

ORIGINAL ARTICLE

Zinc-L-carnosine mouthwash in oral mucositis patients: a single-blind, randomized, controlled trial

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ABSTRACT

BACKGROUND: The study aims to evaluate the therapeutic efficacy of a zinc-L-carnosine mouthwash (Hepilor®) in the treatment of oral mucositis in cancer patients treated by radiation and/or chemotherapy.

METHODS: The study included 42 patients, randomly allocated to the Test Group (N.=22) or to the Control Group (N.=20), referred to University Hospital of Marche Region, Ancona, Italy. The oral mucositis and its adverse manifestation were evaluated by the National Cancer Institute Common Toxicity Criteria scales. Hepilor® (4 rinses/day with 10 mL of pure product, for 3 minutes, for 30 days) was administered to the Test Group. To Control Group was prescribed 2 daily rinses with water and sodium bicarbonate, for one minute, for 30 days. Each evaluation was performed at the time of patient enrolment (t0), after 15 days (t1) and 30 days (t2) from the beginning of the treatment.

RESULTS: In Test Group, the moderate and severe mucositis (t0: 61%), its related symptoms (t0: 5-59%), and the use of analgesics (t0: 63%) were significantly reduced, both at t1 (28%; 0-14%; 14%; P<0.0001) and at t2 (14%; 0-5%; 0%; P<0.0001). In Control Group, the patients with severe mucositis (t0: 10%) and oral symptoms (t0: 0-56%) notably increased, especially at t2 (35%; 10-75%), as well as analgesic drugs intake (t0: 35%; t2: 75%; P<0.0001).

CONCLUSIONS: These data confirm the clinical efficacy of Hepilor® in the treatment of oral mucositis in cancer patients. Together with an adequate oral hygiene, it reduced the severity of oral mucositis and its related symptoms, improving patients' quality of life.

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KEY WORDS: Stomatitis; Polaprezinc; Mouthwashes; Neoadjuvant therapy; Dysgeusia; Xerostomia.

Introduction

Oral mucositis (OM) is a painful inflammatory and/or ulcerative condition of the oral mucosa. It represents the most frequent complication of cancer therapy which affects up to 80%

of patients treated by radiation therapy (RT) or high-dose chemotherapy (CT).¹⁻⁵

The main oral symptoms and manifestations are dysgeusia, dysphagia, xerostomia, and difficulty swallowing.⁶ Currently, OM pathophysiology identifies four stages of the disease: 1) initial

damage to the oral mucosa due to the systemic cytotoxic effect of CT and/or RT, leading to reactive oxygen species (ROS) release and basal and suprabasal epithelial cell death. This primary damage leads to the second stage of mucositis: 2) damage amplification due to host inflammatory response. In particular, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is the main transcriptional mediator modulating over 200 genes associated with pro-inflammatory cytokines, cell adhesion molecules, and cytokine modulators. Usually, in this stage, patients exhibit few symptoms, and the mucosa does not reveal any macroscopic lesions. Clinical manifestations of mucositis are appreciable in the third stage of OM, called the ulceration phase (3), where ulceration is the result of the epithelial apoptosis and necrosis. The presence of submucosal detachments promotes the invasion of the underlying tissues by several microorganisms, leading to a mononuclear inflammatory response and promoting the release of pro-inflammatory cytokines; thus increasing the expression of pro-apoptotic mediators and tissue damage. The last OM stage (4) is self-resolution of mucositis, which occurs during the end of anticancer treatment.^{3, 7-9} Despite the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines,¹⁰ current treatment strategies, including anti-inflammatory agents, cryotherapy, photobiomodulation (PBM), and patient-controlled analgesics, are not effective in preventing and treating OM.¹¹ Basic oral care (BOC) is considered the cornerstone of chemoradiation therapy (CRT)-induced OM management. BOC includes the professional oral care, patient education, tooth brushing with a soft toothbrush and its regular replacement, and the use of bland rinses and moisturizers such as sodium bicarbonate mouthwash, mixed medication mouthwash, and calcium phosphate mouthwash. The application of honey, povidone, aloe vera and sucralfate shows unreliable evidence; only the cryotherapy (ice chips) seems to provide some benefits in the OM prevention;¹²⁻¹⁵ however, there is no strong evidence of its efficacy.^{8, 13} To date, OM medical management is based on palliative therapies, such as topical or systemic

analgesics and the application of barrier agents to cover the injured mucosa. Lidocaine, antifungal agents, topical steroids, or antibiotics represent the most widely adopted therapies.¹⁶⁻¹⁸ However, none of these studies have shown reproducible protective effects.¹⁹ Therefore, a comprehensive guideline for OM prevention and protocols for dental evaluation and treatment of oncological patients are necessary.

Recently, it has been demonstrated the therapeutic efficacy of PBM in reducing the incidence, severity and duration of OM in head and neck cancer (NHC) treated by CRT.²⁰⁻²³ Moreover, small molecules targeting oxidative stress, innate immune response, NF- κ B and pro-inflammatory cytokine production are being developed.²⁴ The Zinc L-carnosine (ZL-c) is a chelate compound of zinc and L-carnosine, used since the 2000s for the *Helicobacter pylori* eradication, gastrointestinal mucosal injury, and ulcerative colitis.²⁵ Japanese studies have reported promising results in HNC and OM patients undergoing to RT and / or CT.^{25, 26} Indeed, it has been reported that ZL-c has antioxidant properties, inhibiting ROS release and tumor necrosis factor (TNF)- α cellular signaling.^{27, 28}

Therefore, the present study investigated the clinical efficacy of a ZL-c-based mouthwash (Hepilor®) in the prevention of OM and its related symptoms, compared with a standard solution of water and sodium bicarbonate, in a cohort of oncological patients affected by OM.

Materials and methods

The single-center, single-blind, randomized, parallel-group, clinical trial was conducted according to the Helsinki Declaration²⁹ and to the CONSORT Statement.³⁰ Informed consent was obtained from all patients who accepted to kept unaware of the treatment they are receiving. The study included adult patients (age ≥ 18 years) underwent to RT or/and CT at the University Hospital of Marche Region, Ancona, Italy. Only patients with diagnosis of OM (Grade 0-3), according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) rating scale (v.5.0-2017) (Table I),³¹ who had life expectancy greater than three months and physical and mental conditions

TABLE I.—Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Publish Date: November 27, 2017.

	Grade 0	Grade 1	Grade 2	Grade 3
Xerostomia	Asymptomatic	Symptomatic (e.g. dry or thick saliva) without significant dietary alterations; unstimulated saliva flow >0.2 mL/min	Moderate symptoms; oral alterations intake (e.g. water, other liquids, limited diet); unstimulated saliva 0.1-0.2 mL/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 mL/min
Dysgeusia	Asymptomatic	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	
Dysphagia	Asymptomatic	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/ swallowing; tube feeding, TPN, or hospitalization indicated
Oral Pain	Asymptomatic	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL
Mucositis	Asymptomatic	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake

TPN: enteral or parenteral nutrition; ADL: activities of daily living.

allowing the implementation of the protocol, were enrolled in the study.

Patients with diagnosis of OM-4 (life-threatening consequences; urgent intervention indicated) or OM-5 (death), poor cooperation and/or general health conditions, and allergy to one or more components of the mouthwashes were excluded.

At baseline (t0), all patients underwent to an odontostomatologic examination and clinical-pathological data were recorded. All eligible volunteers were provided with oral and written information regarding the protocol and the detailed composition of the tested mouth rinses. Then, the enrolled patients were randomly divided into two groups, through a computer-generated random table.

For the Test Group (TG), two bottles of 150 mL ZL-c-based mouthwash were distributed to be used in a pure form using a 10 mL measuring cup and rinsed for 3 min, four times a day for 30 days. The control group (CG) was prescribed rinses with a solution of half a glass of water and a level teaspoon of sodium bicarbonate twice daily. All patients were instructed to shake the bottle before rinsing and to avoid food and drinks for at least 30 minutes after rinsing. The use of a soft bristle toothbrush and a neutral toothpaste (Elmex sensitive professional®) was recommended to all participants.

After 15 days (t1) and 30 days (t2) from the beginning of the study, all patients underwent to an odontostomatologic examination, to re-evaluate the oral symptoms and the use of analgesic drugs.

The primary endpoint was the evaluation of efficacy of the ZL-c-based mouthwash in the prevention of OM and its related symptoms, such as oral pain, xerostomia, dysgeusia, and dysphagia, according to the NCI-CTCAE v. 5.0-2017 rating scale^{32, 33} (Table I), and the analgesic drugs intake.

Statistical analysis

All the statistical analyses were performed using GraphPad Prism software version 8.02 for Windows (<http://www.graphpad.com>; GraphPad Software, San Diego, CA, USA). The comparison of frequencies between the two groups, from baseline (t0) to 15 days (t1) and 30 days (t2), was performed by the χ^2 test and the Fisher's exact test. For each parameter, the categorization was performed between Grade 0-1 vs. Grade ≥ 2 . A P value <0.05 was considered statistically significant.

Assuming independence between parameters, the sample size was estimated by considering two independent groups (TG vs. CG) for binary data ("Grade 0-1" and "Grade ≥ 2 "), a confidence level of 95%, a statistical power of 80%,

TABLE II.—Main clinical-pathological features of the patients included in the study.

	TG	CG
N.	22	20
Sex		
M	10 (45%)	8 (40%)
F	14 (55%)	10 (60%)
Age (Years)		
Range	47-80	55-80
Mean±DS	62. 2±7.4	67. 4±6.7
Diagnosis		
HNC	7 (32%)	7 (35%)
Others	15 (68%)	13 (65%)
Therapy		
RT	0	0
CT	13 (59%)	16 (80%)
IT	4 (18%)	0
RCT	5 (23%)	4 (20%)

TG: Test Group; CG: Control Group; M: male; F: female; HNC: head and neck cancer; RT: radiation therapy; CT: chemotherapy; IT: immunotherapy; RCT: radiochemotherapy.

and a margin of error of 5%. A minimum difference between groups of 35%, a case-to-control ratio of 1:1, and a dropout rate of 10% were set. Under these assumptions, the minimum required sample size was estimated to be 19, using standard formulas as reported by Machin D. *et al.*³⁴

Results

Forty-two patients, allocated to the TG (n. 22) and CG (n. 20), were enrolled in the study, consisting of 18 males (42.9%) and 24 females (57.1%) with a mean age at diagnosis of 64.4 ± 16.1 years (range: 47-80 years). A total of 33.3% of patients (14/42) were diagnosed HNC, equally distributed in the TG and CG, and most patients (87.5%) received CT and/or RT (Table II). Two patients were excluded from the study because they did not meet the inclusion criteria and declined to participate, respectively. The flow chart of the randomized clinical trial, CONSORT 2010, is represented in Figure 1.

At t0, according to the NIC-CTCAE rating scale, in the TG, 9 patients (41.0%) were Grade 1, 8 patients (36.0%) were Grade 2, and 5 patients (23.0%) belonged to Grade 3. In the CG, most of the cases (55.0%) were Grade 2, 7 cases (35.0%) were Grade 1 and 2 cases (10.0%) were Grade 3. At the baseline, no significant differences were observed between the TG and the CG (Table III).

At t1 and t2, OM was resolved in 18% and 55% of patients in the TG, respectively.

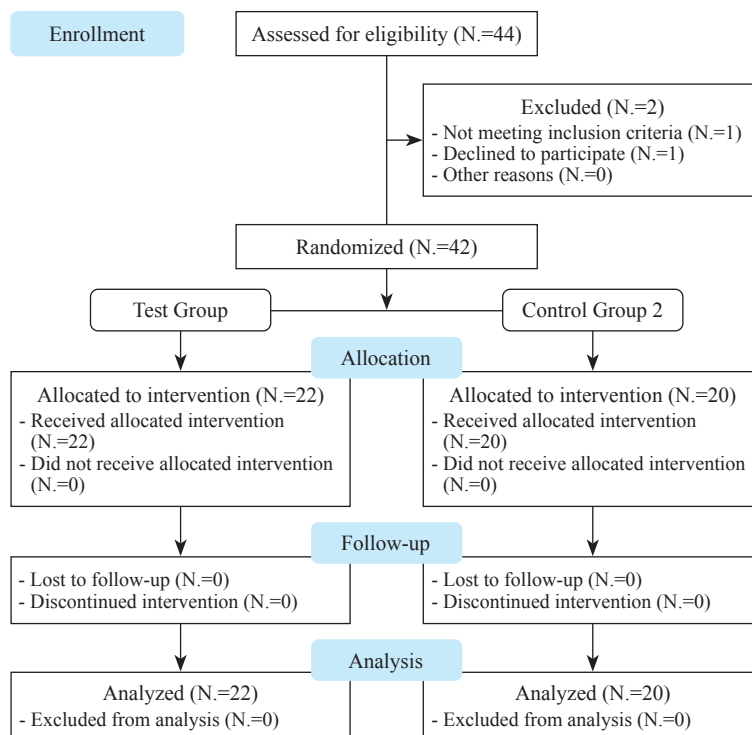


Figure 1.—CONSORT 2010 flow chart, Guidelines for publishing random control trials.

TABLE III.— *Grade of oral mucositis and its related symptoms and analgesic drugs intake at baseline (t0) and after 15 days (t1) and 30 days (t2) from the beginning of the study, in the Test Group and Control Group.*

	t0		P value	t1		P value	t2		P value
	TG N. (%)	CG N. (%)		TG N. (%)	CG N. (%)		TG N. (%)	CG N. (%)	
Oral mucositis									
Grade 0	0 (0%)	0 (0%)	0.7581	4 (18%)	0 (0%)	0.0048	12 (55%)	0 (0%)	<0.0001
Grade 1	9 (41%)	7 (35%)		12 (55%)	5 (25%)		7 (32%)	2 (10%)	
Grade 2	8 (36%)	11 (55%)		5 (23%)	11 (55%)		3 (14%)	11 (55%)	
Grade 3	5 (23%)	2 (10%)		1 (5%)	4 (20%)		0 (0%)	7 (35%)	
Grade ≥2	13 (61%)	13 (65%)		6 (28%)	15 (75%)		3 (14%)	18 (90%)	
Oral pain									
Grade 0	0 (0%)	0 (0%)	0.9999	8 (38%)	0 (0%)	<0.0001	12 (57%)	0 (0%)	<0.0001
Grade 1	9 (41%)	9 (45%)		10 (48)	2 (10%)		8 (38%)	5 (25%)	
Grade 2	12 (54%)	11 (55%)		3 (14%)	15 (75%)		1 (5%)	13 (65%)	
Grade 3	1 (5%)	0 (0%)		0 (0%)	3 (15%)		0 (0%)	2 (10%)	
Grade ≥2	13 (59%)	11 (55%)		3 (14%)	18 (90%)		1 (5%)	15 (75%)	
Xerostomia									
Grade 0	15 (68%)	11 (45%)	0.9999	18 (82%)	9 (45%)	0.2207	19 (86%)	11 (55%)	0.2207
Grade 1	6 (27%)	9 (55%)		4 (18%)	9 (45%)		3 (14%)	7 (35%)	
Grade 2	1 (5%)	0 (0%)		0 (0%)	2 (10%)		0 (0%)	2 (10%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade ≥2	1 (5%)	0 (0%)		0 (0%)	2 (10%)		0 (0%)	2 (10%)	
Dysphagia									
Grade 0	14 (63%)	9 (45%)	0.2984	15 (68%)	7 (35%)	0.0408	18 (82%)	9 (45%)	0.0031
Grade 1	4 (18%)	4 (20%)		6 (27%)	7 (35%)		3 (13%)	2 (10%)	
Grade 2	3 (14%)	7 (35%)		1 (5%)	4 (20%)		1 (5%)	7 (35%)	
Grade 3	1 (5%)	0 (0%)		0 (0%)	2 (10%)		0 (0%)	2 (10%)	
Grade ≥2	4 (19%)	7 (35%)		1 (5%)	6 (30%)		1 (5%)	9 (45%)	
Dysgeusia									
Grade 0	12 (54%)	11 (55%)	0.4890	21 (95%)	14 (70%)	0.2207	22 (100%)	14 (70%)	0.2207
Grade 1	8 (36%)	9 (45%)		1 (5%)	4 (20%)		0 (0%)	4 (20%)	
Grade 2	2 (9%)	0 (0%)		0 (0%)	2 (10%)		0 (0%)	2 (10%)	
Analgesic									
Yes	14 (63%)	7 (35%)	0.1215	3 (14%)	13 (65%)	0.0012	0 (0%)	15 (75%)	<0.0001
No	8 (37%)	13 (65%)		19 (86%)	7 (35%)		22 (100%)	5 (35%)	
TG: Test Group; CG: Control Group.									

TG: Test Group; CG: Control Group.

Similarly, at t2, OM ≥ 2 improved in almost 50% of patients (from 61% to 14%), and no cases showed OM-3 (Figure 2A). In contrast, at t2, in the CG, cases with OM-3 increased from 10% to 35%. Significant differences were observed in OM between the TG and CG at both t1 (P=0.0048) and t2 (P<0.0001) (Figure 3A, Table III).

Similar results were obtained for oral pain (t1, t2: P<0.0001) (Figure 3B, Table III). In the TG, oral pain disappeared in 57% of cases and no patients reported a Grade 3 oral pain (Figure 2B). Contrary, in the CG, the number of patients with oral pain ≥ 2 increased up to 75%. The dysphagia exhibited significant improvements in the TG compared to GC (t1: P=0.0048); and, at t2, only two TG patients showed a moderate dysphagia (P=0.0031) (Figure 2D). On the contrary, in the

CG, no swallowing improvement was observed (Table III). No patient exhibited severe xerostomia. In the TG, a complete recovered was obtained both at t1 and t2 (Figure 2C). While, in the CG, the xerostomia remained almost the same. However, no significant differences were observed between the two groups (P=0.2207) (Table III). Dysgeusia was resolved in the 100% of TG patients, but no significant differences were reached between the groups (P=0.2207) (Figure 2E, Table III).

Evaluating OM and oral pain, the use of ZL-c-based mouthwash significant decreased the Grade ≥ 2 cases from t0 to t2 (OM: P=0.0046; oral pain: P=0.0005) (Figure 2A, B, Figure 3A, B). Notably, the ZL-c-based mouthwash also significantly reduced the analgesic drugs intake, at t1 (P=0.0012), and at t2, all TG patients sus-

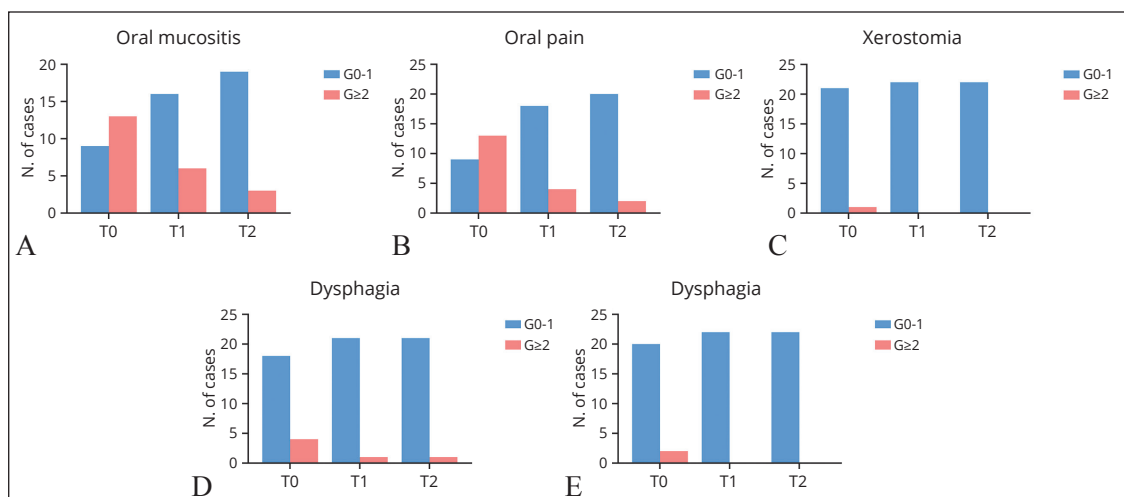


Figure 2.—Number of Test Group patients with Grade 0-1 vs. Grade ≥ 2 with oral mucositis (2A), oral pain (2B), xerostomia (2C), dysphagia (2D), and dysgeusia (2E), at baseline (t0), after 15 days (t1) and 30 days (t2) from the beginning of the study.

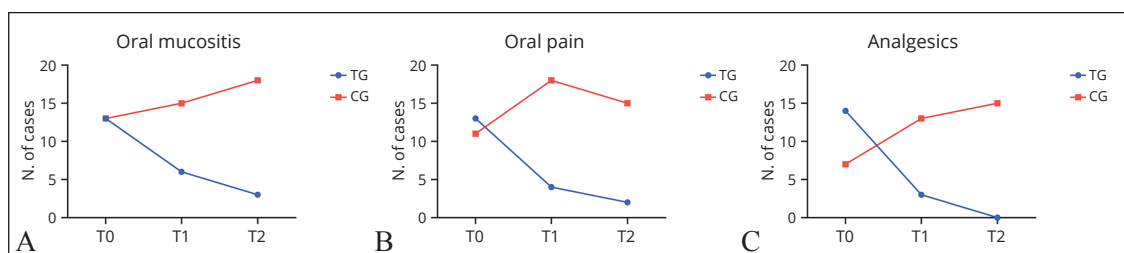


Figure 3.—Number of patients with moderate/severe (Grade ≥ 2) oral mucositis (3A), oral pain (3B), and taking analgesic drugs (3C) in the Test Group and in the Control Group, at baseline (t0), after 15 days (t1) and 30 days (t2) from the beginning of the study.

pendent their use ($P < 0.0001$). On the contrary, in the CG, the number of cases requiring analgesic drugs increased from 35% to 75% (Figure 3C, Table III).

Discussion

The chelate compound of ZL-c is an antiulcer agent developed in Japan, consisting of zinc iron and L-carnosine. The Carnosine (β -alanyl-L-histidine) is a natural antioxidant found in the skeletal muscles and brains of animals and humans (1-20 mM), which has metal-chelating, anti-glycation, anti-aggregation and pH-buffering effects.³⁵ Furthermore, it has been shown to play a protective role in wound healing and in tissue restoration.^{36, 37} ZL-c supplementation has been shown to inhibit NF- κ B²⁷ and increase the secretion of antioxidant markers, such as super-

oxide dismutase 1 and 2, hemeoxygenase-1, peroxiredoxin-1, and peroxiredoxin-V.³⁸ It is also involved in the upregulation of several growth factors, including vascular endothelial growth factor, nerve growth factor, and platelet-derived growth factor.³⁹

Several studies demonstrated its efficacy in restoring the gastric lining, as well as its role in managing gastrointestinal disorders, taste disorders, and OM resulting from CRT.³⁶ Hayashi *et al.* reported the reduction in OM severity in patient treated with ZL-c mouthwash (4 times per day for 2 min) compared to the control group treated with Azulene (Grade 2: 20% versus 82%, $P < 0.01$; Grade 3: 0% versus 45%, $P < 0.01$).⁴⁰ In a study of pediatric hematology patients undergoing high-dose CT and hematopoietic stem cell transplantation, the incidence of Grade ≥ 3 OM was significantly lower in the ZL-c group than in

the Azulene group (20% vs. 83.3%, $P=0.035$).⁴¹ Furthermore, Watanabe *et al.* demonstrated total recovery of OM one month after ZL-c mouthwash administration in a cohort of HNC patients treated by RT or CRT, compared to the Azulene group. One month later, a severe OM was diagnosed in 66.7% and 6.3% of Azulene and ZL-c group, respectively ($P<0.0006$).⁴²

The results of the present study confirm the literature data. Hepilor® significantly decreased the moderate and severe mucositis, both from baseline to t1 ($P=0.00048$), and to t2 ($P<0.0001$). In particular, in the TG, the percentage of patients with a Grade ≥ 2 OM decreased from 61% (t0) to 28% (t1) and to 14% (t2). On the contrary, in the CG, it increased progressively from 65% (t0) up to 90% (t2). Moreover, at t2, no TG patients exhibited OM-3, whereas it was diagnosed in 35% of CG cases.

OM is associated with several oral symptoms and adverse manifestations, which severely impair patients' quality of life. Several studies have demonstrated the effectiveness of ZL-c in preventing OM-related symptoms.^{25, 36} In particular, it had been shown to significantly reduce the incidence of moderate and severe oral pain (Grade ≥ 2) ($P=0.004$)⁴⁰ and opioid analgesic intake.^{40, 41} Our results confirmed the clinical benefits of ZL-c. Indeed, all OM-related symptoms improved in the TG. Notably, oral pain and dysphagia decreased significantly from baseline to t1 (oral pain: $P<0.0001$; dysphagia: $P=0.0408$) and t2 (oral pain: $P<0.0001$; dysphagia: $P=0.0031$). Moreover, at t2, no TG patients reported xerostomia and dysgeusia, and analgesic drugs use ($P<0.0001$). Also, Hayashi *et al.* reported a significant reduction in analgesic drug use, after the administration of ZL-c compared with azulene ($P=0.025$).⁴⁰ Same results were observed in HNC treated by RT and CT⁴² and in pediatric patients undergoing to high-dose CM and autologous stem cell transplantation.⁴¹

The administration of other medical agents to control OM-related symptoms did not show any clinical benefit. Antifungals such as fluconazole and miconazole⁴³ and compound of sucrose sulphate and aluminum hydroxide (sucralfate) are not recommended for OM management. Contrary, topical morphine appears to alleviate the

severity of OM.¹⁹ It is related to opioid receptors in the peripheral terminals of primary afferent nerves, which mediating potent antinociceptive effects.⁴⁴ Furthermore, thalidomide (THD) has recently been shown to reduce the severity of OM induced by CRT, in both animal models,^{45, 46} and in human patients, due to its anti-inflammatory and antineoplastic properties.⁴⁷ However, its systemic administration is associated with several adverse effects.

Regarding the HNC patients, some author have tried to evaluate the effect of other compounds in preventing OM induced by CRT. Belfiore *et al.*, focused on polyphenols, suggesting the development of innovative delivery systems to facilitate the topical administration and to improve their efficacy.⁴⁸ Interesting, Zhang *et al.*, demonstrated the efficacy of salivary amylase (SA)-responsive buccal tablets in the healing of CT-induced OM, by restoring a positive oral microenvironment and decreasing the recovery time.⁴⁹ Moreover, it has been shown that Glutamine delays the onset of OM and decreases its severity.⁵⁰ On the contrary, Martins *et al.*, failed to assess the efficacy of a mucoadhesive herbal medicine containing curcuminoids and a glycerinated extract of *Bidens pilosa* L. in association with PBM.⁵¹

The data of the present study confirm the clinical efficacy of Hepilor® in the treatment of OM in cancer patients undergoing to RT and/or CT. Together with an adequate oral hygiene, it has been demonstrated to reduce the severity of OM and its related symptoms, improving patients' quality of life.

Limitations of the study

The major limitations of the study are the small sample size, the single-blind design, and the lack of long-term outcome evaluation. Furthermore, the lack of a placebo-controlled rinse limits the ability to accurately assess the true efficacy of the treatment, potentially leading to an overestimation of its benefits.

The evaluation of short-term clinical outcomes is limited by the challenges in recruiting non-hospitalized cancer patients. Moreover, the administration and variability of poly-pharmacological therapies may influence clinical out-

comes, potentially obscuring the beneficial effects of topical treatment.

Thus, further double-blind and placebo-controlled clinical trials, including a grater sample size and a long-term outcome evaluation are required.

Conclusions

RT and/or CT related OM can extend the hospital stay and lead to the premature interruption of therapy in oncological patients. Therefore, the OM prevention is essential to improve the clinical outcomes and the patients' quality of life. This study demonstrates the clinical efficacy of a ZL-c based mouthwash in preventing OM and its related symptoms. Together with an adequate oral hygiene, it has been demonstrated to reduce the severity of OM and its related symptoms, improving patients' quality of life.

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Conflicts of interest

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

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Ethical approval

All procedures performed in this study involving human participants received ethical approval from the competent authorities, as described in the appropriate section of the manuscript, and have been conducted in accordance with the 1964 Helsinki Declaration and its later amendments. The authors confirm that this article does not report any studies involving embryos, gametes and human

embryonic stem cells conducted by the authors. The authors confirm that this article does not report any studies involving animals conducted by the authors.

Informed consent

Written informed consent was obtained from all participants prior to inclusion in the study and for publication of their data.

Authors' contributions

Lucrezia Togni and Scilla Sparabombe have contributed equally to this work. Lucrezia Togni, Scilla Sparabombe and Alberta Barlatani made substantial contributions to the conception and to the design of the manuscript; Marco Mascitti, Gaetano Isola and Lucio Lo Russo to acquisition, analysis, and interpretation of the data. All authors have participated in drafting the manuscript, Lucrezia Togni and Andrea Santarelli revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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