Oral Oncology 75 (2017) 89–94

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

A network meta-analysis in comparing prophylactic treatments of radiotherapy-induced oral mucositis for patients with head and neck cancers receiving radiotherapy

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ARTICLE INFO

Keywords:
Head and neck cancers
Radiotherapy
Supportive care
Oral mucositis
Network meta-analysis

ABSTRACT

Objectives: The objective of this network meta-analysis is to optimize the prophylactic treatment for radiotherapy-induced oral mucositis in patients with head and neck cancer (HNSCC) receiving postoperative or definitive radiotherapy with or without chemotherapy.
Materials and methods: We searched electronic databases to identify all eligible randomized clinical trials on oral mucositis. The endpoint was grade 0–2 oral mucositis. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were extracted. Network meta-analysis was performed using the frequentist approach to conduct multiple treatment comparisons.
Results: In total, 57 trials with 5261 patients were eligible for this study. Both direct and network meta-analysis revealed that low-level laser additional to standard oral care (SOC) was better than most of the other treatments and achieved the highest effect on grade 0–2 oral mucositis, with a surface under the cumulative ranking curve (SUCRA) of 95.8%; however, SOC with or without placebo had worse effect than most of the other treatments and was ranked worst (SUCRA = 0.4%). Moreover, sensitivity analysis performed after we had combined the SOC and placebo groups (non-medication treatment, NMT) yielded similar results, with SUCRA of 91.3% and 3.5% for low-level laser and NMT, respectively.
Conclusions: Low-level laser additional to SOC may be a more effective prophylactic treatment for reducing severe radiotherapy-induced oral mucositis; SOC alone is insufficient for patients with HNSCC receiving postoperative or definitive radiotherapy with or without chemotherapy.

Introduction

Head and neck cancers (HNSCC) account for 5% of all cancers, and squamous cell carcinoma or a variant is the main histologic type in more than 90% of these tumors [1]. Single-modality treatment with surgery or radiotherapy is usually recommended for early disease (stage I or II). Due to complicated anatomy and the wide extension of local or regionally advanced disease, the combined treatment strategy of radical radiotherapy with chemotherapy or cetuximab [2] is a preferred option for unresectable disease. Despite the important therapeutic role of radiotherapy for managing HNSCC, the associated acute adverse effects such as mucositis, taste loss, and xerostomia [3] caused by radiotherapy are also crucial for both patients and clinicians.

Oral mucositis, which presents with the symptoms of pain and erythema and/or ulceration of the oral mucosa, occurs in approximately 20–40% of patients receiving conventional chemotherapy and in nearly all patients receiving radiotherapy for HNSCC [4–6]. It disrupts the function and integrity of the mouth, and impairs nutritional intake and quality of life [7,8]. Moreover, treatment for secondary oral infection and hospitalization have a negative economic impact on patients [9,10]. More seriously, severe mucositis can also result in chemotherapy dosage reduction or treatment interruption of radiotherapy,

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http://dx.doi.org/10.1016/j.oraloncology.2017.11.001
Received 3 July 2017; Received in revised form 24 October 2017; Accepted 2 November 2017

which could adversely affect prognosis [9,11]. Consequently, the management of mucositis is highly important.

Routine care for oral mucositis is standard oral care including tooth brushing, flossing and mouth rinses to maintain oral hygiene. Also, many prophylactic managements of oral mucositis like low-level laser (wavelength at 650 nm, power of 40 mW) were also recommended by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) [12–14]. However, the most appropriate treatment has not established. Given the lack of sufficient evidence in the literature comparing the various related treatments, we conducted the present network meta-analysis to optimize the management of oral mucositis in patients with HNSCC receiving definitive or postoperative radiotherapy with or without chemotherapy, integrating direct and indirect methods.

Materials and methods

Literature search strategy and study recruitment

We searched the electronic databases of PubMed, Web of Science, and the Cochrane Library to identify all potentially eligible clinical trials. Additionally, Chinese databases such as the WangFang database and National Knowledge Infrastructure were searched to select Chinese literature. Key words for searching included head and neck cancer or carcinoma or neoplasm, nasopharyngeal carcinoma or cancer or neoplasm, radiotherapy and mucositis. Detailed information on the literature search and study recruitment criteria is presented in the Supplementary Methods.

Quality control and data extraction

Three oncologists (H.P, B.B.C, L.C) from our center assessed the quality of the included studies independently by reviewing the randomization procedure, establishment of sample size, adoption of blinding in the study design, allocation concealment, if intention-to-treatment analysis was followed, loss to follow-up, and dropout. The Jadad/Oxford quality scoring system was used to quantify study quality [15]. Another three oncologists (Y.P.C, X.L, L.L.T) from our hospital reviewed the articles and extracted the data independently. Data on the first author, study time, number of patients, treatment of experimental and control arms, administration of experimental drug, study intention, radiation dosage, chemotherapy, and study endpoints were simplified. Any discrepancies during quality assessment and data extraction were resolved by consensus or referred to two oncologists (Y.S. and J.M.) with more than 20 years' experience with HNSCC.

Classification of medication

According to the MASCC/ISOO guidelines [12], eight treatments have been proposed for oral mucositis: (1) basic standard oral care (SOC); (2) growth factors and cytokines; (3) anti-inflammatory agents; (4) coating agents with anesthetic and analgesic effects; (5) antimicrobials or antifungal agents; (6) laser or light therapy; (7) cryotherapy; (8) natural and miscellaneous agents. We categorized the medications used in these trials as one group if they had similar mechanisms as the abovementioned treatments. If the medication was in the natural and miscellaneous agents group, we treated this medication as a single group (Supplementary Methods). Notably, the medications used in mouthwash were not restricted because there was no consensus on this and clinicians mainly used the medication according to their experience.

Statistical analysis

In the present study, patients with grade 3–4 oral mucositis (different criteria in Supplementary Table S1) were considered non-responders; those with grade 0–2 oral mucositis were considered responders. Therefore, the primary endpoint of our network meta-analysis was grade 0–2 oral mucositis. The minimum number of responders during the entire radiotherapy treatment in both arms was extracted. Treatment effects were expressed as the odds ratio (OR) and corresponding 95% confidence interval (CI). Intention-to-treatment analysis was performed.

First, traditional pairwise meta-analysis was performed using Review Manager (Version 5.0; the Cochrane Collaboration; Oxford, England). The OR and 95% CI were obtained through the number of responders and non-responders in each arm. Heterogeneity across studies was tested using the χ^2 test and I^2 statistic. Statistically significant heterogeneity was defined as a χ^2 P-value < 0.1 or an I^2 statistic $> 50\%$.

The network meta-analysis was carried out using Stata software (version 13.0; StataCorp LP, College Station, TX, USA) using the *mvmeta* package and the frequentist approach [16]. Inconsistency factor (*IF*) and its 95% CI were derived using the z test [17,18] to evaluate inconsistency between direct and indirect estimates within a triangular loop. *IF* values close to zero and 95% CIs not compatible with zero indicated that the two estimates were in agreement. Comparison-adjusted funnel plots were used to assess the presence of small-study effects [19]. Sensitivity analysis and the multidimensional scaling model (MSD) [20] were used if there was inconsistency and small-study effects. Forest plots of network meta-analysis were constructed to estimate the OR and 95% CI for all comparisons. Lastly, treatment arms were ranked using the surface under the cumulative ranking curve (SUCRA) [16,21]. A treatment was ranked best if it had the highest SUCRA value or smallest rank value. Detailed information on the network meta-analysis is described in the Supplementary Methods.

Results

Eligible studies

Up to May 1, 2017, we identified 112 randomized clinical trials (Supplementary Fig. S1). Among them, we excluded 10 studies that did not adopt the required criteria to evaluate oral mucositis, 28 studies or conference abstracts that did not provide a detailed number of responders and non-responders, two trials that recruited patients with previous chemotherapy, five studies that only evaluated mucositis-related pain, and 10 studies with the intention of treatment. Fifty-seven studies were eventually eligible for the network meta-analysis (Supplementary Reference). The baseline characteristics of the included studies are summarized in Supplementary Table S2.

In total, 5261 patients were randomly assigned: 765 received antibiotics + SOC (ABS), 282 received growth factor + SOC (GFS), 237 received coating agents + SOC (CAS), 417 received laser + SOC (LS), 400 received anti-inflammatory + SOC (AIS), 233 received honey + SOC (HS), 183 received granulocyte-macrophage colony–stimulating factor + SOC (GCS), 82 received glutamine + SOC (GS), 214 received Chinese herbs + SOC (CHS), 43 received aloe vera + SOC (AVS), 1860 received placebo + SOC (PS), and 545 received SOC. Quality assessment of the included studies is presented in Supplementary Table S3.

Direct meta-analysis

A total 22 comparisons (one study [22] had three arms) were identified for the included studies; the results are presented in Supplementary Fig. S2. Significantly better outcomes for grade 0–2 oral mucositis were achieved when ABS was compared with SOC (OR, 2.94; 95% CI, 1.85–4.67), AIS with PS (OR, 3.17; 95% CI, 2.07–4.84), AVS with PS (OR, 10.09; 95% CI, 1.18–86.57), CHS with PS (OR, 8.32; 95% CI, 1.65–41.91), GFS with PS (OR, 2.01; 95% CI, 1.40–2.90), GS with PS (OR, 5.36; 95% CI, 1.00–28.79), GS with SOC (OR, 3.85; 95% CI,