouth rinse in treatment of chemotherapy induced oral mucositis: a pilot study. Eur J Oncol Nurs 2015;19:136–41.

27. Sahebjamee M, Mansourian A, Hajimirzamohammad M, Zadeh MT, Bekhradi R, Kazemian A, *et al.* Comparative Efficacy of Aloe vera and Benzydamine Mouthwashes on Radiation-induced Oral Mucositis: A Triple-blind, Randomised, Controlled Clinical Trial. Oral Health Prev Dent 2015;13:309–15.

28. Oton-Leite AF, Silva GB, Morais MO, Silva TA, Leles CR, Valadares MC, *et al.* Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers Surg Med 2015;47:296–305.

29. Kudrimoti M, Curtis A, Azawi S, Worden F, Katz S, Adkins D, *et al.* Dusquetide: A novel innate defense regulator demonstrating a significant and consistent reduction in the duration of oral mucositis in preclinical data and a randomized, placebo-controlled phase 2a clinical study. J Biotechnol 2016;239:115–25.

30. AkhavanKarbassi MH, Yazdi MF, Ahadian H, SadrAbad MJ. Randomized DoubleBlind PlaceboControlled Trial of Propolis for Oral Mucositis in Patients Receiving Chemotherapy for Head and Neck Cancer. Asian Pac J Cancer Prev 2016;17:3611–4.

31. Onseng K, Johns NP, Khuayjarernpanishk T, Subongkot S, Priprem A, Hurst C, *et al.* Beneficial Effects of Adjuvant Melatonin in Minimizing Oral Mucositis Complications in Head and Neck Cancer Patients Receiving Concurrent Chemoradiation. J Altern Complement Med 2017;23:957–63.

32. Lopez-Vaquero D, Gutierrez-Bayard L, Rodriguez-Ruiz JA, Saldaña-Valderas M, Infante-Cossio P. Double-blind randomized study of oral glutamine on the management of radio/chemotherapy-induced mucositis and dermatitis in head and neck cancer. Mol Clin Oncol 2017;6:931–6.

33. Yokota T, Ogawa T, Takahashi S, Okami K, Fujii T, Tanaka K, *et al.* Efficacy and safety of rebamipide liquid for chemoradiotherapy-induced oral mucositis in patients with head and neck cancer: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II study. BMC Cancer 2017;17:314.

34. Rao S, Hegde SK, Rao P, Dinkar C, Thilakchand KR, George T, *et al.* Honey Mitigates Radiation-Induced Oral Mucositis in Head and Neck Cancer Patients without Affecting the Tumor Response. Foods 2017;6:77.

35. Jiang C, Wang H, Xia C, Dong Q, Chen E, Qiu Y, *et al.* A randomized, double-blind, placebo-controlled trial of probiotics to reduce the severity of oral mucositis induced by chemoradiotherapy for patients with nasopharyngeal carcinoma. Cancer 2019;125:1081–90.

36. Soares RG, Farias LC, da Silva Menezes AS, de Oliveira E Silva CS, Tabosa AT, Chagas PV, *et al.* Treatment of mucositis with combined 660- and 808-nm-wavelength low-level laser therapy reduced mucositis grade, pain, and use of analgesics: a parallel, single-blind, two-arm controlled study. Lasers Med Sci 2018;33:1813–9.

37. Ameen H, Mohammed M, Ahmed K, *et al.* Anti-inflammatory effect of nigella sativa oil on chemoradiation-induced oral mucositis in patients with head and neck cancers. Int J Curr Pharm 2019;11:58–64.

38. Sio TT, Le-Rademacher JG, Leenstra JL, Loprinzi CL, Rine G, Curtis A, *et al.* Effect of Doxepin Mouthwash or Diphenhydramine-Lidocaine-Antacid Mouthwash vs Placebo on Radiotherapy-Related Oral Mucositis Pain: The Alliance A221304 Randomized Clinical Trial. JAMA 2019;321:1481–90.

39. Hasheminasab FS, Hashemi SM, Dehghan A, Sharififar F, Setayesh M, Sasanpour P, *et al.* Effects of a Plantago ovata-based herbal compound in prevention and treatment of oral mucositis in patients with breast cancer receiving chemotherapy: A double-blind, randomized, controlled crossover trial. J Integr Med 2020;18:214–21.

40. Martins AF, Morais MO, de Sousa-Neto SS, de Jesus AP, Nogueira TE, Valadares MC, *et al.* Photobiomodulation reduces the impact of radiotherapy on oral health-related quality of life due to mucositis-related symptoms in head and neck cancer patients. Lasers Med Sci 2021;36:903–12.

41. Taira K, Fujiwara K, Fukuhara T, Koyama S, Takeuchi H. The effect of Hangeshashinto on Oral Mucositis Caused by Induction Chemotherapy in Patients with Head and Neck Cancer. Yonago Acta Med 2020;63:183–7.

42. Agha-Hosseini F, Pourpasha M, Amanlou M, Moosavi MS. Mouthwash Containing Vitamin E, Triamcinolon, and Hyaluronic Acid Compared to Triamcinolone Mouthwash Alone in Patients With Radiotherapy-Induced Oral Mucositis: Randomized Clinical Trial. Front Oncol 2021;11:614877.

43. Rezazadeh F, Mohammadi-Samani S, Talei F, *et al.* Efficacy of Phenytoin Mucoadhesive Tablet versus Mouthwash on Chemotherapy-Induced Oral Mucositis: A Randomized Clinical Trial. Middle East J Cancer 2019;10:341–9.

44. Cunha CB, Eduardo FP, Zezell DM, Bezinelli LM, Shitara PP, Correa L. Effect of irradiation with red and infrared laser in the treatment of oral mucositis: a pilot study with patients undergoing chemotherapy with 5-FU. Lasers Med Sci 2012;27:1233–40.

45. Xing SZ, Zhang Y. Efficacy and safety of transdermal fentanyl for the treatment of oral mucositis pain caused by chemoradiotherapy in patients with esophageal squamous cell carcinoma. Support Care Cancer 2015;23:753–9.

46. Bonfili P, Gravina GL, Marampon F, Rughetti A, Di Staso M, Dell'Orso L, *et al.* Oral Platelet Gel Supernatant Plus Supportive Medical Treatment Versus Supportive Medical Treatment in the Management of Radiation-induced Oral Mucositis: A Matched Explorative Active Control Trial by Propensity Analysis. Am J Clin Oncol 2017;40:336–41.

47. Tanaka Y, Ueno T, Yoshida N, Akutsu Y, Takeuchi H, Baba H, *et al.* The effect of an elemental diet on oral mucositis of esophageal cancer patients treated with DCF chemotherapy: a multi-center prospective feasibility study (EPOC study). Esophagus 2018;15:239–48.

48. Rezk-Allah SS, Abd Elshaf HM, Farid RJ, Hassan MA, Alsirafy SA. Effect of Low-Level Laser Therapy in Treatment of Chemotherapy Induced Oral Mucositis. J Lasers Med Sci 2019;10:125–30.

49. Pinheiro SL, Bonadiman AC, Borges Lemos AL, Annicchino BM, Segatti B, Pucca DS, *et al.* Photobiomodulation Therapy in Cancer Patients with Mucositis: A Clinical Evaluation. Photobiomodul Photomed Laser Surg 2019;37:142–50.

50. Ioroi T, Kiyota N, Imamura Y, Tanda M, Aoki S, Okuno M, *et al.* Ibuprofen gargle for chemo- or Chemoradiotherapy-induced Oral Mucositis: a feasibility study. J Pharm Health Care Sci 2020;6:12.

51. Wei J, Wu J, Wang H, Wang B, Zhao T, Meng L, *et al.* A Bioadhesive Barrier-Forming Oral Liquid Gel Improved Oral Mucositis and Nutritional Status in Patients With Head and Neck Cancers Undergoing Radiotherapy: A Retrospective Single Center Study. Front Oncol 2021;11:617392.

52. Dao VA, Bilstein A, Overhagen S, Géczi L, Baráth Z, Mösges R. Effectiveness, Tolerability, and Safety of Ectoine-Containing Mouthwash Versus Those of a Calcium Phosphate Mouthwash for the Treatment of Chemotherapy-Induced Oral Mucositis: A Prospective, Active-Controlled, Non-interventional Study. Oncol Ther 2018;6:59–72.

53. Eminagić D, Lokvančić A, Hasanbegović B, Mekić-Abazović A, Avdičević A, Marijanović I, *et al.* Efficacy and safety of local lysozyme treatment in patients with oral mucositis after chemotherapy and radiotherapy. Acta Pharm 2019;69:695–704.

54. Chen J, Seabrook J, Fulford A, Rajakumar I. Icing oral mucositis: oral cryotherapy in multiple myeloma patients undergoing autologous hematopoietic stem cell transplant. J Oncol Pharm Pract 2017;23:116–20.

55. Roldan CJ, Chung M, Feng L, Bruera E. Methylene Blue for the Treatment of Intractable Pain From Oral Mucositis Related to Cancer Treatment: An Uncontrolled Cohort. J Natl Compr Canc Netw 2021;19:521–7.

56. Lino MD, Carvalho FB, Oliveira LR, Magalhães EB, Pinheiro AL, Ramalho LM. Laser phototherapy as a treatment for radiotherapy-induced oral mucositis. Braz Dent J 2011;22:162–5.

57. Mobadder ME, Farhat F, Mobadder WE, Nammour S. Photobiomodulation Therapy in the Treatment of Oral Mucositis, Dysgeusia and Oral Dryness as Side-Effects of Head and Neck Radiotherapy in a Cancer Patient: A Case Report. Dent J 2018;6:64.

58. Soltani GM, Hemati S, Sarvizadeh M, Kamalinejad M, Tafazoli V, Latifi SA. Efficacy of the plantago major L. syrup on radiation induced oral mucositis in head and neck cancer patients: A randomized, double blind, placebo-controlled clinical trial. Complement Ther Med 2020;51:102397.

59. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, *et al.* Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66:253–62.

60. Çakmak S, Nural N. Incidence of and risk factors for development of oral mucositis in outpatients undergoing cancer chemotherapy. Int J Nurs Pract 2019;25:e12710.

61. Al-Ansari S, Zecha JA, Barasch A, de Lange J, Rozema FR, Raber-Durlacher JE. Oral Mucositis Induced By Anticancer Therapies. Curr Oral Health Rep 2015;2:202–11.

62. Raber-Durlacher JE, Elad S, Barasch A. Oral mucositis. Oral Oncol 2010;46:452–6.

63. WHO. Tobacco; 2022 [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/tobacco [cited 2023, Mar 8].

64. Centers for Disease Control and Prevention. Excessive Alcohol Use and Risks to Men's Health | CDC; 2022 [Internet]. Available from: https://www.cdc.gov/alcohol/fact-sheets/mens-health.htm [cited 2023, Mar 8].

65. UICC. GLOBOCAN 2020: New Global Cancer Data | UICC; 2020 [Internet]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf [cited 2023, Mar 8].

66. Maria OM, Eliopoulos N, Muanza T. Radiation-Induced Oral Mucositis. Front Oncol 2017;7:89.

67. Vychaktami KK, Amtha R, Gunardi I, *et al.* The effect of herbal medicine in reducing the severity of oral lichen planus: A systematic review and meta-analysis. Dent J 2022;55:165–73.

68. Aggarwal BB, Prasad S, Reuter S, Kannappan R, Yadev VR, Park B, *et al.* Identification of novel anti-inflammatory agents from Ayurvedic medicine for prevention of chronic diseases: "reverse pharmacology" and "bedside to bench" approach. Curr Drug Targets 2011;12:1595–653.

69. Saeidnia S, Gohari A, Mokhber-Dezfuli N, Kiuchi F. A review on phytochemistry and medicinal properties of the genus Achillea. Daru 2011;19:173–86.

70. Amtha R, Kanagalingam J. Povidone-iodine in dental and oral health: A narrative review. J Int Oral Health 2023;12:407.

71. Brandão TB, Morais-Faria K, Ribeiro AC, Rivera C, Salvajoli JV, Lopes MA, *et al.* Locally advanced oral squamous cell carcinoma patients treated with photobiomodulation for prevention of oral mucositis: retrospective outcomes and safety analyses. Support Care Cancer 2018;26:2417–23.

72. Garcez AS, Núñez SC, Azambuja N Jr, Fregnani ER, Rodriguez HM, Hamblin MR, *et al.* Effects of photodynamic therapy on Gram-positive and Gram-negative bacterial biofilms by bioluminescence imaging and scanning electron microscopic analysis. Photomed Laser Surg 2013;31:519–25.

73. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 2014;740:364–78.

74. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon (FR): International Agency for Re-

search on Cancer. MELPHALAN. In: Pharmaceuticals; 2012 [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK304320/ [cited 2023, Mar 8].

75. Bensinger W, Schubert M, Ang KK, Brizel D, Brown E, Eilers JG, *et al.* NCCN Task Force Report. prevention and management of mucositis in cancer care. J Natl Compr Canc Netw 2008;6(Suppl 1):S1–21, quiz S22–4.

76. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, *et al.*; Intergroupe Francophone du Myélome. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. Blood 2002;99:731–5.

77. Curra M, Soares Junior LA, Martins MD, Santos PS. Chemotherapy protocols and incidence of oral mucositis. An integrative review. Einstein (Sao Paulo) 2018;16:eRW4007.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Joey Danwiek and Indrayadi Gunardi were responsible for data acquisition and investigation; Joey Danwiek also did administration for projects, resources, and visualization of charts and tables; Joey Danwiek and Rahmi Amtha were responsible for analysis and interpretation of data; Rahmi Amtha and Indrayadi Gunardi were responsible for methodology, supervision and validation of collected data. All authors have participated to drafting the manuscript, Rahmi Amtha revised it critically. All authors read and approved the final version of the manuscript.

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