

RESEARCH

Open Access



A prospective interventional study of recombinant human interleukin-11 mouthwash in chemotherapy-induced oral mucositis

Hangping Wei , Juan Wei and Xiaofang Dong*

Abstract

Background: This prospective interventional study aimed to evaluate and analyse the efficacy of rhIL-11 mouthwash compared to Kangfuxin fluid in treatment and blank control in prevention of oral mucositis (OM) in patients receiving chemotherapy.

Materials and Methods: In total, 50 patients in the treatment group and 62 patients in the prevention group were included. Subsequently, each group was divided into an experimental group and a control group. In the treatment group, the experimental patients received recombinant human interleukin-11 (rhIL-11) mouthwash, whereas the control group received Kangfuxin fluid. In the prevention group, experimental patients still received rhIL-11 mouthwash based on routine oral care, whereas the control group only received routine oral care. Meanwhile, we observed and recorded the efficacy in the treatment group, and the occurrence and grades of OM in the prevention group.

Results: Through statistical analysis, the results showed that on the seventh day of treatment, the experimental group showed more improvement compared to the control group, and it was statistically significant ($p=0.032$). The average healing time in the experimental group (3.59 ± 1.927 days) was shorter than that in the control group (4.96 ± 2.421 days; $p=0.031$). In the prevention group, we observed the incidence of oral mucositis. No significant differences were found in the occurrence and grades of OM in the experimental and control groups ($p=0.175$).

Conclusion: Our preliminary results indicate that rhIL-11 mouthwash may be a superior option to treat OM, especially in severe cases, compared to Kangfuxin fluid. However, there is no advantage in prevention.

Keywords: Oral mucositis, Recombinant human interleukin-11, Chemotherapy, Treatment, Prevention

Background

Oral mucositis (OM) is a frequent complication of cancer treatment toxicities, occurring in approximately 20–60% of cancer patients receiving conventional antineoplastic therapies [1–3]. Previous research demonstrates that the

pathophysiology of OM is a complex, multistage phenomenon that can result from oral mucosal cell damage caused by free radicals produced by chemotherapy drugs [4]. It involves amplified inflammatory responses, reduced cell proliferation, increased cell senescence/apoptosis, and impaired regenerative potential in both the mucosal and submucosal compartments [1, 5, 6]. Lesions may be erosive or ulcerative and can cause mild to severe pain. Although the condition is self-limiting, it usually leads to a significant decrease in the quality of life

*Correspondence: dongxiaofang2022@163.com

Department of Medical Oncology, Affiliated Dongyang Hospital of Wenzhou Medical University, No. 60 West Wuning Road, Dongyang 322100, Zhejiang, People's Republic of China



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

due to prolonged hospital stay, altered nutritional status, increased risk of infection, and increased prescription of opioids. Moreover, it has a negative impact on the delivery of optimal cancer treatments [5, 6]. For these reasons, it is extremely necessary to treat OM, with the goal of preventing or reducing the severity of lesions and managing the associated symptoms, thereby allowing the continuation of cancer therapy [1, 7, 8].

Recently, a growing number of OM remedies has been suggested in the literature, including basic oral care, antimicrobial agents, anaesthetics and analgesics, laser therapy, and oral cryotherapy [1, 8]. Basic oral care is considered the backbone of supportive care for patients receiving cancer treatment, which could reduce the incidence of moderate to severe OM [4, 8]. At present, mixed medication mouthwashes, which include antibacterial drugs, analgesics, vitamin B12, Xilei powder and hormone therapy, are widely used clinically [9, 10].

The glycoprotein recombinant human interleukin-11 (rhIL-11) is a pleiotropic cytokine that exhibits diverse therapeutic effects [11]. It has been widely used for treating bone marrow suppression caused by chemotherapy and radiotherapy since its discovery in a mouse lung-conditioned medium in 1977 [12]. Recent studies have found that rhIL-11 can directly promote the proliferation and migration of endothelial cells, enhance the activity of other angiogenic factors, and promote healing of the mucosa [7, 13]. Currently, there are a few articles focusing on the value of rhIL-11 in OM, and there is no strong evidence that rhIL-11 can be recommended for the prevention and treatment of OM.

Therefore, we predict that rhIL-11, combined with normal saline, can directly act on oral epithelial cells when used as an oral wash and promote the healing of OM by accelerating the proliferation of oral epithelial cells. The purpose of this research is to prospectively evaluate whether rhIL-11 is more effective, compared to Kangfuxin fluid in treatment and blank control in prevention of oral mucositis (OM) in patients receiving chemotherapy.

Materials and methods

Patients

This prospective interventional study was a randomized control trial conducted from January 2019 to March 2022 on patients receiving chemotherapy in the Department of Oncology at Affiliated Dongyang Hospital of Wenzhou Medical University. Patients older than 18 years; those receiving non-systemic medication; those with previous head and neck radiotherapy time of less than 1 year; those with allergies, oral lesions, or serious illnesses (transaminase more than twice the normal value, renal failure, and infection, among others); or an Eastern Cooperative

Oncology Group performance status score of >2 were excluded. Those who failed to gargle as directed were also excluded. The study rationale was explained to the trial participants, and written informed consent was obtained prior to enrolment. Finally, 50 patients in the treatment group and 62 patients in the prevention group completed the study and were analysed.

Study design

Patients who would receive a systemic chemotherapy were assigned to the prevention group ($n=62$) and were selected using a random distribution into the experimental group ($n=34$) and control group ($n=28$). A random number table was used for random distribution. Patients in the experimental group received rhIL-11 mouthwash (3 mg lyophilised powder of rhIL-11, which was dissolved in distilled water and added to 100 mL normal saline) based on routine oral care (brushing teeth, gargling, and daily oral hygiene monitoring) during chemotherapy, whereas the control group only received routine oral care. Patients were instructed to gargle 10 mL of solution four times per day (morning, lunch, after dinner, and before going to bed) for 2–3 min each time.

Patients with OM of degree II or above after the current round of chemotherapy were assigned to the treatment group ($n=50$) and were selected using a random distribution into the experimental ($n=27$) and control groups ($n=23$). A random number table was also used for random distribution. Patients in the experimental group received rhIL-11 mouthwash (3 mg lyophilised powder of rhIL-11, which was dissolved in distilled water and added to 100 mL normal saline) compared to Kangfuxin fluid (its main chemical component is *Periplaneta americana* extract, a liquid drug that can significantly promote angiogenesis and growth of granulation tissue, accelerate the shedding of necrotic tissue, and rapidly repair ulcers and wounds; it has been used widely used in clinic and has been shown the effect in the treatment of oral mucositis [14–17]) in the control group in those patients with OM after chemotherapy. Instructions for the two mouthwashes were the same as those for the prevention group. The ulcer was also smeared with a cotton ball, and treatment continued until the ulcer healed. Local treatment helps to accelerate the healing of oral mucositis.

Evaluation

The scale proposed by the World Health Organization classifies OM in five degrees: Grade 0, incipient and asymptomatic lesions; Grade I, slight oral soreness and erythema; Grade II, oral erythema, small ulcers, solid diet tolerated; Grade III, large oral ulcers, liquid diet only; Grade IV, severe ulcers, bleeding, pain, and oral

alimentation impossible. On this scale, Grades III and IV correspond to severe OM. Oral mucositis healing refers to OM of degree 0, that is, the elimination of ulcers and reduction of pain.

Every morning before administration, medication record, curative effect observation, and effect evaluation were made by specialised staff (a trained nurse blinded to the intervention), and the injury site, ulcer area size, ulcer number, and pain degree were evaluated according to the OM grading standards. The treatment group was followed up to the basic healing of oral mucositis, and the preventive group was followed up to the beginning of the next cycle of chemotherapy.

Ethics approval and consent to participate

The study has been approved by the ethics committee of our hospital.

Statistical analysis

The clinical data were described using medians, frequencies, and percentages. SPSS 22.0 software was used for statistical analysis. The measurement data were analysed using the T-test, and counting data were analysed using the chi-square test or wilcoxon test. A p value of <0.05 was considered statistically significant.

Results

Efficacy of rhIL-11 in the treatment group

Patient demographics and baseline characteristics

In the experimental and control groups, the ratio of males to females was 1.17:1, and the median age was 63.6 years (range, 26–81 years). The patients included were mostly undergoing treatment for thoracic and abdominal tumours, such as lung and intestinal cancer. The majority comprised stage IV patients who had received chemotherapy previously. There was no significant difference in general characteristics among the groups ($p > 0.05$) (Table 1).

Comparison of the efficacy of experimental and control groups

OM in this study was predominantly classified as stage II, accounting for 76% of all cases, and the severity of OM before treatment in the two groups was not statistically significant ($p = 0.696$) (Table 2). On the second and fourth days of treatment, there was no significant improvement in the two groups. ($p = 0.793, 0.069$) (Table 2). However, on the seventh day of treatment, the experimental group showed more improvement compared to the control group, and it was statistically significant ($p = 0.032$) (Table 2). The average healing time was 3.59 ± 1.927 days in the experimental group and 4.96 ± 2.421 days in the control group ($p = 0.031$) (Table 3). As a result, among

Table 1 Patient characteristics in the treatment group

Characteristics	Experimental group n (%)	Control group n (%)	p value
Age			$p = 0.643$
≥ 65 years	17(63)	13(56.5)	
< 65 years	10(37)	10(43.5)	
Gender			$p = 0.811$
Male	15(55.6)	12(52.2)	
Female	12(44.4)	11(47.8)	
Tumour site			$p = 0.817$
Head and neck	3(11.1)	2(8.7)	
Chest	10(37.0)	10(43.5)	
Abdomen	11(40.7)	10(43.5)	
Other	3(11.1)	1(4.3)	
Disease stage			$p = 0.167$
II	1(3.7)	0(0)	
III	7(25.9)	2(8.7)	
IV	19(70.4)	21(91.3)	
PS			$p = 0.403$
0	0(0)	1(4.3)	
1	20(74.1)	14(60.9)	
2	7(25.9)	8(34.8)	
Chemotherapeutic drugs			$p = 0.475$
Platinum ± 5-FU	9(33.3)	5(21.7)	
Paclitaxel	8(29.6)	11(47.8)	
EN Huan	2(7.4)	2(8.7)	
Target	6(22.2)	2(8.7)	
Other	2(7.4)	3(13)	
Previous chemotherapy			$p = 0.114$
Yes	20(74.1)	21(91.3)	
No	7(25.9)	2(8.7)	
Previous radiotherapy			$p = 0.857$
Yes	4(14.8)	3(13)	
No	23(85.2)	20(87)	

all the treatment patients, the efficacy was higher in the experimental group than in the control group. The average healing time of the experimental group was shorter than that of the control group.

Efficacy of rhIL-11 in the prevention group

Patient demographics and baseline characteristics

The ratio of males to females was 1.21:1, and the median age was 62.6 years. Most of them (98.3%) were thoracic or abdominal tumors and were in the advanced stage of the disease. There was no difference in gender, age, disease location, chemotherapeutic drugs and disease condition between the two groups (Table 4, $p > 0.05$).

Table 2 Oral mucositis in the experimental and control groups on the second, fourth, and seventh day of treatment within the treatment group (the wilcoxon test was adopted)

Classification of oral mucositis	Before treatment		D2		D4		D7	
	Experimental group (n)	Control group (n)	Experimental group (n)	Control group (n)	Experimental group (n)	Control group (n)	Experimental group (n)	Control group (n)
0	0	0	2	0	15	7	24	15
I	0	0	1	4	8	10	3	4
II	21	17	19	13	3	2	0	1
III	4	3	5	5	1	4	0	3
IV	2	3	0	1	0	0	0	0
P value	$p = 0.696$		$p = 0.793$		$p = 0.069$		$p = 0.032$	

Table 3 Healing rate of the experimental and control groups within the treatment group

Treatment	No. of patients	Healing time (days)	T value	p value
Experimental group	27	3.59 ± 1.927	2.218	0.031
Control group	23	4.96 ± 2.421		

Table 4 Patient characteristics in the prevention group

Characteristics	Experimental group n (%)	Control group n (%)	p value
Age			$p = 0.368$
≥ 65 years	16(47.1)	10(35.7)	
< 65 years	18(52.9)	18(64.3)	
Gender			$p = 0.368$
Male	16(47.1)	10(35.7)	
Female	18(52.9)	18(64.3)	
Tumour site			$p = 0.311$
Head and neck	0(0)	1(3.6)	
Chest	15(44.1)	17(60.7)	
Abdomen	18(52.9)	9(32.1)	
Other	1(2.9)	1(3.6)	
PS			$p = 0.990$
0	4(11.8)	3(10.7)	
1	7(20.6)	6(21.4)	
2	23(67.6)	19(67.9)	
Chemotherapeutic drugs			$p = 0.857$
Platinum ± 5-FU	15(44.1)	16(57.1)	
Paclitaxel	10(29.4)	7(25)	
EN Huan	1(2.9)	1(3.6)	
Target	6(17.6)	3(10.7)	
Other	2(5.9)	1(3.6)	

Comparison of the experimental and control groups in the prevention group

The OM incidence rates were 11.8% and 25% in the experimental and control groups, respectively (Chi square test was used according to the incidence of OM, $p = 0.175$). In order to further analyse the severity of oral mucositis, the wilcoxon test was used ($p = 0.16$ Table 5). As a result, the occurrence and grades of OM in the experimental and control group showed no significant differences.

Discussion

OM is a common adverse effect of anticancer therapy, typically occurring within 1 week of undergoing chemotherapy. In addition to causing discomfort and pain, OM may affect the quality of life of cancer patients by prolonging hospitalisation and increasing financial expenses. Therefore, it is increasingly important to understand the mechanisms of OM lesions to provide effective prevention and treatment. Clinically, different chemotherapy regimens can cause different degrees of OM. Current research indicates that antimetabolites, which affect DNA synthesis, are associated with 40–60% of OM incidences, with the use of 5-FU and platinum derivatives (cisplatin and oxaliplatin) resulting in more severe OM [18–20]. Although no evidence for a cumulative effect with repeated chemotherapy cycles has been found, considering the use of the same drugs and the sensitivity of the body, it remains necessary to consider using prophylactic drugs for patients with a history of severe OM [21].

Prevention and treatment of OM is necessary to relieve symptoms, accelerate tissue repair, and promote successful chemotherapy. Many treatments, including basic oral care, antimicrobial agents, and natural medicine using substances such as honey, aim to reduce both the

Table 5 OM incidence rate in the experimental and control groups within the prevention group

Prevention	No. of patients	Classification of oral mucositis					Incidence rate
		0	I	II	III	IV	
Experimental group	34	30(88.2%)	3(8.8%)	1(3%)	0(0%)	0(0%)	11.8%
Control group	28	21(75%)	4(14.3%)	2(7.1%)	1(3.6%)	0(0%)	25.0%
P value		$p = 0.16$ (the wilcoxon test was adopted)					$p = 0.175$

incidence and severity of OM [2, 10, 22, 23]. However, these treatments have their own limitations, including cariogenic effects and adherence to teeth following prolonged ingestion of honey [24]. Previous studies suggest that preventive oral spray can delay the occurrence of OM [9, 14]. Some studies showed that laser therapy and cryotherapy reduced the incidence of severe oral mucositis and reduced pain [14]. Though much research has been done on the role of cytokines (mostly GM-CSF and G-CSF) in oral mucositis, results have been inconsistent [25–27].

RhIL-11 is a pleiotropic cytokine which stimulates myeloid, erythroid, and megakaryocyte differentiation, modulates macrophage and T cell inflammatory functions, and protects the function of the mucosal epithelium [11, 12, 21]. It is also known to promote mitosis and proliferation by inhibiting apoptosis and improving the mitotic activity of small intestinal villi stem progenitor cells, and it has a good protective effect on gastrointestinal tract injuries caused by radiotherapy and chemotherapy. The oral mucosa is similar to the intestinal mucosa in terms of continuous self-renewal and rapid proliferation [28]. Thus, rhIL-11 has the potential to reduce chemotherapy-related OM. Moreover, epithelial cells contain the colony-stimulating factor receptor, which is bound by rhIL-11 to stimulate the migration and proliferation of epithelial cells and promote the growth of keratinocytes and fibroblasts [7]. Thus, rhIL-11 may promote the proliferation and maturation of endothelial cells to accelerate the healing of OM caused by chemotherapy.

Our data were collected prospectively, eliminating potential recall bias and increasing credibility compared to a retrospective design. Prior research in an animal model found that rhIL-11 favourably modulates acute radiation-induced mucositis by attenuating pro-inflammatory cytokine expression [29]. Unfortunately, there is no relevant prospective research to support these findings. In the present study, the results showed that rhIL-11 therapy significantly reduced the recovery time of OM (3.59 ± 1.927 days vs. 4.96 ± 2.421 days; $p = 0.031$) and improved the efficiency of treatments compared with Kangfuxin fluid, supporting the ability of rhIL-11 to accelerate recovery from OM. In addition, this study demonstrates there was no significant difference in the

efficacy of rhIL-11 or Kangfuxin fluid in the first few days, but after 1 week of treatment, the efficacy of rhIL-11 in OM was better than Kangfuxin fluid. This further indicates that rhIL-11 may shorten the treatment time of severe OM. This study also found that no advantage of rhIL-11 treatment in preventing OM, both the incidence and degree of oral mucositis. At present, many studies have shown that low-intensity laser therapy, honey and probiotics play a role in prevention.

However, there are few a samples after radiotherapy in this study. According to previous studies, the incidence of OM related to radiotherapy of head and neck tumours is high and the treatment time is long, which need to be further investigated. Moreover, the severity of chemotherapy-induced OM in this study is low, which may offset the results. In addition, the main limitation of our experiment is the small sample size of this study; therefore, further high-quality, large-scale studies are needed to verify our conclusions.

Conclusions

In summary, our preliminary results indicate that recombinant human interleukin-11 mouthwash may be a superior option to treat OM, especially in severe cases, compared to Kangfuxin fluid. Considering the cost of rhIL-11, recombinant human interleukin-11 mouthwash is not recommended for preventing OM in patients receiving chemotherapy.

Abbreviations

OM: Oral mucositis; rhIL-11: Recombinant human interleukin-11; PS: Performance status.

Acknowledgements

The authors would like to acknowledge the following people, who have made the completion of the present study possible: department colleagues, such as Yifang Lu and Xiaoyan Hu, for their assistance, and the patients, for their support.

Author contributions

DXF and WHP were responsible for conceiving and designing the study. WHP and WJ carried out the acquisition and analysis of the data. WHP drafted the manuscript. WHP and WJ revised and edited the manuscript. All authors contributed significantly, read and approved the final manuscript.

Funding

This study was supported by a grant from the natural science foundation of Zhejiang Province (LGF19H160003).

Availability of data and materials

All data generated or analysed during this study are included in this published article. And the primary data could be achieved from the corresponding author.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All the stages of the research were carried out under the Declaration of Helsinki. All participants volunteered for the study, were informed of its scope, provided written consent. This research protocol was approved by Dongyang Hospital Affiliated to Wenzhou Medical University institutional research committee, registration number: 2019-YX-011. All participants signed an informed consent form before data gathering.

Consent for publication

Not applicable.

Conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Received: 8 April 2022 Accepted: 21 July 2022

Published online: 29 July 2022

References

- Chen C, Zhang Q, Yu W, Chang B, Le AD. Oral mucositis: an update on innate immunity and new interventional targets. *J Dent Res*. 2020;99(10):1122–30. <https://doi.org/10.1177/0022034520925421>.
- Hong BY, Sobue T, Choquette L, Dupuy AK, Thompson A, Burleson JA. Chemotherapy-induced oral mucositis is associated with detrimental bacterial dysbiosis. *Microbiome*. 2019;7(1):66. <https://doi.org/10.1186/s40168-019-0679-5>.
- Potten CS. Protection of the small intestinal clonogenic stem cells from radiation-induced damage by pretreatment with interleukin 11 also increases murine survival time. *Stem Cell*. 1996;14(4):452–9. <https://doi.org/10.1002/stem.140452>.
- Sonis ST, Peterson RL, Edwards LJ, Lucey CA, Mason WL, et al. Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncol*. 2000;36(4):373–81. [https://doi.org/10.1016/s1368-8375\(00\)00012-9](https://doi.org/10.1016/s1368-8375(00)00012-9).
- Cinausero M, Aprile G, Ermacora P, Basile D, Vitale MG, Fanotto V, et al. New frontiers in the pathobiology and treatment of cancer regimen-related mucosal injury. *Front Pharmacol*. 2017;8(8):354.
- Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. *Front Oncol*. 2017;22(7):89. <https://doi.org/10.3389/fonc.2017.00089>.
- López-González Á, García-Quintanilla M, Guerrero-Agenjo CM, Tenderso JL, Guisado-Requena LM, Rabanales-Sotos J. Efficacy of cryotherapy in the prevention of oral mucositis in adult patients with chemotherapy. *Int J Environ Res Public Health*. 2021;18(3):994. <https://doi.org/10.3390/ijerph18030994>.
- Yu YT, Deng JL, Jin XR, Zhang ZZ, Zhang XH, Zhou X. Effects of 9 oral care solutions on the prevention of oral mucositis: a network meta-analysis of randomized controlled trials. *Medicine*. 2020;99(16):e19661. <https://doi.org/10.1097/MD.00000000000019661>.
- Kusiak A, Jereczek-Fossa BA, Cichońska D, Alterio D. Oncological-therapy related oral mucositis as an interdisciplinary problem—literature review. *Int J Environ Res Public Health*. 2020;17(7):2464. <https://doi.org/10.3390/ijerph17072464>.
- Mubarak S, Pani SC, Alseraihy A, Abed H, Alkhayal Z. The efficacy of two different oral hygiene regimens on the incidence and severity of oral mucositis in pediatric patients receiving hematopoietic stem cell transplantation: a prospective interventional study. *Spec Care Dentist*. 2020;40(6):566–73. <https://doi.org/10.1111/scd.12525> (Epub 2020 Sep 21).
- Wu S, Zhang Y, Xu L, Dai Y, Teng Y, Ma S, et al. Multicenter, randomized study of genetically modified recombinant Human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in cancer patients receiving chemotherapy. *Support Care Cancer*. 2012;20(8):1875–84. <https://doi.org/10.1007/s00520-011-1290-x>.
- Liu Z, Wang Y, Yan J, Liu J, Chen B, Zhang L, et al. Efficacy and safety of recombinant human interleukin-11 in the treatment of acute leukaemia patients with chemotherapy-induced thrombocytopenia: a systematic review and meta-analysis. *J Eval Clin Pract*. 2020;26(1):262–71. <https://doi.org/10.1111/jep.13152>.
- Antin J, Lee SJ, Neuberg D, Alyea E, Soiffer RJ, Sonis S, et al. A phase I/II double-blind, placebo-controlled study of recombinant human interleukin-11 for mucositis and acute GVHD prevention in allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2002;29(5):373–7. <https://doi.org/10.1038/sj.bmt.1703394>.
- Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, Filipauskas A. Prevention and treatment of chemotherapy and radiotherapy induced oral mucositis. *Medicina*. 2019;55(2):25. <https://doi.org/10.3390/medicina55020025>.
- Tian M, Dong J, Wang Z, Shuliang Lu, Gong F. The effects and mechanism of Kangfuxin on improving healing quality and preventing recurrence of gastric ulcer. *Biomed Pharmacother*. 2021;138:111513. <https://doi.org/10.1016/j.biopha.2021.111513>.
- Wei J, Jie W, 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;22(11):617392. <https://doi.org/10.3389/fonc.2021.617392>.
- Liu Z, Dou H. Effects of four types of watermelon frost combination medications for the treatment of oral ulcers: a network meta-analysis. *J Healthc Eng*. 2022;2022:2712403. <https://doi.org/10.1155/2022/2712403>.
- Bano N, Najam R, Qazi F, Mateen A. Gastrointestinal adverse effects in advanced colorectal carcinoma patients treated with different schedules of FOLFOX. *Asian Pac J Cancer Prev*. 2014;15(19):8089–93. <https://doi.org/10.7314/apjcp>.
- Chibaudel B, Lacave R, Lefevre M, Soussan P, Antoine M, Périé S, et al. Induction therapy with cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (ETPF) in patients with resectable nonmetastatic stage III or IV squamous cell carcinoma of the oropharynx. A GERCOR phase II ECHO-07 study. *Cancer Med*. 2015;4(5):721–31. <https://doi.org/10.1002/cam4.408>.
- Curra M, Soares Junior LAV, Martins MD, Santos PS. Chemotherapy protocols and incidence of oral mucositis. An integrative review. *Einstein*. 2018;16(1):eRW4007. <https://doi.org/10.1590/s1679-45082018rw4007>.
- Leng SX, Elias JA. Interleukin-11. *Int J Biochem Cell Biol*. 1994;15(1–2):45–9. <https://doi.org/10.3109/10428199409051676>.
- Boerma M, Wang J, Burnett AF, Santin AD, Roman JJ, Hauer-Jensen M. Local administration of interleukin-11 ameliorates intestinal radiation injury in rats. *Cancer Res*. 2007;67(19):9501–6. <https://doi.org/10.1158/0008-5472>.
- Yang C, Gong G, Jin E, Han X, Zhuo Y, Yang S, et al. Topical application of honey in the management of chemo/radiotherapy-induced oral mucositis: a systematic review and network meta-analysis. *Int J Nurs Stud*. 2019;89:80–7. <https://doi.org/10.1016/j.ijnurstu>.
- Yarom N, Hovan A, Bossi P, Ariyawardana A, Jensen SB, Gobbo M, et al. Systematic review of natural and miscellaneous agents, for the management of oral mucositis in cancer patients and clinical practice guidelines—part 2: honey, herbal compounds, saliva stimulants, probiotics, and miscellaneous agents. *Support Care Cancer*. 2020;28(5):2457–72. <https://doi.org/10.1007/s00520-019-05256-4>.
- Dodd MJ, Cho MH, Cooper BA, MacPhail L, Miaszkowski C. A randomized clinical trial of granulocyte macrophage colony stimulating factor mouthwash for oral mucositis in head and neck cancer. *Eur J Oncol Nurs*. 2022;56:102093. <https://doi.org/10.1016/j.ejon.2022.102093>.
- Logan RM, Al-Azri AR, Bossi P, Stringer AM, Joy JK, Soga Y, et al. Systematic review of growth factors and cytokines for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*. 2020;28(5):2485–98. <https://doi.org/10.1007/s00520-019-05170-9>.
- Ya-Ting Yu, Deng J-L, Jin X-R, Zhang Z-Z, Zhang X-H, Zhou X. Effects of 9 oral care solutions on the prevention of oral mucositis: a network

meta-analysis of randomized controlled trials. *Medicine*. 2020;99(16):e19661. <https://doi.org/10.1097/MD.00000000000019661>.

28. Nicolatou-Galitis O, Bossi P, Orlandi E, Bensadoun RJ. The role of benzydamine in prevention and treatment of chemoradiotherapy-induced mucositis. *Support Care Cancer*. 2021;29(10):5701–9. <https://doi.org/10.1007/s00520-021-06048-5>.
29. Villa A, Sonis ST. Mucositis: pathobiology and management. *Curr Opin Oncol*. 2015;27(3):159–64. <https://doi.org/10.1097/CCO.00000000000000180>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

