Comparative efficacy and safety of interventions for preventing chemotherapy-induced oral mucositis in adult cancer patients: a systematic review and network meta-analysis

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ABSTRACT

Objective To examine the comparative efficacy and safety of interventions for preventing chemotherapy-induced oral mucositis (OM) in adult cancer patients.

Methods We searched PubMed, Embase and the Cochrane Central systematically for the randomised control trials (RCTs) of interventions for preventing OM. Network meta-analysis (NMA) was performed to estimate risk ratios (RR) and 95% confidence intervals (CI) from both direct and indirect evidence. The primary outcome was any grade of OM. Secondary outcomes were mild-moderate OM, severe OM and adverse events, such as taste disturbance and gastrointestinal adverse events. This study was registered with PROSPERO, number CRD42016052489.

Results A total of 29 RCTs with 2348 patients (median age, 56.1 years; 57.5% male) were included. Cryotherapy was associated with a significantly lower risk of OM than control (RR 0.51, 95% CI 0.38 to 0.68), and zinc sulphate (RR 0.47, 95% CI 0.23 to 0.97), but not significantly lower than sucralfate and palifermin. No significant differences were observed between cryotherapy and control for taste disturbance and gastrointestinal adverse events. Palifermin was associated with the highest risk of taste disturbance.

Conclusions This NMA suggests that cryotherapy was the most effective intervention for preventing chemotherapy-induced OM with a safety profile similar to control, but not significantly lower than sucralfate and palifermin. Large RCTs are needed to confirm these findings.

INTRODUCTION

Oral mucositis (OM) is one of the most debilitating side effects of chemotherapy, which is characterised by inflammatory and ulcerative reactions in the oral cavity.[1] It occurs in approximately 20% to 40% of patients receiving conventional chemotherapy and up to 90% of patients administered high-dose chemotherapy.[2 3] OM is associated with pain, malnutrition, oral lesions representing a gateway for opportunistic infections and significant reductions in quality of life.[4] Patients with severe mucositis often require dose reduction, treatment delays and hospitalisation which can potentially compromise treatment response and increase mortality.[5 6]

The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) recommended cryotherapy for preventing OM in cancer patients receiving bolus 5-fluorouracil- (5-FU) based chemotherapy regimens and suggests use in those receiving high-dose melphalan regimens.[7] Palifermin, a recombinant human keratinocyte growth factor, is also suggested for preventing OM in patients receiving high-dose chemotherapy.[7] Emerging evidence suggests that amifostine is also potentially effective in the prevention of OM.[8 9] To date, there is no direct evidence from RCTs comparing different interventions used for preventing OM for patients with cancer.

A previous meta-analysis based on randomised control trials (RCTS) demonstrated cryotherapy is effective in reducing the incidence of OM compared with control.[10–12] Palifermin also demonstrated efficacy in preventing OM.[10] Glutamine significantly reduces the risk and severity of OM during radiotherapy or chemotherapy.[13] However, most of these studies considered only direct comparisons of the intervention and included patient populations receiving multimodal therapy including surgery and radiation, in addition to chemotherapy.[14]

Network meta-analysis is a methodology suited to assessing multiple interventions using indirect comparisons. This allows comparisons of interventions for which there have been no head-to-head comparison.[15 16] Therefore, we performed a systematic review and network meta-analysis to comprehensively compare and rank the efficacy and safety of interventions used for preventing OM in adult cancer patients receiving chemotherapy.

METHODS

Study design

A systematic review (SR) and network meta-analysis (NMA) of RCTs is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement extension for network meta-analysis.[17] This study was conducted following an a priori-established protocol registered with PROSPERO, number CRD42016052489.[18] We also appraised quality of evidence and strength of recommendation by the

Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[19 20]

Search strategy and selection criteria

We searched publicly available databases including, PubMed, Embase, the Cochrane Central Register of Controlled Trials and Clinicaltrials.gov, for relevant RCTs comparing interventions preventing OM in adult cancer patients receiving chemotherapy. The literature search was performed in November 2016. We included RCTs evaluating interventions assessing prevention of OM. Comparisons of the following interventions were considered: amifostine (910 mg/m^2 intravenous infusion 15 mins); cryotherapy (ice pieces or ice-cold water held in the mouth 5–30 mins before chemotherapy, during chemotherapy and within 5–30 mins after chemotherapy); chlorhexidine 0.10%–0.15% mouthwash every 8–12 hours; glutamine 4–10 g orally every 8–12 hours; granulocyte-macrophage colony-stimulating factor (GM-CSF) 1–1.5 mcg/ml mouthwash every 6 hours; misoprostol 250 mcg orally every 8 hours; recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) 40–180 mg/kg/day; sucralfate 15% 10 mL mouthwash every 6 hours; and zinc sulphate 220 mg orally every 12 hours. There was no restriction on language, publication date and publication status. Details of the search strategy and study selection procedures are shown in the supplementary materials.

Studies with the following characteristics were excluded: assessments of patients receiving radiotherapy or chemoradiotherapy and studies conducted to evaluate the treatment effects of interventions by non-RCTs designs such as systematic review and meta-analysis, review article, guideline, observational study and non-human studies.

Participants

Adult patients (18 years' of age or older) receiving treatment with chemotherapy for any invasive cancer type, including haematological malignancies, solid tumours or mixed cancer types were included.[21]

Study selection and data extraction

Four investigators (J.K., T.K., S.R. and C.S.) screened the titles and abstracts of retrieved citations independently to identify potentially eligible trials. Disagreements were resolved through discussions with a third reviewer (P.W. or K.K.). All identified potentially eligible citations were accessed in full text and reviewed by investigators (J.K., T.K., S.R., C.S. and P.W.) against the eligibility criteria. Final decisions regarding eligibility were independently, double-checked by a third investigator (P.W. or K.K.). Studies in the non-English-language were formally translated before assessment. Extracted data included the characteristics of the studies (first author, publication year, country, study size), characteristics of patients (cancer type, chemotherapy regimen, mean age, proportion of males, the Eastern Cooperative Oncology Group (ECOG)), characteristics of interventions (details of interventions, co-interventions, treatment duration], and outcomes (definition of mucositis, time to measurement)). If studies were performed over many cycles, we extracted a number of events in the first cycle only. Data from the intention-to-treat analysis were used. All extracted data were independently verified by two investigators (P.W. and K.K.).

Outcomes

The primary outcome was any grade OM. The mucositis scale was defined according to WHO criteria,[22] and the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE).[23] Secondary outcomes were mild to moderate OM (grade 1–2), severe OM (grade 3–4) and adverse events were taste disturbance, gastrointestinal adverse events (nausea, vomiting or diarrhoea) and skin reaction.

Quality of evidence

The risk of bias of individual studies was independently assessed by investigators (P.W., J.K., T.K., S.R. and C.S.) using the Cochrane Risk of Bias assessment tool.[24]

The GRADE approach was also assessed to rate the quality of evidence for articles included in the network meta-analysis. RCTs could be downgraded from a high-quality rating based on risk of bias, inconsistency (heterogeneity), indirectness, imprecision and publication bias for direct estimates and network meta-analysis estimates.[19 20]

Statistical analysis

First, we used pairwise meta-analysis to analyse direct treatment comparisons with a random-effects model (DerSimonian and Laird) to estimate pooled risks ratios (RR) with 95% confidence intervals.[25] The statistical heterogeneity among studies was assessed by the I^2 statistic.[26]

Then, we used random effects NMA to combine direct and indirect evidence of all treatment effects using STATA 14 (College station, TX: StataCorp LP).[27–29] Placebo, normal saline or no treatment were combined into the same node and used as a reference (control) in the analyses. Inconsistency between direct and indirect sources of evidence was assessed for global inconsistency using design-by-treatment interaction models. Loop inconsistency was assessed using an inconsistency factor to examine the presence of inconsistency in loop and significant inconsistency between direct and indirect evidence ($P<0.10$) calculations of the difference between direct and indirect estimates in closed loops of the network.[30 31] The node splitting method was used to explore within network inconsistency.[32] We estimated the ranking probabilities for all interventions and hierarchy reported as surface under the cumulative ranking curve (SUCRA), with higher scores reflecting inventions with a greater probability of preventing mucositis. The small-study effects were tested using a comparison-adjusted funnel plot and Egger regression test ($P<0.05$).[27 28 33]

To determine whether the results were affected by study characteristics, we carried out subgroup network meta-analyses for primary outcome according to the following variables: cancer type; chemotherapy regimens: 5-FU-based or antimetabolite regimens; and dose of chemotherapy: high or low dose chemotherapy. Additionally, we did a sensitivity NMA for primary outcome by: omitting studies with non-WHO criteria; inappropriate of time to measurement; small sample size (less than 25th percentile); and studies with high risk of bias. Statistical testing with $P<0.05$ was considered statistically significant.

RESULTS

Overall, 2577 records were identified. After removing duplicated articles, 1697 eligible articles were screened by title and abstract from which 1622 articles were excluded. There were 83 articles retrieved in full text (figure 1). We excluded 54 articles and included 29 studies in the systematic review.[8 9 34–59] Finally, 29 studies were incorporated in the network meta-analysis.[8 9 34–60]

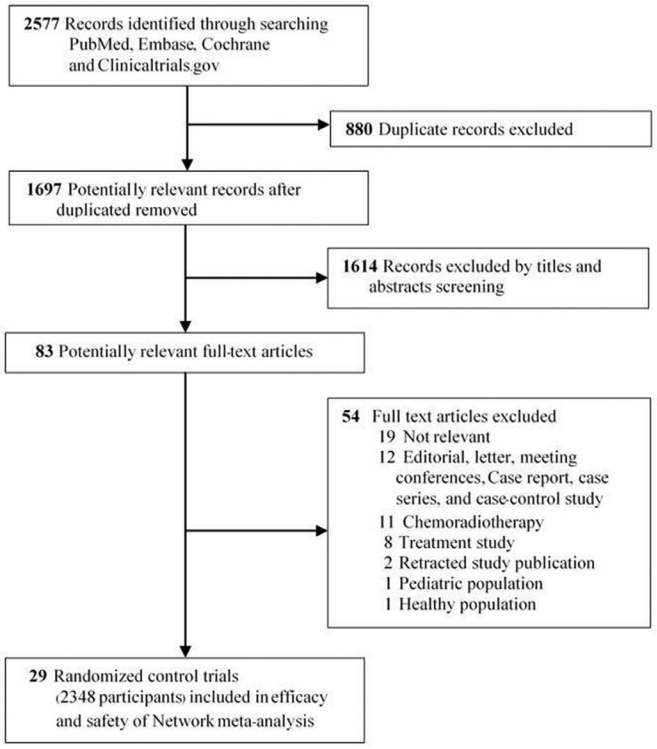

Figure 1 Study identification and selection.

Characteristics and quality of included studies

The characteristics of included studies are described in table 1. Overall, these 29 trials included 2348 participants (the range of size was 16 to 225 participants). The median age of study participants was 56.1 years (IQR, 45.0–60.8) and 57.5% of participants were males (IQR, 51.6%–66.7%). Twenty trials (69.0%) were performed exclusively in solid cancer,[8 34 35 38–42 45 46 48 51–54 56–60] six trials (20.7%) in haematological cancer[9 36 37 47 49 50] and three trials (10.3%) in mixed cancer types.[43 44 55] Most trials (18 trials, 62.1%) were conducted in patients receiving antimetabolite therapy,[34 35 37–40 42 46 48 50–54 56–58 60] 16 trials (55.2%) receiving 5-FU-based regimens[34 35 38–40 42 46 48 51–54 56–58 60] and 11 trials (31.9%) receiving other chemotherapy regimens.[8 9 36 41 43–45 47 49 55 59] The most commonly investigated interventions were cryotherapy (nine trials, 31.0%),[35 39 45–48 54 57 60] palifermin (five trials, 17.2%)[36 37 51 56 59] and chlorhexidine (five trials, 17.2%).[32 44 50 55 57]

In terms of study quality (risk of bias), 16 trials (55.2%) were rated as high risk of bias in blinding of outcome assessment,[8 9 35 39 40 42 44–48 50 54 55 57 60] 10 trials (34.5%) were considered unclear risk because they could not be graded due to inadequate information[36–38 41 43 51–53 56 58] and three trials (10.4%) had low risk of bias.[34 49 59]

Direct meta-analysis

Treatment effects in pairwise meta-analyses are shown in online supplementary appendix. Evidence of statistical heterogeneity was identified for some pairwise comparisons.

Network consistency

The network plots of treatment outcomes for any grade of mucositis and adverse events (taste disturbance) are presented in figure 2. Inconsistencies between direct and indirect evidence are noted for some network comparisons. The design-by-treatment interaction model did not identify global inconsistency within any network, except for taste disturbance.

NMA results

Any grade OM

A total of 29 studies involving 2348 patients evaluated any grade OM of nine interventions. NMA suggests that cryotherapy is the best intervention to prevent OM (figure 3). Cryotherapy was associated with a significantly lower risk of OM than GM-CSF (RR 0.50, 95% CI 0.25 to 0.97; moderate-quality evidence), zinc sulphate (RR 0.47, 95% CI 0.23 to 0.97; low-quality evidence), misoprostol (RR 0.16, 95% CI 0.04 to 0.65) and control (0.51, 95% CI 0.38 to 0.68; moderate-quality evidence); and no significant differences were noted in cryotherapy compared with palifermin and sucralfate. Sucralfate (RR 0.52, 95% CI 0.27 to 0.99; moderate-quality evidence) and palifermin (RR 0.72, 95% CI 0.51 to 0.99; high-quality evidence) were significantly more effective in preventing any grade OM than control. Misoprostol was significantly less effective in preventing OM than sucralfate and palifermin. No significant differences were found in the other comparisons. The ranking of interventions based on SUCRAs and clustered ranking are presented in online supplementary appendix.

Mild-moderate OM

Mild-moderate OM was evaluated in 20 studies involving 1776 patients and eight interventions. NMA suggests that only cryotherapy was associated with statistically significant reductions in mild-moderate OM compared with control (RR 0.66, 95% CI 0.47 to 0.93; moderate-quality evidence). No significant differences were found in the other comparisons.

Severe OM

Severe mucositis was assessed in 20 studies involving 1807 patients and eight interventions. NMA suggests that sucralfate is the best intervention to prevent severe grade OM. Sucralfate (RR 0.31, 95% CI 0.10 to 0.93; moderate-quality evidence), cryotherapy (RR 0.37, 95% CI 0.24 to 0.58; moderate-quality evidence), amifostine (RR 0.42, 95% CI 0.20 to 0.86; high-quality evidence) and chlorhexidine (RR 0.46, 95% CI 0.22 to 0.95; moderate-quality evidence) significantly prevented severe mucositis compared with control. Cryotherapy was significantly more effective than GM-CSF (RR 0.37, 95% CI 0.16 to 0.83). No other statistically significant differences in the other comparison were observed.

Adverse events

Few studies reported the adverse events of the interventions. Eight trials[8 37 43 51 52 56 58 59] examined GI adverse events, while five[51 56–59] and four trials[36 37 51 56] reported taste disturbances and skin reactions, respectively. The results from NMA demontrated no statistically significant differences were found between cryotherapy and control (RR 0.96, 95% CI 0.61 to 1.52) in terms of taste disturbance. However, palifermin was associated with a significantly increased risk of taste disturbance compared with controls (RR 2.94, 95% CI 1.30 to 6.66) and cryotherapy (RR 3.06, 95% CI 1.20 to 7.82) (figure 3). No statistically significant differences in gastrointestinal and skin reaction adverse events were observed between treatment options.

NMA suggested that cryotherapy was associated with the highest probability of preventing any grade OM (SUCRA, 0.92), followed by sucralfate (SUCRA, 0.85) and palifermin (SUCRA, 0.65). Similarly, glutamine was associated with the highest probability of the fewest taste disturbances (SUCRA, 0.89), followed by cryotherapy (SUCRA, 0.67). Palifermin was associated with the highest risk of

Table 1 Characteristics of included studies

Author (year)	Type of cancer	Chemotherapy regimen	Intervention (n)	Study size (n)	Mean age (years)	Male (%)	ECOG performance status
Ala *et al* (2016)[34]	Solid cancer	5-FU-based regimens	Sucralfate (26) Placebo (26)	52	56.8	68.5	NA
Baydar *et al* (2005)[35]	Solid cancer	5-FU-based regimens	Cryotherapy (45) Control (54)	99	54.2	NA	NA
Blijilevens *et al* (2013)[36]	Haematological cancer	HDM regimens	Palifermin (115) Placebo (57)	172	56.1	56.5	0 (45.0%) 1 (43.3%)
Bradstock *et al* (2014)[37]	Haematological cancer	ICE regimens	Palifermin (79) Placebo (81)	160	45.0	64.0	0 (52%) 1 (43%)
Cartee *et al* (1995)[38]	Solid cancer	AFM regimens	GM-CSF (36) 0.1% albumin (9)	45	43.5	NA	NA
Cascinu *et al* (1994)[39]	Solid cancer	5-FU-based regimens	Cryotherapy (44) Control (40)	84	57.9	69.1	0 (50%) 1 (33.3%) 2 (16.7%)
Choi *et al* (2007)[40]	Solid cancer	5-FU/leucovorin regimens	Glutamine (22) Supportive care (29)	51	52.5	64.6	0 (29.7%) 1 (70.3%)
Dazzi *et al* (2003)[41]	Solid cancer	Thiotepa and melphalan, Mitoxantrone, thiotepa and cyclophosphamide, Busulfan and melplalan	GM-CSF (46) Placebo (44)	90	33.3	56.6	NA
Dodd *et al* (1996)[42]	Solid cancer	Doxorubicin, bleomycin, etoposide, 5-FU, MTX, paclitaxel or fludarabine	Chlorhexidine (112) Placebo (110)	222	56.7	32.5	NA
Duenas-Gonzalez *et al* (1996)[43]	Mixed cancer	ICE regimens	Misoprostol (9) Placebo (7)	16	39.3	36.5	NA
Ferretti *et al* (1990)[44]	Mixed cancer	High-dose chemotherapy	Chlorhexidine (19) Placebo (21)	40	32.0	NA	NA
Hartmann *et al* (2001)[8]	Solid cancer	VIC regimens	Amifostine (20) Control (20)	40	45.8	10.0	0–1 (100%)
Heydari *et al* (2012)[60]	Solid cancer	5-FU-based regimens	Cryotherapy (40) No intervention (40)	80	61.4	NA	NA
Karagozoglu (2005)[45]	Solid cancer	Etoposide and cisplatin regimens	Cryotherapy (30) Control (30)	60	NA	NA	NA
Katranci *et al* (2012)[46]	Solid cancer	5-FU/leucovorin regimens	Cryotherapy (30) Control (30)	60	NA	50.0	NA
Lilleby *et al* (2006)[47]	Haematological cancer	HDM regimens	Cryotherapy (21) Normal saline (19)	40	57.4	69.7	NA
Mahood *et al* (1991)[48]	Solid cancer	5-FU/leucovorin regimens	Cryotherapy (50) Control (45)	95	NA	NA	NA
Mansouri *et al* (2012)[49]	Haematological cancer	Busulfan-based regimens	Zinc sulphate (30) Placebo (30)	60	29.0	66.7	NA
McGaw (1985)[50]	Haematological cancer	Cytarabine, doxorubicin and amsacrine	Chlorhexidine (8) Control (8)	16	NA	NA	NA
Meropol *et al* (2003)[51]	Solid cancer	5-FU/leucovorin regimens	KGF (54) Placebo (27)	81	63.8	58.4	0–2 (100%)
Nottage *et al* (2003)[52]	Solid cancer	5-FU/leucovorin regimens	Sucralfate (41) Placebo (40)	81	60.8	55.0	0 (63.9 %) 1 (31.3%)
Okuno *et al* (1999)[53]	Solid cancer	5-FU-based regimens	Glutamine (66) Placebo (68)	134	62.7	53.8	NA
Papadeas *et al* (2007)[54]	Solid cancer	5-FU/leucovorin regimens	Cryotherapy (36) Placebo (40)	76	62.4	34.2	NA
Pitten *et al* (2003)[55]	Mixed cancer	NA	Chlorhexidine (24) Placebo (23)	47	51.5	63.8	NA
Rosen *et al* (2006)[56]	Solid cancer	5-FU/leucovorin regimens	Palifermin (36) Placebo (28)	64	65.0	64.7	0 (46%) 1 (44%) 2 (8.5%) Other (2.5%)
Sorensen *et al* (2008)[57]	Solid cancer	5-FU/leucovorin regimens	Chlorhexidine (75) Placebo (75) Cryotherapy (75)	225	59.3	55.4	NA
Spencer *et al* (2005)[9]	Haematological cancer	HDM regimens	Amifostine (43) Control (47)	90	51.8	67.2	2 (100%)
Tanaka *et al* (2016)[58]	Solid cancer	DCF regimens	Glutamine (10) Control (10)	20	70.0	80.0	NA
Vadhan-Raj *et al* (2010)[59]	Solid cancer	Doxorubicin-based regimens	Palifermin (32) Placebo (16)	48	40.13	51.6	NA

AFM regimens, Adriamycin (doxorubicin) +5-FU+MTX; CALGB criteria, Cancer and Leukaemia Group B; CTCAE v3.0, Common Terminology Criteria for Adverse Events version 3.0; DCF regimens, Docetaxel+cisplatin+5 FU; DGS regimens; Docetaxel+nedaplatin+ S-1; HDM regimens, High-dose melphalan; ICE regimens, Idarubicin +cytarbine+ etoposide or Ifosfamide +carboplastin+ etoposide; NA, not available; NCI-CTC, National Cancer Institute Common Toxicity Criteria; VIC regimens, High-dose etoposide +ifosfamide+ carboplastin; WHO, World Health Organization grading system.

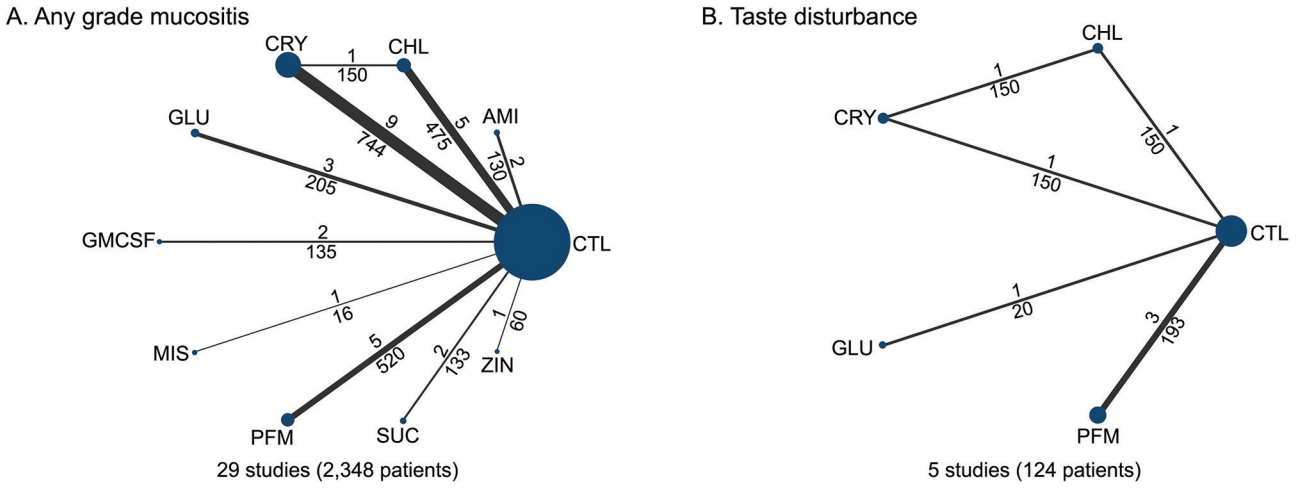

Figure 2 Network comparisons of included studies in the analyses. The size of the nodes and the thickness of the lines are weighted according to the number of studies assessing each treatment and direct comparison. Numbers above and below the lines indicate studies and patients respectively. AMI, amifostine; CHL, chlorhexidine; CRY, cryotherapy; CTL, control; GLU, glutamine; GM-CSF, granulocyte-monocyte colony-stimulating factor; MIS, misoprostol; PFM, palifermin; SUC, sucralfate; ZIN,zinc sulphate.

taste disturbance (SUCRA, 0.02) (figure 4). The individual ranking of interventions based on cumulative probability plots and SUCRAs are presented in online supplementary appendix.

Subgroup and sensitivity analyses

The results from subgroup analyses confirm cryotherapy is the best intervention in preventing any grade OM in any type of cancer and all chemotherapy regimens. Sensitivity analyses demonstrated similar results to the main analysis.

Publication bias

There was no evidence of small-study effects, either qualitatively based on funnel-plot asymmetry or quantitatively (Egger regression test, P>0.05 for all comparisons), although the number of studies included in each comparison was small.

DISCUSSION

This is the first SR and NMA comparing the effectiveness of interventions for the prevention of OM in adult cancer patients.

Risk ratio (95% CI) for any grade mucositis \ Risk ratio (95% CI) for taste disturbance										
	CRY	NA	**0.33 (0.13,0.83)**	NA	0.69 (0.46,1.03)	2.88 (0.34,24.38)	NA	NA	0.96 (0.61,1.52)	NA
	0.98 (0.48,1.99)	**SUC**	NA	NA	NA	NA	NA	NA	NA	NA
	0.71 (0.46,1.10)	0.73 (0.35,1.50)	**PFM**	NA	2.10 (0.85,5.22)	8.82 (0.94, 82.95)	NA	NA	**2.94 (1.30,6.66)**	NA
	0.68 (0.37,1.26)	0.69 (0.30,1.63)	0.96 (0.50,1.82)	**AMI**	NA	NA	NA	NA	NA	NA
	0.64 (0.40,1.04)	0.66 (0.30,1.42)	0.91 (0.53,1.54)	0.95 (0.47,1.90)	**CHL**	4.20 (0.50,35.16)	NA	NA	1.40 (0.94,2.09)	NA
	0.59 (0.35,1.00)	0.60 (0.27,1.32)	0.83 (0.47,1.44)	0.86 (0.42,1.75)	0.91 (0.49,1.69)	**GLU**	NA	NA	0.33 (0.04,2.69)	NA
	0.50 (0.25,0.97)	0.51 (0.21,1.22)	0.70 (0.35,1.37)	0.73 (0.32,1.66)	0.77 (0.38,1.58)	0.85 (0.40,1.80)	**GMCSF**	NA	NA	NA
	0.47 (0.23,0.97)	0.48 (0.19,1.21)	0.66 (0.31,1.38)	0.69 (0.29,1.64)	0.73 (0.33,1.59)	0.80 (0.36,1.79)	0.94 (0.39,2.29)	**ZIN**	NA	NA
	0.51 (0.38,0.68)	**0.52 (0.27,0.99)**	**0.72 (0.51,0.99)**	0.75 (0.43,1.31)	0.79 (0.52,1.20)	0.87 (0.55,1.37)	1.03 (0.57,1.84)	1.09 (0.56,2.12)	**CTL**	NA
	0.16 (0.04,0.65)	**0.17 (0.04,0.74)**	**0.23 (0.06,0.92)**	0.24 (0.06,1.03)	0.25 (0.06,1.04)	0.28 (0.07,1.15)	0.33 (0.08,1.43)	0.35 (0.08,1.56)	0.32 (0.08,1.23)	**MIS**

Figure 3 Comparison incidence of any grade mucositis and adverse events (taste disturbance) in network meta-analysis. Summary estimate represents risk ratio of any grade of mucositis (light blue background) and adverse events (taste disturbance) (light grey background). Interventions are ordered by ranking for any grade of mucositis. Risk ratio for comparisons are in the cell in common between the column-defining and row-defining Intervention. For any grade mucositis outcome, column intervention is compared with row intervention (ie, row treatment is reference). For adverse events (taste disturbance), row intervention is compared with column intervention (ie, column intervention is reference). Numbers in bold represent statistically significant results. AMI, amifostine; CHL, chlorhexidine; CRY, cryotherapy; CTL, control; GLU, glutamine; GM-CSF, granulocyte-monocyte colony-stimulating factor; MIS, misoprostol; NA, not available; PFM, palifermin; SUC, sucralfate; ZIN, zinc sulphate.

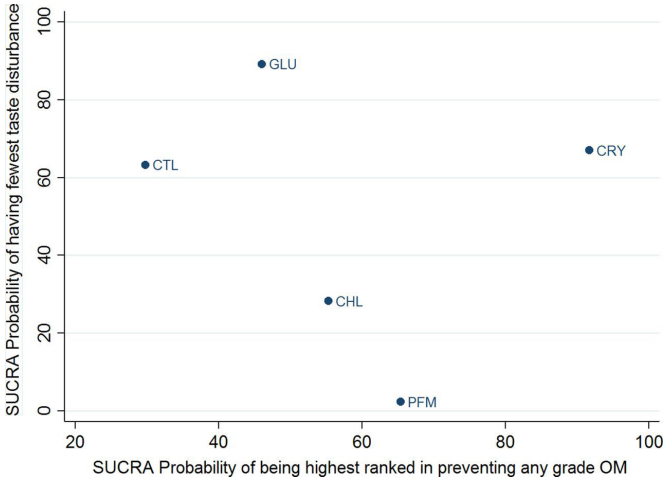

Figure 4 SUCRAs for preventing any grade mucositis and adverse events (taste disturbance). Surface under the cumulative rankings (SUCRAs) between 0 and 100 represent the probability of being ranked highest. For the prevention of any grade OM outcomes, higher score corresponds to higher proportion preventing OM with a particular therapy. For the taste disturbance outcome, higher scores reflect lower probability of taste disturbance.

The study has several key findings. First, cryotherapy was the best intervention to reduce the incidence of OM with few side effects, except mild discomfort during administration. Our findings suggest that cryotherapy should be considered the first-line intervention for preventing OM. Second, palifermin compared with cryotherapy was not statistically nor significantly different in preventing OM. Based on this review, palifermin may be used as an alternative intervention for preventing OM in patients with a contraindication to cryotherapy such as those receiving oxaliplatin-containing regimens. However, palifermin was associated with an increased risk of taste disturbance, a known side effect of the therapy and the cost effectiveness of this agent has yet to be demonstrated.[61 62] Third, the most surprising finding from our NMA found that cancer patients treated with sucralfate mouthwash before receiving chemotherapy significantly reduced the incidence of severe OM compared with control and the reduction was similar to cryotherapy. These results indicate that sucralfate may be the best intervention for preventing severe OM. Finally, zinc sulphate did not significantly reduce the incidence of OM compared with control and therefore should not be recommended for the prevention of OM.

Similar to previous meta-analyses, our findings suggested that cryotherapy was significantly better than control for preventing OM.[1011] Oral cryotherapy also significantly decreased the incidence of severe OM.[12] When compared with chlorhexidine, oral cryotherapy did not significantly reduce in the incidence of OM.[11] Cryotherapy causes local vasoconstriction in the oral mucosa, leading to reduced blood flow and delivery of cytotoxic drugs to the oral mucous membrane.[35] Based on this review, cryotherapy had the highest probability of being the best intervention for preventing OM in patients receiving chemotherapy and is currently recommended for use in the MASCC/ISOO guidelines for preventing OM in those receiving bolus 5-fluorouracil and suggested use for high-dose melphalan.[7]

Moreover, palifermin can prevent OM in patients receiving high-dose chemotherapy.[7] Palifermin has potent epithelial cell proliferative activity and induces epithelial thickening of the non-keratinocyte layers of the oral mucosa and gastrointestinal tract.[63] Palifermin is recommended for use by MASCC/ISOO guidelines and is the only agent approved for use by regulatory agencies in the USA and EU to prevent OM in patients receiving high-dose chemotherapy followed by autologous stem cell transplant.[7]

On the contrary, previous meta-analyses have demonstrated that sucralfate has no significant advantage for preventing OM in patients receiving chemoradiotherapy, and current guidelines recommend against this agent for the prevention of chemotherapy-induced OM.[7 10 64] Our NMA found that sucralfate does provide significant protective effects for chemotherapy-induced OM of all grades. Furthermore, we demonstrated no statistically significant differences between sucralfate and cryotherapy. Sucralfate, a sulphated disaccharide which is not absorbed, acts as a mucoprotective agent to shield nerve endings in the oral mucosa from cytotoxic agents.[34 52] Thus, sucralfate mouthwash could be an alternative intervention for preventing OM. However, the number of included trials in this analysis was limited and this finding should be confirmed by high-quality RCTs.[34 52] Current clinical practice guidelines suggests that zinc sulphate, an antioxidant and trace element involved in tissue repair, may prevent OM in patients receiving radiotherapy or chemoradiotherapy.[7] However, our findings demonstrate zinc sulphate had no benefit for preventing OM in patients receiving chemotherapy.

The major strengths of this study include the explicit eligibility criteria, a comprehensive search strategy, consideration of trials in languages other than English, and the independent and duplicate assessment of eligibility. Furthermore, this is the first NMA of RCTs that include interventions for preventing OM in adult cancer patients for combining direct and indirect evidence.

This study has limitations. First, in the quality of evidence (GRADE), many comparisons were assessed as low quality, which largely restricts the interpretation of these results. Second, this NMA was restricted to trials involving only patients receiving chemotherapy. We excluded trials involving radiotherapy or chemoradiotherapy regimens to reduce heterogeneity and inconsistency among trials in NMA, but we recognised that it restricts the external validity and applicability of the study findings. Thus, our results are less generalisable to adult patients receiving radiotherapy or chemoradiotherapy. Third, we were unable to assess the validity of NMA results because direct and indirect estimates were not available for the outcomes of the comparisons.[31] We tested for the overall inconsistency in the network using a global method, yet we were unable to test loop-specific inconsistency since most pairwise comparisons only have one study. Hence, these results should be interpreted with caution. Fourth, patient characteristics were heterogeneous across the trials, which is a significant limitation of our NMA. Plausible confounder of this analysis includes imbalance of chemotherapy regimens, cancer types and co-interventions. However, we did subgroup and sensitivity analysis with these variables and the findings of which were not materially different from the primary analysis in most of these comparisons. Finally, although the different control interventions including routine care, placebo, normal saline or no treatments were combined, we found that the effect to prevent OM of these control interventions were not statistically different.

In conclusion, our NMA suggests that cryotherapy was the most effective intervention for preventing OM with a safety profile similar to control. Cryotherapy should be considered as the first-line intervention preventing chemotherapy-induced OM in adult cancer patients in the absence of contraindications. Palifermin and sucralfate did not differ significantly from cryotherapy for the prevention of chemotherapy-induced OM and would be reasonable alternatives, however cost needs to be

What this paper adds

What is already known on this subject

- Oral mucositis (OM) is one of the most debilitating side effects of chemotherapy.
- Interventions such as cryotherapy, palifermin, glutamine and sucralfate have demonstrated efficacy in preventing oral mucositis
- Strong evidence with ranking of available interventions by safety and efficacy is needed to guide clinical practice.

What this study adds

- This study provides the first comprehensive systematic review and network meta-analysis of randomised trials, comparing and ranking interventions for preventing chemotherapy-induced oral mucositis.
- Cryotherapy was identified as the best intervention to prevent chemotherapy-induced oral mucositis, followed by palifermin and sucralfate mouthwash.
- Therefore, cryotherapy should be considered a first-line intervention for the prevention of chemotherapy-induced OM in adult cancer patients in the absence of contraindications.

considered especially with the use of palifermin. Further large RCTs are needed to confirm these findings.

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