Supplementary appendix

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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Table S1 Search algorithms

Database	Step	Search algorithm	Item found
Pubmed	#1	mucositis	7938
	#2	stomatitis	26523
	#3	chemotherapy	2833741
	#4	amifostine	1780
	#5	chlorhexidine	9952
	#6	cryotherapy	27051
	#7	ice*	47270
	#8	G-CSF	38993
	#9	GCSF	495
	#10	GM-CSF	26729
	#11	GMCSF	20900
	#12	rhGM-CSF	647
	#13	rhG-CSF	1171
	#14	glutamine	39009
	#15	misoprostol	4737
	#16	palifermin	1444
	#17	KGF	1604
	#18	pilocarpine	8474
	#19	sucralfate	1946
	#20	zinc*	124468
	#21	filgrastim	2255
	#22	cancer	3377783
	#23	tumor	3321854
	#24	neoplasm	2898064
	#25	malignancy	2888204
	#26	oncol*	632018
	#27	(mucositis) OR stomatitis	32594
	#28	((((((((((((((((amifostine) OR chlorhexidine) OR cryotherapy) OR ice*) OR G-CSF) OR GCSF) OR GM-CSF) OR GMCSF) OR rhGM-CSF) OR rhG-CSF) OR glutamine) OR misoprostol) OR palifermin) OR KGF) OR pilocarpine) OR sucralfate) OR zinc*) OR filgrastim	308231
	#29	((((cancer) OR tumor) OR neoplasm) OR malignancy) OR oncol*	3839609
	#30	(((((mucositis) OR stomatitis)) AND chemotherapy) AND ((((((((((((((((amifostine) OR chlorhexidine) OR cryotherapy) OR ice*) OR G-CSF) OR GCSF) OR GM-CSF) OR GMCSF) OR rhGM-CSF) OR rhG-CSF) OR glutamine) OR misoprostol) OR palifermin) OR KGF) OR pilocarpine) OR sucralfate) OR zinc*) OR filgrastim)) AND (((((cancer) OR tumor) OR neoplasm) OR malignancy) OR oncol*)	959
Embase	#1	mucositis	13166
	#2	stomatitis	37271
	#3	chemotherapy	702754
	#4	cancer	3131730
	#5	tumor	2343948
	#6	neoplasm	703303
	#7	malignancy	182791
	#8	oncol*	1142957
	#9	amifostine	3707
	#10	chlorhexidine	18171
	#11	cryotherapy	17341
	#12	ice*	68822
	#13	G-CSF	1245
	#14	GCSF	1041

Database	Step	Search algorithm	Item found
	#16	'rhg csf'	1376
	#17	glutamine	61145
	#18	misoprostol	10726
	#19	palifermin	610
	#20	kgf	1920
	#21	pilocarpine	15084
	#22	sucralfate	6494
	#23	zinc*	195881
	#24	filgrastim	4469
	#25	'gm csf'	22362
	#26	gmcsf	1269
	#27	neoplasm	22362
	#28	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	438833
	#29	#1 OR #2	48962
	#30	#4 OR #5 OR #6 OR #7 OR #8	4548406
	#31	#3 AND #29 AND #30 AND #31	1408
Cochrane	#1	mucositis	2049
	#2	stomatitis	2557
	#3	chemotherapy	46195
	#4	cancer	102898
	#5	tumor	27860
	#6	neoplasm	19201
	#7	malignancy	4071
	#8	oncol*	48183
	#9	amifostine	362
	#10	chlorhexidine	2893
	#11	cryotherapy	1320
	#12	ice*	3347
	#13	G-CSF	1924
	#14	GCSF	104
	#15	GM-CSF	186
	#16	GMCSF	62
	#17	rhGM-CSF	162
	#18	rhG-CSF	185
	#19	glutamine	1368
	#20	misoprostol	2359
	#21	palifermin	60
	#22	KGF	55
	#23	pilocarpine	610
	#24	sucralfate	769
	#25	zinc*	4191
	#26	filgrastim	784
	#27	#1 OR #2	4104
	#28	#4 OR #5 OR #6 OR #7 OR #8	125571
	#29	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	19956
	#30	#3 AND #27 AND #28 AND #29	199
ClinicalTrial	#1	(((((“mucositis” OR “stomatitis”)) AND (prevent* OR “prophylaxis”)) AND “chemotherapy”) AND (“amifostine” OR “chlorhexidine” OR “cryotherapy” OR “erythropoietin” OR “G-CSF” OR "GM-CSF" OR “glutamine” OR ice* OR “misoprostal” OR “palifermin” OR “pilocarpine” OR “sucralfate” OR zinc*)) AND (cancer* OR tumor* OR neoplasm*)	11

Table S2 Description of participants of included studies

Study ID	First Author (year)	Type of cancer	Details of cancer type	Chemotherapy regimens	Detail of chemotherapy regimen	Strength of chemotherapy	Intervention (N)	Treatment details	Treatment duration (day)	Co-interventions
1	Ala (2016)[1]	Solid cancer	Gastric cancer, esophageal cancer and colorectal cancer	5-FU based regimens	5-FU 600-1500 mg/cycle	high dose	Sucralfate (n=26) Placebo (n=26)	Sucralfate mouthwash 10 ml q 6 hr Non-Sucralfate mouthwash 10 ml q 6 hr	10	NA
7	Baydar (2005)[2]	Solid cancer	Colorectal cancer, stomach cancer, head of pancreas cancer, cecum cancer, sigmoid cancer, neuroendocrine cancer and metastatic liver cancer	5-FU based regimens	5-FU 450 mg/m^2	usual dose	Cryotherapy (n=45) Control (n=54)	Patients kept ice pieces in their mouth from the beginning of IV 5-FU until 10 min after the treatment Control group don't do anything before IV 5-FU	21	Folinic acid 20 mg/m^2 in 10 min and 30 min prior 5-FU administration
9	Blijlevens (2013)[3]	Hematological cancer	Multiple myeloma	HDM regimens	Melphalan 140-200 mg/m^2	high dose	Palifermin (n=115) Placebo (n=57)	Palifermin 60 mg/kg/day IV infusion pre-/post-HDM Placebo IV	6	NA
10	Bradstock (2014)[4]	Hematological cancer	Acute myeloid leukemia	ICE regimens	Idarubicin 9 mg/m^2 on days 1-3, etoposide 75 mg/m^2 on days 1-7, and cytarabine 3 g/m^2 on days 1, 3, 5 and 7	high dose	Palifermin (n=79) Placebo (n=81)	Palifermin 60 mg/kg/day IV infusion before chemotherapy Placebo IV infusion before chemotherapy	6	Supportive treatment, e.g. filgastrim, red cell and platelet concentrates
13	Cartee (1994)[5]	Solid cancer	Breast cancer	AFM regimens	5-FU 500 mg/kg/day on days 1-5, adriamycin 25 mg/m^2 on day 3-5, MTX IV 250 mg/m^2 on day 15	usual dose	GM-CSF (n=36) 0.1% Albumin (n=9)	GM-CSF 1 mcg/ml mouthwash 15 ml during the chemotherapy QID 0.1%albumin mouthwash 15 ml during the chemotherapy QID	21	G-CSF 5 mcg/kg/day SC on days 7-13 and from day 16 until resolution of neutropenia
15	Cascinu (1994)[6]	Solid cancer	Colon-rectum cancer, pancreas cancer, stomach cancer and prostate cancer	5-FU based regimens	5-FU 370-500 mg/m^2	usual dose	Cryotherapy (n=44) Control (n=40)	Patients placing ice chips in their mouths 5 min prior to each dose of 5-FU for a total 30 min Control group don't do anything	21	NA
17	Choi (2006)[7]	Solid cancer	Stomach cancer, esophageal cancer, colorectal cancer, head and neck cancer, periampullar cancer and biliary cancer	5-FU/leucovorin regimens	Leucovorin 100 mg/m^2 over 30 min followed 5-FU 500 mg/m^2 continuous infusion for 5 days	usual dose	Glutamine (n=22) Supportive care (n=29)	Glutamine 30 g/day TID initiated 3 days before the inception of chemotherapy continued Control group patients received supportive care before the inception of chemotherapy continued	15	All patient received 30 min of oral cryotherapy QID during chemotherapy

Study ID	First Author (year)	Type of cancer	Details of cancer type	Chemotherapy regimens	Detail of chemotherapy regimen	Strength of chemotherapy	Intervention (N)	Treatment details	Treatment duration (day)	Co-interventions
20	Dazzi (2002)[8]	Solid cancer	Breast cancer, ewing's sarcoma, osteosarcoma, non-Hodgkin lymphoma, germ cell tumors, small-cell lung cancer and soft tissue sarcoma	Thiotepa and melphalan regimens Mitoxantrone, thiotepa and cyclophosphamide regimens Busulfan and melplalan regimens	Thiotepa 600 mg/m^2 and melphalan 140 mg/m^2 Mitoxantrone 40 mg/m^2 day1, thiotepa 500 mg/m^2 day 2, cyclophosphamide 100 mg/kg days 3-4 Busulfan 4 mg/kg days 1-4, melplalan 140 mg/m^2 day 5	high dose	GM-CSF (n=46) Placebo (n=44)	GM-CSF mouthwash 150 mcg/day in 100 cm^3 of sterile water QID Sterile water 100 cm^3 QID	NA	0.2% oral chlorhexidine and amphotericin B
21	Dodd (1996)[9]	Solid cancer	Breast cancer, lung cancer and colon cancer	Doxorubicin, bleomycin, etoposide, 5-FU, MTX, paclitaxel or fludarabine	NA	NA	Chlorhexidine (n=112) Placebo (n=110)	Chlorhexidine mouth rinse for 30 second BID Sterile water as placebo rinse for 30 second BID	30	NA
22	Duenas-Gonzalez (1996)[10]	Mixed cancer	Hodgkin's lymphoma, non-Hodgkin lymphoma, breast cancer, soft tissue sarcoma, uterine-cervix cancer and testicular cancer	ICE regimens	Ifosfamide 10 g/m^2, carboplatin 1.5 g/m^2 and etoposide 2.1 g/m^2	high dose	Misoprostol (n=9) Placebo (n=7)	Misoprostol 250 mcg TID PO from the first day of chemotherapy until day post-transplantation Placebo TID PO from the first day of chemotherapy until day post-transplantation	21	Supportive care: ranitidine, ketoconazole, ciprofloxacin, ceftazidime plus amikacin after the first febrile episode and acyclovir 500 mg/m^2/day if developed oral mucositis until lesions healed
25	Ferretti (1990)[11]	Mixed cancer	Leukemia, lymphoma, squamous cell carcinoma, rhabdomyosarcoma and lung cancer	High dose chemotherapy	NA	high dose	Chlorhexidine (n=19) Placebo (n=21)	0.12% Chlorhexidine digluconate mouthwash 30 seconds TID Non-chlorhexidine mouthwash 30 seconds TID	21	NA
27	Hartmann (2001)[12]	Solid cancer	Breast cancer, testicular cancer, sarcoma and ovarian cancer	VIC regimens	Etoposide 500 mg/m^2 4 hr/day, ifosfamide 4000 mg/m^2 18 hr/day and carboplatin 500 mg/m^2 18 hr/day for 3 days	high dose	Amifostine (n=20) Control (n=20)	Amifostine 910 mg/m^2 as a 15 minutes IV infusion before chemotherapy Pretreatment without amifostine	3	Supportive treatment, e.g. ofloxacin, fluconazole, transfuse red blood cell and platelet, G-CSF
29	Heydari (2012)[13]	Solid cancer	Breast cancer and colorectal cancer	5-FU based regimens	MAYO regimen: 5-FU 425 mg/m^2 and leucovorin 25 mg/m^2 for days CAF regimen: cyclophosphamide 500 mg/m^2, adriamycin 50	usual dose	Cryotherapy (n=40) No intervention (n=40)	Application of ice chips in the mouthwash for 5 minutes before chemotherapy to 5 minutes after chemotherapy Control group received no intervention	21	NA

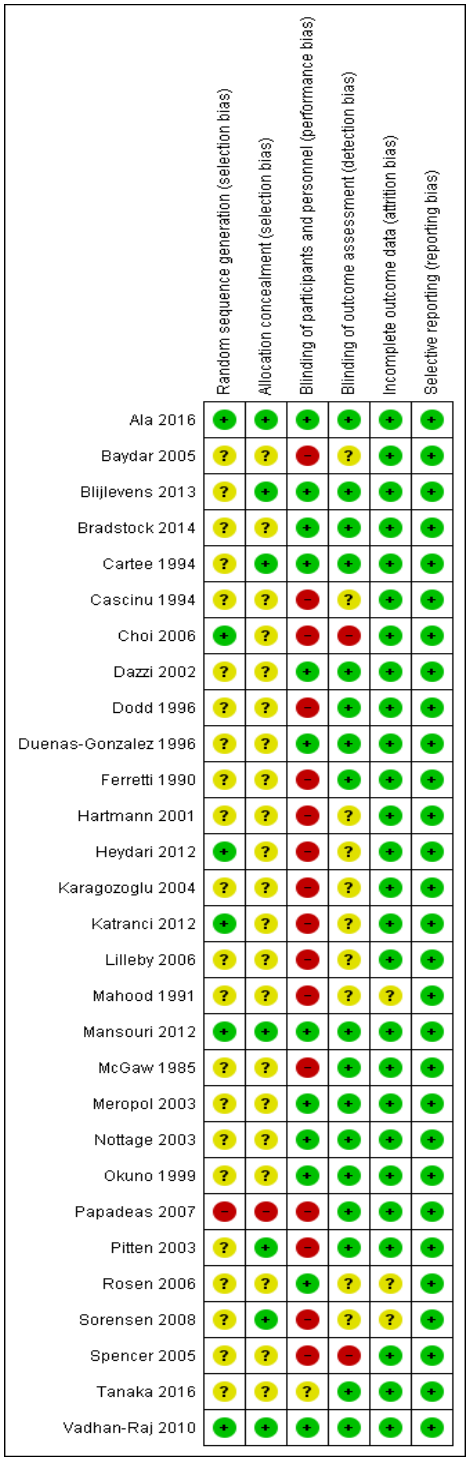
Study ID	First Author (year)	Type of cancer	Details of cancer type	Chemotherapy regimens	Detail of chemotherapy regimen	Strength of chemotherapy	Intervention (N)	Treatment details	Treatment duration (day)	Co-interventions
					mg/m^2 and 5-FU 500 mg/m^2 for the first day of the cycle CMF regimen: cyclophosphamide 600 mg/m^2, MTX 40 mg/m^2 and 5-FU 600 mg/m^2 for the first day of the cycle					
35	Karagozoglu (2004)[14]	Solid cancer	Epidermoid cancer, small cell cancer, adenocarcinoma and mesothelioma	Etoposide and cisplatin regimens	Etoposide, cisplatin, mitomycin (Mitomycin-C) and vinblastin	NA	Cryotherapy (n=30) Control (n=30)	Oral cryotherapy before chemotherapy 5 minutes mouthwash and maintained infusion chemotherapy Control group received no intervention	21	NA
38	Katranci (2012)[15]	Solid cancer	Gastric cancer, colorectal cancer and pancreatic cancer	5-FU/leucovorin regimens	5-FU and leucovorin	NA	Cryotherapy (n=30) Control (n=30)	Cryotherapy 5 minutes mouthwash before treatment, during treatment, and within 15 minutes after treatment for a total of 30 minutes Control group receiving routine care	5	NA
41	Lilleby (2006)[16]	Hematological cancer	Multiple myeloma	HDM regimens	Melphalan 200 mg/m^2	high dose	Cryotherapy (n=21) Normal saline (n=19)	Cryotherapy in mouthwash 30 minutes before, during and after received chemotherapy Normal saline rinses before, during and after received chemotherapy	2	NA
46	Mahood (1991)[17]	Solid cancer	Colon cancer	5-FU/leucovorin regimens	5-FU 425 mg/m^2/day and leucovorin 20 mg/m^2/day for 5 days	usual dose	Cryotherapy (n=50) Control (n=45)	Cryotherapy in mouths 5 minutes mouthwash prior to each dose of 5-FU and for a total of 30 minutes Control group received no intervention	5	NA
47	Mansouri (2012)[18]	Hematological cancer	Acute myeloid leukemia, acute lymphoblastic leukemia and chronic myelogenous leukemia	Busulfan based regimens	Busulfan 16 mg/kg for 4 days followed by cyclophosphamide 60 mg/kg daily for 2 days Fludarabine 30 mg/m^2/day for 5 days plus busulfan 14 mg/kg for 4 days	high dose	Zinc sulfate (n=30) Placebo (n=30)	Zinc sulfate capsule 220 mg PO twice a day Placebo capsule PO twice a day	6-9	Nystatin q 3 hr, chewable tablet sucralfate 500 mg q 8 hr, chlorhexidine 0.02% mouthwash 10 ml, diluted vial of amphotericin and diluted povidone iodine 10 ml q 3 hr

Study ID	First Author (year)	Type of cancer	Details of cancer type	Chemotherapy regimens	Detail of chemotherapy regimen	Strength of chemotherapy	Intervention (N)	Treatment details	Treatment duration (day)	Co-interventions
48	McGaw (1985)[19]	Hematological cancer	Acute myeloblastic leukemia	Cytosine-arabinoside (cytarabine), adriamycin (doxorubicin) and amsacrine	Cytosine-arabinoside (cytarabine) 200 mg/m^2/day for 5 days, adriamycin (doxorubicin) 40 mg/m^2 day 1 and day 2 and amsacrine 100 mg/m^2/day for 5 days	high dose	Chlorhexidine (n=8) Control (n=8)	0.1% chlorhexidine gluconate 10 ml mouthwash twice daily for 2 minutes Placebo solution is 0.1% quinine chloride	5	NA
50	Meropol (2003)[20]	Solid cancer	Colorectal cancer	5-FU/leucovorin regimens	Leucovorin 20 mg/m^2, followed by 5-FU 425 mg/m^2 for 5 days	usual dose	KGF (n=54) Placebo (n=27)	KGF 1-80 g/kg/day IV bolus on days 1-3 of each cycle before chemotherapy Placebo IV on days 1-3 of each cycle before chemotherapy	3	NA
53	Nottage (2003)[21]	Solid cancer	Colorectal cancer	5-FU/leucovorin regimens	5-FU 370-425 mg/m^2/day and leucovorin 20-200 mg/m^2/day	usual dose	Sucralfate (n=41) Placebo (n=40)	Sucralfate mouthwash 10 ml for 2 minutes daily Placebo mouthwash 10 ml for 2 minutes daily	15	Oral cryotherapy immediately prior to the administration of chemotherapy
55	Okuno (1999)[22]	Solid cancer	NA	5-FU based regimens	5-FU 370-450 mg/m^2/day	usual dose	Glutamine (n=66) Placebo (n=68)	Glutamine 4 g PO twice daily for 14 days Placebo PO twice daily for 14 days	14	Oral cryotherapy 5 minutes before each 5-FU administration
56	Papadeas (2007)[23]	Solid cancer	Colorectal cancer and breast cancer	5-FU/leucovorin regimens	Leucovorin 20 mg/m^2/day plus 5-FU 600 mg/m^2/day for 5 days	usual dose	Cryotherapy (n=36) Placebo (n=40)	Cryotherapy swish around in oral cavity 5 minutes before, during and until 30 minutes after 5-FU administration No intervention in placebo group	5	NA
61	Pitten (2003)[24]	Mixed cancer	Leukaemias, lymphoma, multiplemyeloma, germcell cancer, ewing's sarcoma, neuroectodermal cancer and renal cell cancer	NA	NA	NA	Chlorhexidine (n=24) Placebo (n=23)	Chlorhexidine mouthwash three times a day (30 minutes after the meals) Placebo mouthwash three times a day	NA	Amphotericin B
64	Rosen (2006)[25]	Solid cancer	Colorectal cancer	5-FU/leucovorin regimens	Leucovorin 20 mg/m^2/day followed by 5-FU 425 mg/m^2/day for 5 days	usual dose	Palifermin (n=36) Placebo (n=28)	Palifermin 40 mg/kg IV for 3 consecutive days before chemotherapy Placebo IV for 3 consecutive days before chemotherapy	3	NA
70	Sorensen (2008)[26]	Solid cancer	Gastric cancer and colorectal cancer	5-FU/leucovorin regimens	Leucovorin 20 mg/m^2 followed by 5-FU 425	usual dsoe	Chlorhexidine (n=75) Placebo (n=75) Cryotherapy (n=75)	Chlorhexidine 0.1% mouthwash 10 mL and the patients swirled it around in the mouth for 1 minute 3 times a day	21	NA

Study ID	First Author (year)	Type of cancer	Details of cancer type	Chemotherapy regimens	Detail of chemotherapy regimen	Strength of chemotherapy	Intervention (N)	Treatment details	Treatment duration (day)	Co-interventions
					mg/m^2 daily in 5 days every 4 weeks			Cryotherapy with crushed ice in the mouth from 10 minutes before until 35 minutes after the start of each chemotherapy		
72	Spencer (2005)[27]	Hematological cancer	Multiple myeloma	HDM regimens	Melphalan 200 mg/m^2	high dose	Amifostine (n=43) Control (n=47)	Amifostine 910 mg/m^2 continuous infusion over 15 minutes Non-amifostine	1	Interferon alpha-2b, Ciprofloxacin 500 mg BID 2 days, Norfloxacin 400 mg BID 2 days, Fluconazole 100 mg BID, Dexamethasone 20 mg 5HT3 antagonist 30-60 minutes
73	Tanaka (2016)[28]	Solid cancer	Esophageal cancer	DCF regimens DGS regimens	DCF regimens: docetaxel 35 mg/m^2, cisplatin 40 mg/m^2 on days 1 and 15, 5-FU 400 mg/m^2 on days 1-5 and 15-19 of q 28-day cycle DGS regimens: docetaxel 35 mg/m^2, nedaplatin 40 mg/m^2 on day 7 and S-1 80 mg/m^2 on days 1-14 of q 28-day cycle	high dose	Glutamine (n=10) Control (n=10)	Glutamine 8910 mg PO daily Non-glutamine 8910 mg PO daily	26	NA
80	Vadhan-Raj (2010)[29]	Solid cancer	Sarcoma	Doxorubicin-based regimen	Doxorubicin 90 mg/m^2 72 hr and Ifosfamide 10 g/m^2 4 days, Cisplatin 120 mg/m^2 Doxorubicin 90 mg/m^2 and cisplatin 120 mg/m^2	high dose	Palifermin (n=32) Placebo (n=16)	Palifermin 180 mg/kg IV 3 days before chemotherapy Placebo IV 3 days before chemotherapy	3	NA

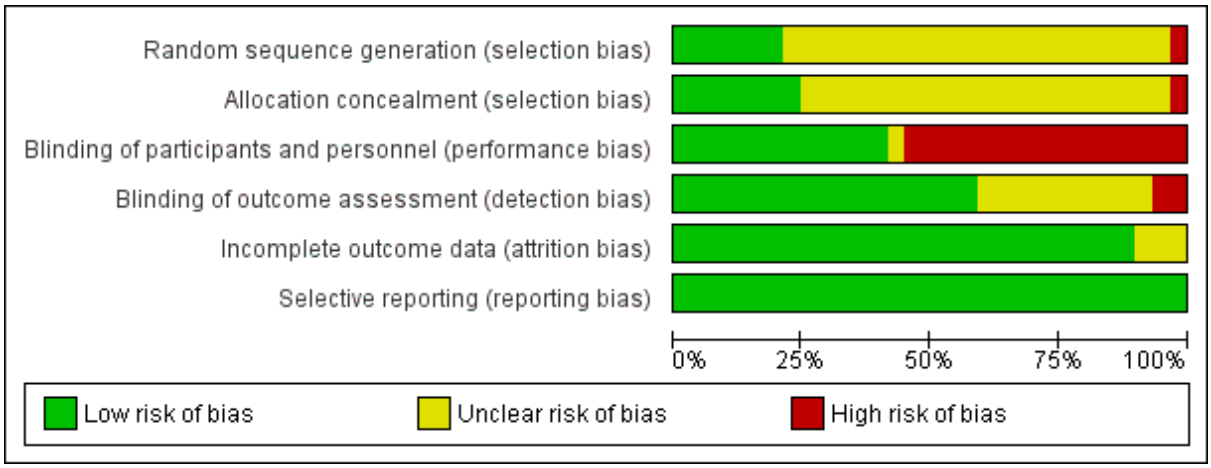
Abbreviations: NA, Not available; HDM regimens, High dose melphalan; ICE regimens, Idarubicin+cytarbine+etoposide or Ifosfamide+carboplastin+etoposide; AFM regimens, Adriamycin (doxorubicin)+5-FU+MTX; DCF regimens, Docetaxel+cisplatin+5-FU; DGS regimens; Docetaxel+nedaplatin+S-1; VIC regimens, High dose etoposide+ifosfamide+carboplastin

Figure S1 Summarized risk of bias of included randomized control trials.



This report followed the recommended approach for assessing risk of bias in twenty-nine randomized control trials included in Cochrane reviews. This tool addresses specific bias domains including methods for generating the random sequence, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incompleteness of outcome data and selective outcome reporting. Each item is adjudicated within each study and the results are represented in a risk of bias table. The adjudication of the risk of bias is achieved by answering pre-specified questions about the methods reported by each study in relation to the risk domain, such that the conclusion is either low risk of bias, unclear risk of bias or high risk of bias.

Figure S2 Risk of bias graph: review authors' judgements (Low, Unclear and High) about each risk of bias item presented as percentages across all included studies.



We found the overall quality of studies to be good, although most of the studies did not report the details about the method of random sequence generation and allocation concealment

Table S3 Pairwise meta-analysis risk ratio (95% CI) for all dichotomous outcome

Comparisons		No. studies	No. of events/ Total No. of Treatment 1	No. of events/ Total No. of Treatment 2	Pairwise meta-analysis risk ratio (95% CI)	Heterogeneity I^2 (variation in RR attributable to heterogeneity)
Any grade mucositis						
AMI vs.	CTL	2	39/63	53/67	0.75 (0.43, 1.30)	49.4%
CHL vs.	CRY	1	34/75	39/75	0.87 (0.63, 1.21)	NA
	CTL	5	79/238	91/237	0.85 (0.56, 1.30)	46.2%
CRY vs.	CTL	9	118/371	226/373	0.52 (0.41, 0.66)	48.4%
GLU vs.	CTL	3	60/98	72/107	0.84 (0.47, 1.47)	77.1%
GMCSF vs.	CTL	2	55/82	44/53	1.11 (0.48, 2.57)	53.4%
MIS vs.	CTL	1	8/9	2/7	3.11 (0.94, 10.27)	NA
PFM vs.	CTL	5	175/305	161/215	0.72 (0.54, 0.96)	76.1%
SUC vs.	CTL	2	19/67	37/66	0.51 (0.12, 2.17)	89.1%
ZIN vs.	CTL	1	25/30	23/30	1.09 (0.84, 1.40)	NA
Mild-moderate mucositis (grade 1-2)						
AMI vs.	CTL	1	29/43	27/47	1.17 (0.85, 1.62)	NA
CHL vs.	CTL	1	30/75	28/75	1.07 (0.72, 1.60)	NA
CRY vs.	CTL	8	86/341	130/343	0.65 (0.43, 0.96)	60.4%
	CHL	1	27/75	30/75	0.90 (0.60, 1.36)	NA
GLU vs.	CTL	3	54/98	59/107	0.95 (0.54, 1,65)	60.9%
GMCSF vs.	CTL	1	25/46	25/44	0.96 (0.66, 1.38)	NA
PFM vs.	CTL	4	114/251	113/188	0.80 (0.67, 0.96)	0.00%
SUC vs.	CTL	2	12/67	24/66	0.41 (0.08, 2.02)	76.2%
ZIN vs.	CTL	1	18/30	15/30	1.20 (0.76, 1.90)	NA
Severe mucositis (grade 3-4)						
AMI vs.	CTL	2	10/63	26/67	0.42 (0.22, 0.78)	0.0%
CHL vs.	CRY	1	7/75	9/75	0.78 (0.31, 1.98)	NA
	CTL	2	11/83	25/83	0.44 (0.23, 0.83)	0.0%
CRY vs.	CTL	5	29/230	75/219	0.38 (0.26, 0.56)	0.0%
GLU vs.	CTL	3	6/98	13/107	0.56 (0.21, 1.47)	0.0%
GMCSF vs.	CTL	2	30/82	19/53	1.02 (0.52, 1.99)	22.1%
PFM vs.	CTL	5	61/305	48/215	0.56 (0.30, 1.05)	53.4%
SUC vs.	CTL	1	4/26	13/26	0.31 (0.12, 0.82)	NA
ZIN vs.	CTL	1	7/30	8/30	0.88 (0.36, 2.11)	NA
Taste disturbance						
CHL vs.	CRY	1	24/75	35/75	0.69 (0.46, 1.03)	NA
	CTL	1	35/75	25/75	1.40 (0.94, 2.09)	NA
CRY vs.	CTL	1	24/75	25/75	0.96 (0.61, 1.52)	NA
GLU vs.	CTL	1	1/10	3/10	0.33 (0.04, 2.69)	NA
PFM vs.	CTL	3	30/114	6/79	2.94 (1.30, 6.66)	0.0%
Gastrointestinal adverse events						
AMI vs.	CTL	1	5/20	10/20	0.50 (0.21, 1.20)	NA
GLU vs.	CTL	1	4/10	4/10	1.00 (0.34, 2.93)	NA
MIS vs.	CTL	1	3/9	4/7	0.58 (0.19, 1.80)	NA
PFM vs.	CTL	4	113/190	97/158	0.98 (0.86, 1.10)	0.0%
SUC vs.	CTL	1	16/41	14/40	1.11 (0.63, 1.97)	NA
Skin reaction adverse events						
PFM vs.	CTL	4	78/273	40/199	1.32 (0.74, 2.34)	56.4%

Abbreviations: NA, Not available; AMI, Amifostine; CHL, Chlorhexidine; CRY, Cryotherapy; GLU, Glutamine; GM-CSF, Granulocyte macrophage colony-stimulating factor; MIS, Misoprostol; PFM, Palifermin; SUC, Sucralfate; ZIN, Zinc sulfate; CTL, Control

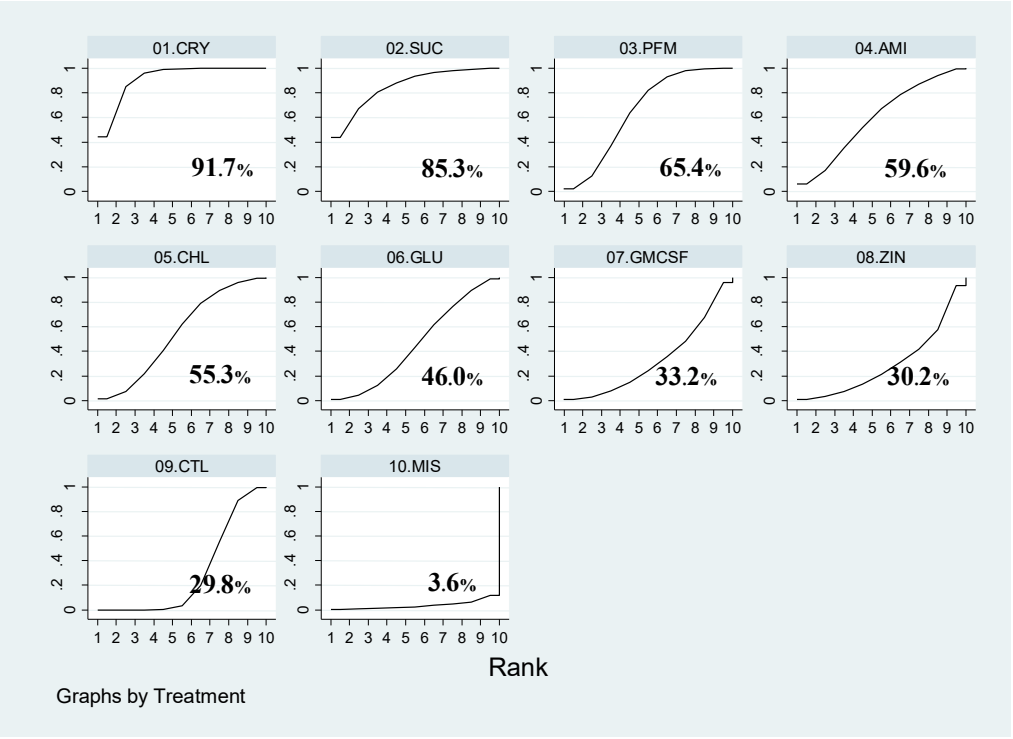
Table S4 Assessment of loop inconsistency in networks

Closed triangular of quadratic loop of evidence	Inconsistency factor (95% confidence interval)	P value	Loop heterogeneity tau2
Any grade mucositis			
CTL-CHL-CRY	0.30 (0.00, 0.87)	0.301	0.000
Mild to moderate mucositis (grade 1-2)			
CTL-CHL-CRY	0.49 (0.00, 2.14)	0.557	0.235
Severe mucositis (grade 3-4)			
CTL-CHL-CRY	0.13 (0.00, 1.34)	0.833	0.000

Table S5 Assessment of global inconsistency in networks using 'design-by-treatment' interaction model

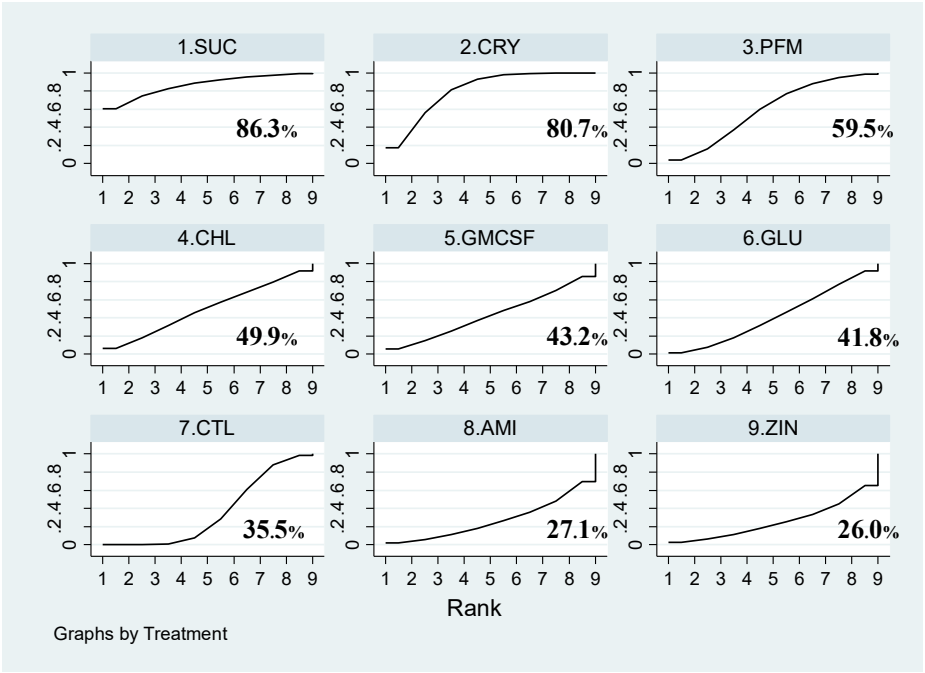
Network outcome	Chi-square	P value for test of global inconsistency
Mucositis any grade	1.28	0.526
Mild to moderate mucositis (grade 1-2)	1.25	0.264
Severe mucositis (grade 3-4)	0.07	0.966
Taste disturbance	6.69	0.009
Gastrointestinal adverse events	0.14	0.708
Skin reaction adverse events	0.91	0.341

Figure S3 SUCRA ranking curve of treatment options for any grade mucositis



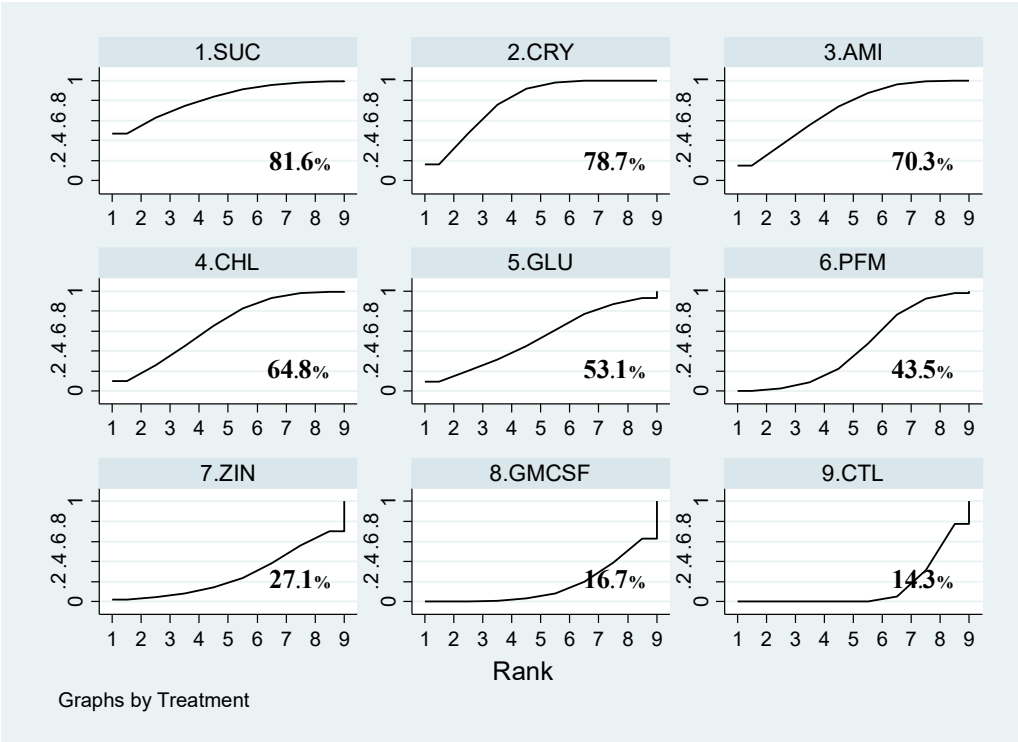
Abbreviations: AMI, Amifostine; CRY, Cryotherapy; CHL, Chlorhexdine; GLU, Glutamine; GM-CSF, Granulocyte-macrophage colony-stimulating factor; MIS, Misoprostol; PFM, Palifermin; SUC, Sucralfate; ZIN, Zinc sulfate; CTL, Control

Figure S4 SUCRA ranking curve of treatment options for mild to moderate mucositis (grade 1-2)



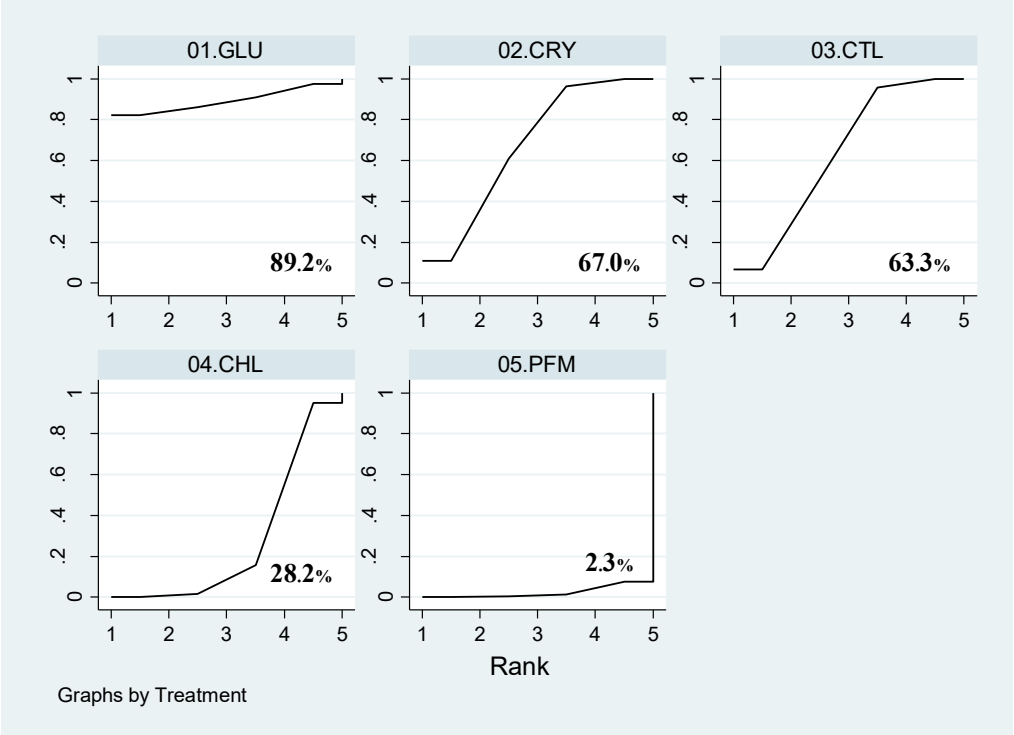
Abbreviations: AMI, Amifostine; CRY, Cryotherapy; CHL, Chlorhexdine; GLU, Glutamine; GM-CSF, Granulocyte-macrophage colony-stimulating factor; PFM, Palifermin; SUC, Sucralfate; ZIN, Zinc sulfate; CTL, Control

Figure S5 SUCRA ranking curve of treatment options for severe mucositis (grade 3-4)



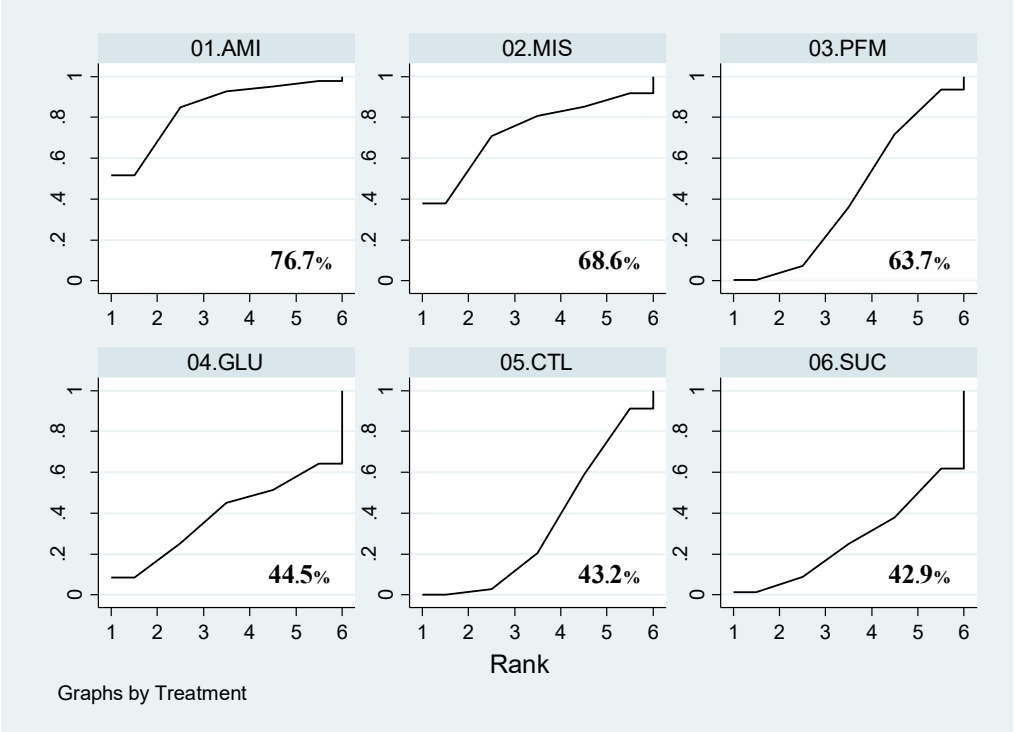
Abbreviations: AMI, Amifostine; CRY, Cryotherapy; CHL, Chlorhexdine; GLU, Glutamine; GM-CSF, Granulocyte-macrophage colony-stimulating factor; PFM, Palifermin; SUC, Sucralfate; ZIN, Zinc sulfate; CTL, Control

eFigure S6 SUCRA ranking curve of taste disturbance



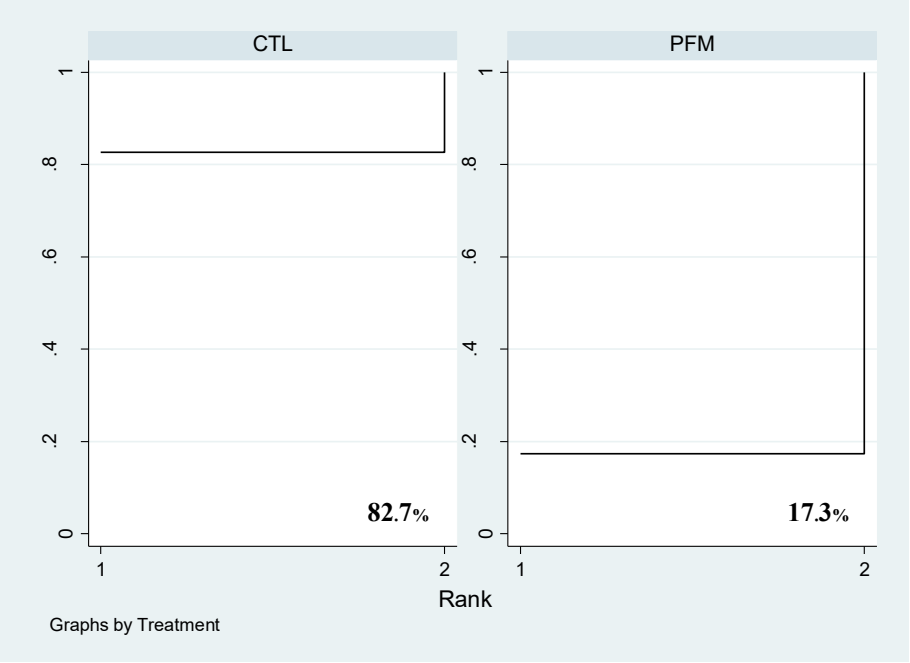
Abbreviations: CRY, Cryotherapy; CHL, Chlorhexdine; GLU, Glutamine; PFM, Palifermin; CTL, Control

Figure S7 SUCRA ranking curve of gastrointestinal adverse events



Abbreviations: AMI, Amifostine; GLU, Glutamine; MIS, Misoprostol; PFM, Palifermin; SUC, Sucralfate; CTL, Control

Figure S8 SUCRA ranking curve of skin reaction adverse events



Abbreviations: PFM, Palifermin; CTL, Control

Table S5 Subgroup analyses for preventing chemotherapy induced oral mucositis in adult cancer patients

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to control before (standard analysis) and after subgroup analyses.

Treatment name	Standard analysis	SUCRA rank	Hematological cancer	SUCRA rank	Solid cancer	SUCRA rank	Mixed cancer	SUCRA rank	5FU regimen	SUCRA rank	N5FU regimen	SUCRA rank	AMET regimen	SUCRA rank	NAMET regimen	SUCRA rank	High dose regimen	SUCRA rank	Usual dose regimen	SUCRA rank
CRY	0.51 (0.38, 0.68)	1	0.63 (0.45, 0.88)	1	0.49 (0.37, 0.65)	1	NA		0.49 (0.32, 0.73)	1	0.46 (0.22, 0.97)	1	0.49 (0.34, 0.71)	1	0.43 (0.17, 1.07)	1	0.63 (0.32,1.23)	3	0.55 (0.40,0.75)	1
SUC	0.52 (0.27, 0.99)	2	NA		0.51 (0.12, 2.17)	2	NA		0.52 (0.24, 1.11)	2	NA		0.52 (0.26, 1.04)	2	NA		0.24 (0.10,0.60)	1	1.06 (0.47,2.38)	5
PFM	0.72 (0.51, 0.99)	3	0.87 (0.59, 1.27)	3	0.58 (0.45, 0.76)	4	NA		0.64 (0.31, 1.34)	3	0.74 (0.47, 1.18)	2	0.67 (0.41, 1.10)	4	0.74 (0.35, 1.58)	3	0.75 (0.52,1.09)	4	0.46 (0.38,1.08)	2
AMI	0.75 (0.43, 1.31)	4	0.86 (0.72, 1.03)	4	0.50 (0.21, 1.20)	3	NA		NA		0.73 (0.38, 1.40)	3	NA		0.71 (0.31, 1.61)	2	0.75 (0.44,1.03)	5	NA	
CHL	0.79 (0.52, 1.20)	5	0.50 (0.13, 2.00)	2	0.82 (0.65, 1.04)	5	1.29 (0.13, 12.82)	2	0.67 (0.30, 1.50)	4	0.90 (0.48, 1.67)	4	0.65 (0.34, 1.22)	3	0.97 (0.43, 2.20)	4	0.45 (0.17,1.21)	2	0.72 (0.43,1.20)	3
GLU	0.87 (0.55, 1.37)	6	NA		0.84 (0.47, 1.47)	6	NA		0.72 (0.36, 1.45)	5	1.14 (0.46, 2.83)	8	0.74 (0.40, 1.38)	5	1.14 (0.37, 3.57)	7	1.14 (0.53,2.47)	9	0.80 (0.46,1.39)	4
GMCSF	1.03 (0.57, 1.84)	7	NA		1.11 (0.48, 2.57)	7	NA		NA		1.06 (0.53, 2.13)	6	NA		1.12 (0.46, 2.72)	8	0.91 (0.50,1.65)	6	1.88 (0.43,7.38)	7
ZIN	1.09 (0.56, 2.12)	8	1.09 (0.84, 1.40)	6	NA		NA		NA		1.09 (0.49, 2.39)	7	NA		1.09 (0.38, 3.11)	6	1.09 (0.58,2.05)	8	NA	
CTL	reference	9	reference	5	reference	8	reference	1	reference	6	reference	5	reference	6	reference	5	reference	7	reference	6
MIS	3.11 (0.81, 11.92)	10	NA		NA		3.11 (0.13, 76.62)	3	NA		3.47 (0.75, 16.19)	9	NA		3.11 (0.65, 14.95)	9	3.11 (0.83,11.73)	10	NA	
Overall inconsistency chi^2 (P value)	1.28 (P=0.526)		0.09 (P=0.770)		1.40 (P=0.496)		0.48 (P=0.488)		0.68 (P=0.409)		0.04 (P=0.836)		0.90 (P=0.637)		0.02 (P=0.876)		0.07 (P=0.796)		0.70 (P=0.401)	
Number of studies	29		6		20		3		13		16		15		14		13		12	

Abbreviations: 5FU regimen, 5FU based regimen; N5FU regimen; Non-5FU based regimen; AMET regimen; Antimetabolite regimen; NAMET regimen. Non-antimetabolite regimen; NA, Not available; AMI, Amifostine; CHL, Chlorhexidine; CRY, Cryotherapy; GLU, Glutamine; GMCSF, Granulocyte macrophage colony-stimulating factor; MIS, Misoprostol; PFM, Palifermin; SUC, Sucralfate; ZIN, Zinc sulfate; CTL, Control

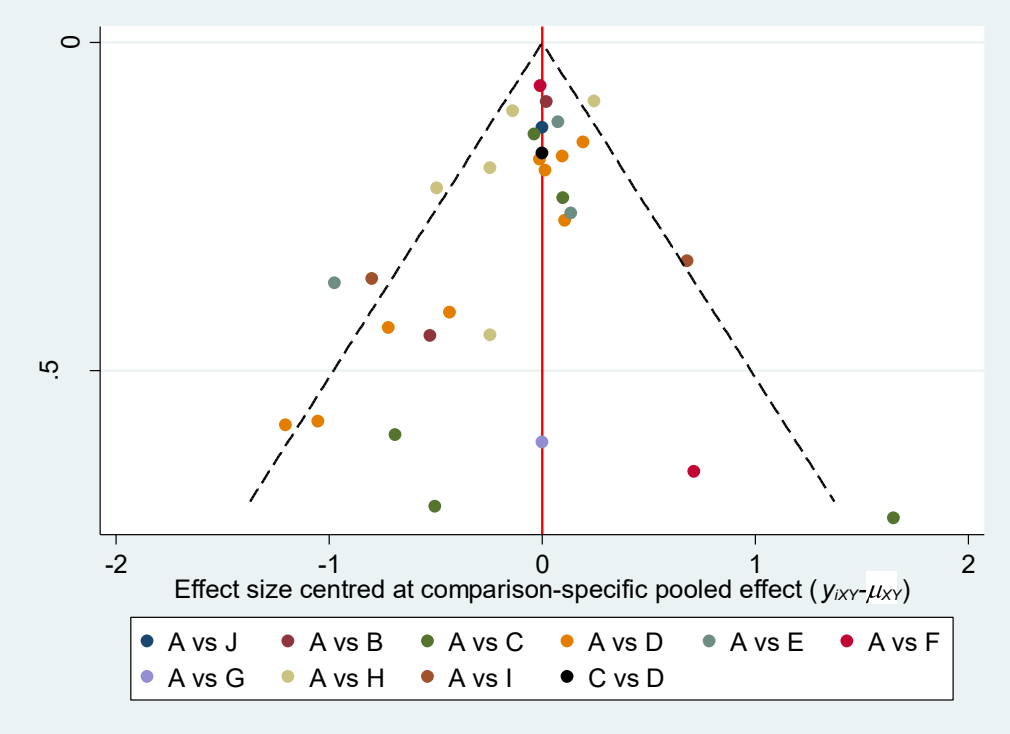
Table S6 Sensitivity analyses for preventing chemotherapy induced oral mucositis in adult cancer patients

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to control before (standard analysis) and after sensitivity analyses.

Treatment name	Standard analysis	SUCRA rank	Excluding studies with non-WHO	SUCRA rank	Excluding studies with inappropriate of Time to measurement mucositis	SUCRA rank	Excluding studies with small sample size (less than 25th Percentile)	SUCRA rank	excluding studies with co-intervention	SUCRA rank	Excluding studies with high risk of bias	SUCRA rank
CRY	0.51 (0.38, 0.68)	1	0.43 (0.26, 0.73)	2	0.51 (0.38, 0.70)	1	0.49 (0.37, 0.65)	1	0.17 (0.05, 0.54)	1	NA	
SUC	0.52 (0.27, 0.99)	2	0.24 (0.12, 0.49)	1	1.06 (0.55, 2.43)	6	0.51 (0.12, 2.17)	2	1.06 (0.55, 2.03)	6	0.51 (0.12, 2.17)	1
PFM	0.72 (0.51, 0.99)	3	0.72 (0.54, 0.96)	3	0.72 (0.54, 0.96)	3	0.72 (0.54, 0.96)	5	0.71 (0.58, 0.88)	4	0.72 (0.54, 0.96)	2
AMI	0.75 (0.43, 1.31)	4	0.75 (0.43, 1.30)	4	0.75 (0.43, 1.30)	4	0.86 (0.72, 1.30)	3	0.75 (0.43, 1.30)	3	NA	
CHL	0.79 (0.52, 1.20)	5	4.31 (1.04, 17.87)	8	0.76 (0.58, 0.98)	2	1.01 (0.60, 1.71)	7	4.31 (1.04, 17.87)	10	NA	
GLU	0.87 (0.55, 1.37)	6	NA		0.67 (0.23, 1.99)	5	0.67 (0.23, 1.99)	4	0.67 (0.23, 1.99)	2	1.09 (0.88, 1.35	6
GMCSF	1.03 (0.57, 1.84)	7	NA		1.11 (0.48, 2.57)	7	0.91 (0.80, 1.04)	6	1.11 (0.48, 2.57)	8	1.11 (0.48, 2.57)	4
ZIN	1.09 (0.56, 2.12)	8	1.09 (0.84, 1.40)	6	1.09 (0.84, 1.40)	9	1.09 (0.84, 1.40)	8	1.09 (0.84, 1.40)	7	1.09 (0.84, 1.40)	5
CTL	reference	9	reference	5	reference	8	reference	9	reference	5	reference	3
MIS	3.11 (0.81, 11.92)	10	3.11 (0.94, 10.27	7	3.11 (0.94, 10.27)	10	NA		3.11 (0.94, 10.27)	9	3.11 (0.94, 10.27)	7
Overall inconsistency chi^2 (P value)	1.28 (P=0.526)		0.08 (P=0.778)		1.52 (P=0.467)		2.45 (P=0.293)		0.03 (P=0.868)		0.06 (P=0.813)	
Number of studies	29		15		23		22		12		13	

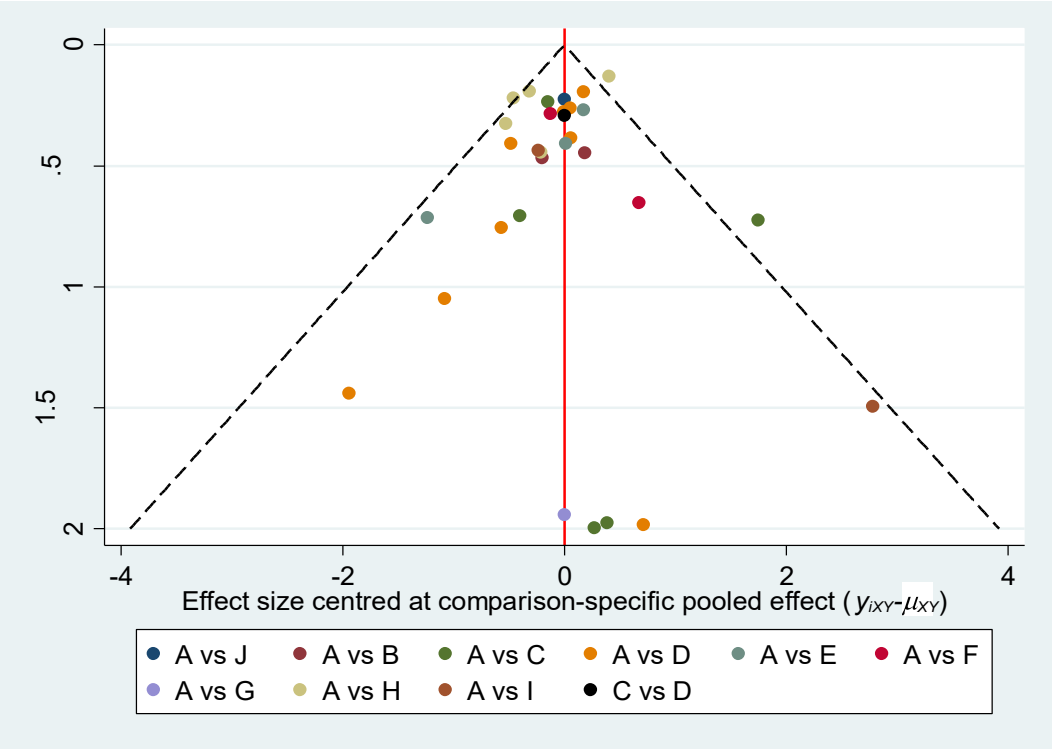
Abbreviations: NA, Not available; AMI, Amifostine; CHL, Chlorhexidine; CRY, Cryotherapy; GLU, Glutamine; GMCSF, Granulocyte macrophage colony-stimulating factor; MIS, Misoprostol; PFM, Palifermin; SUC, Sucralfate; ZIN, Zinc sulfate; CTL, Control

Figure S9 Comparison-adjusted funnel plot for the network of any grade mucositis in all comparison



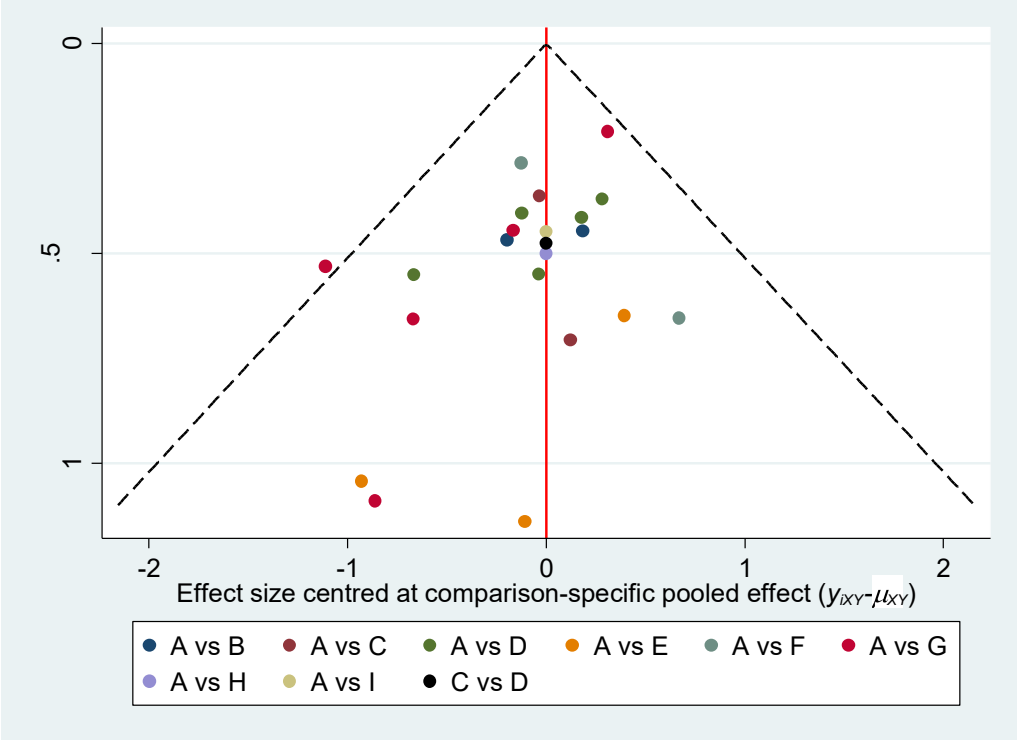
Abbreviations: A=CTL, B=AMI, C=CHL, D=CRY, E=GLU, F=GMCSF, G=MIS, H=PFM, I=SUC, J=ZIN

Figure S10 Comparison-adjusted funnel plot for the network of mild to moderate mucositis (grade 1-2) in all comparisons



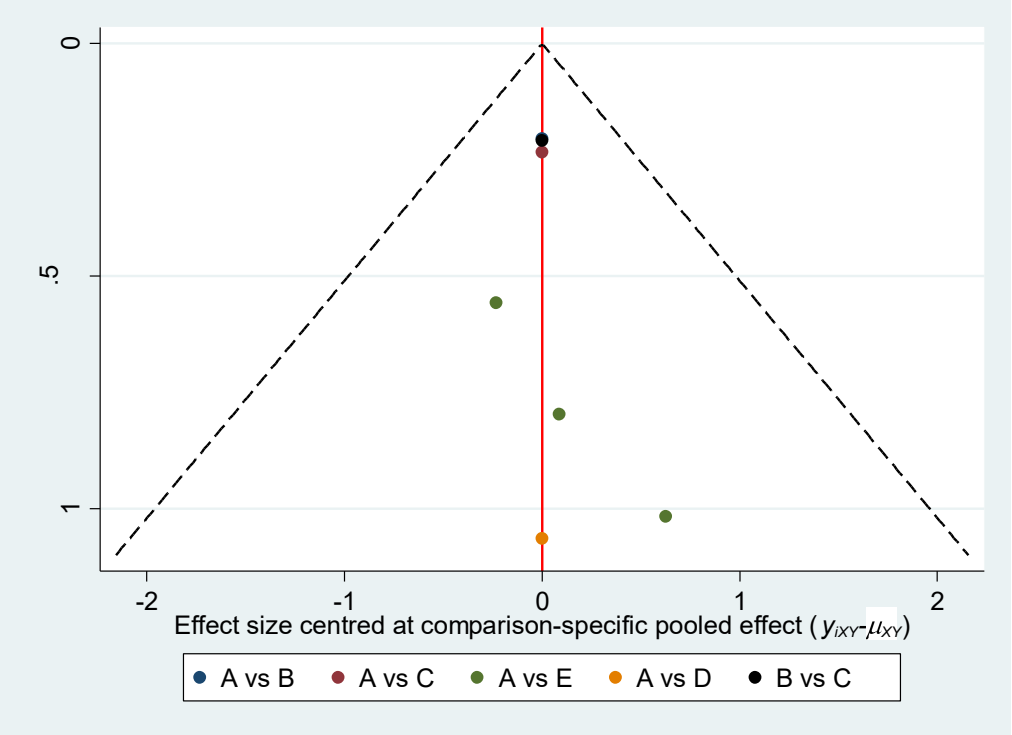
Abbreviations: A=CTL, B=AMI, C=CHL, D=CRY, E=GLU, F=GMCSF, G=PFM, H=SUC, I=ZIN

Figure S11 Comparison-adjusted funnel plot for the network of severe mucositis (grade 3-4) in all comparisons



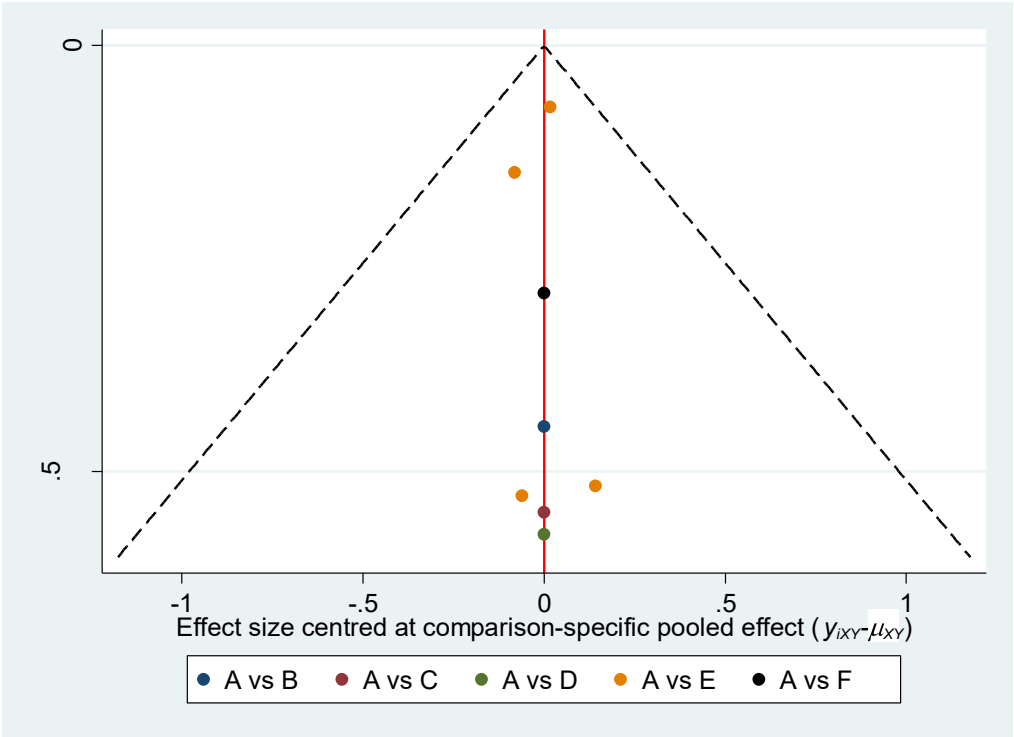
Abbreviations: A=CTL, B=AMI, C=CHL, D=CRY, E=GLU, F=GMCSF, G=PFM, H=SUC, I=ZIN

Figure S12 Comparison-adjusted funnel plot for the network of taste disturbance in all comparisons



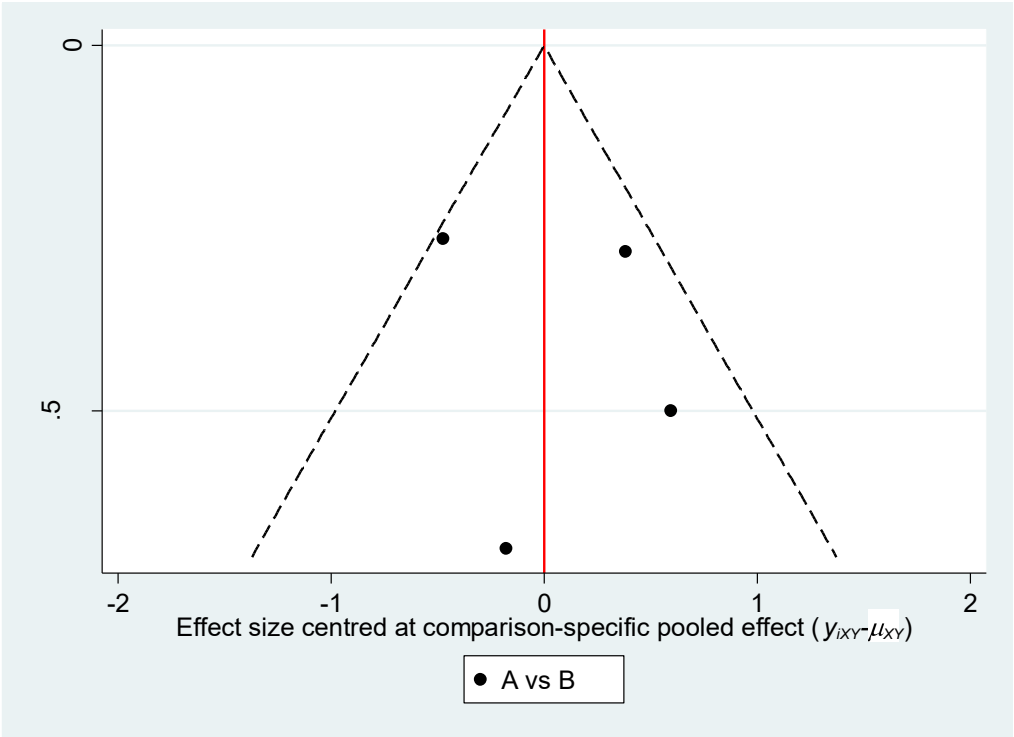
Abbreviations: A=CTL, B=CHL, C=CRY, D=GLU, E=PFM

Figure S13 Comparison-adjusted funnel plot for the network of gastrointestinal adverse events in all comparisons



Abbreviations: A=CTL, B=AMI, C=GLU, D=MIS, E=PFM, F=SUC

Figure S14 Comparison-adjusted funnel plot for the network of skin reaction adverse events in all comparisons



Abbreviations: A=CTL, B=PFM

Table S7 Summary of findings table for intervention vs control for preventing chemotherapy induced oral mucositis in adult cancer patients

Comparison	Direct evidence			Network meta-analysis	
	Effect estimate RR (95% CI)	Heterogeneity I^2	Quality of evidence (GRADE)	Effect estimate RR (95% CI)	Quality of evidence (GRADE)
Any grade mucositis					
AMI vs CTL	0.75 (0.43, 1.30)	49.40%	⊕⊕◯◯ **LOW** [downgraded for imprecision and inconsistency]	0.75 (0.43, 1.31)	⊕⊕⊕◯ **MODERATE** [downgraded for imprecision]
CHL vs CRY	0.87 (0.63, 1.21)	NA	⊕⊕◯◯ **LOW** [downgraded for imprecision and risk of bias]	0.64 (0.40, 1.04)	⊕⊕◯◯ **LOW** [downgraded for imprecision, and risk of bias]
CHL vs CTL	0.85 (0.56, 1.30)	46.20%	⊕⊕◯◯ **LOW** [downgraded for imprecision and inconsistency]	0.79 (0.52, 1.20)	⊕⊕⊕◯ **MODERATE** [downgraded for imprecision]
CRY vs CTL	0.52 (0.41, 0.66)	48.40%	⊕◯◯◯ **VERY LOW** [downgraded for inconsistency, risk of bias and publication bias]	0.51 (0.38, 0.68)	⊕⊕⊕◯ **MODERATE** [downgraded for and risk of bias]
GLU vs CTL	0.84 (0.47, 1.47)	77.10%	⊕◯◯◯ **VERY LOW** [downgraded for imprecision, inconsistency and indirectness]	0.87 (0.55, 1.37)	⊕⊕◯◯ **LOW** [downgraded for imprecision, and indirectness]
GMCSF vs CTL	1.11 (0.48, 2.57)	53.40%	⊕◯◯◯ **VERY LOW** [downgraded for imprecision, inconsistency and indirectness]	1.03 (0.57, 1.84)	⊕⊕◯◯ **LOW** [downgraded for imprecision, and indirectness]
MIS vs CTL	3.11 (0.94, 10.27)	NA	⊕⊕⊕◯ **MODERATE** [downgraded for imprecision]	3.11 (0.81, 11.92)	⊕⊕⊕◯ **MODERATE** [downgraded for imprecision]
PFM vs CTL	0.72 (0.54, 0.96)	76.10%	⊕⊕⊕◯ **MODERATE** [downgraded for inconsistency]	0.72 (0.51, 0.99)	⊕⊕⊕⊕ **HIGH**

Comparison	Direct evidence			Network meta-analysis	
	Effect estimate RR (95% CI)	Heterogeneity I^2	Quality of evidence (GRADE)	Effect estimate RR (95% CI)	Quality of evidence (GRADE)
SUC vs CTL	0.51 (0.12, 2.17)	89.10%	⊕◯◯◯ **VERY LOW** [downgraded for imprecision, inconsistency and indirectness]	0.52 (0.27, 0.99)	⊕⊕⊕◯ **MODERATE** [downgraded for indirectness]
ZIN vs CTL	1.09 (0.84, 1.40)	NA	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]	1.09 (0.56, 2.12)	⊕⊕◯◯ **LOW** [downgraded for imprecision, and indirectness]
Severe mucositis					
AMI vs CTL	0.42 (0.22, 0.78)	0.00%	⊕⊕⊕⊕ **HIGH**	0.42 (0.20, 0.86)	⊕⊕⊕⊕ **HIGH**
CHL vs CRY	0.78 (0.31, 1.98)	NA	⊕⊕◯◯ **LOW** [downgraded for imprecision and risk of bias]	0.82 (0.37, 1.82)	⊕⊕◯◯ **LOW** [downgraded for imprecision and risk of bias]
CHL vs CTL	0.44 (0.23, 0.83)	0.00%	⊕⊕⊕⊕ **HIGH**	0.46 (0.22, 0.95)	⊕⊕⊕⊕ **HIGH**
CRY vs CTL	0.38 (0.26, 0.56)	0.00%	⊕⊕⊕◯ **MODERATE** [downgraded for risk of bias]	0.37 (0.24, 0.58)	⊕⊕⊕◯ **MODERATE** [downgraded for risk of bias]
GLU vs CTL	0.56 (0.21, 1.47)	0.00%	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]	0.54 (0.20, 1.52)	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]
GMCSF vs CTL	1.02 (0.52, 1.09)	22.10%	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]	1.01 (0.52, 1.99)	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]
PFM vs CTL	0.56 (0.30, 1.05)	53.40%	⊕⊕◯◯ **LOW** [downgraded for imprecision and inconsistency]	0.65 (0.38, 1.10)	⊕⊕⊕◯ **MODERATE** [downgraded for imprecision]

Comparison	Direct evidence			Network meta-analysis	
	Effect estimate RR (95% CI)	Heterogeneity I^2	Quality of evidence (GRADE)	Effect estimate RR (95% CI)	Quality of evidence (GRADE)
SUC vs CTL	0.31 (0.12, 0.82)	NA	⊕⊕◯◯ **LOW** [downgraded for inconsistency and indirectness]	0.31 (0.10, 0.93)	⊕⊕⊕◯ **MODERATE** [downgraded for indirectness]
ZIN vs CTL	0.88 (0.36, 2.11)	NA	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]	0.88 (0.32, 2.41)	⊕⊕◯◯ **LOW** [downgraded for imprecision and indirectness]

Abbreviations: NA, not available; AMI, Amifostine; CHL, Chlorhexidine; CRY, Cryotherapy; GLU, Glutamine; GMCSF, Granulocyte macrophage colony-stimulating factor; MIS, Misoprostol; PFM, Palifermin; SUC, sucralfate; ZIN, Zinc sulfate; CTL, Control