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REVIEW ARTICLE

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Improving outcomes in oral mucositis — emerging role of polaprezinc

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ABSTRACT

One of the most common and debilitating complications of cancer treatment is oral mucositis (OM), characterized by erythema and ulcerations of the oral mucosa. It mainly affects head and neck cancer patients receiving radiotherapy and patients treated with high-dose chemotherapy for hematopoietic stem cell transplants. It is associated with excruciating pain, inability to eat or drink, and decreased quality of life. While numerous strategies for managing OM have been explored, few have shown sufficient effectiveness to establish clear treatment guidelines. In recent years, an increasing number of studies have investigated polaprezinc (PZ), an insoluble zinc complex of L-carnosine, as a new promising treatment in OM. We reviewed nine publications, including three randomized controlled trials, published between 2010 and 2023, focusing on polaprezinc's potential benefits in managing OM. To the best of our knowledge, this is the first comprehensive summary of research on PZ in its various forms and its efficacy in OM management. Despite the limited number of studies available, most of the research reviewed supported polaprezinc's potential to reduce the incidence and/or severity of oral mucositis. Additionally, its role in addressing other complications, such as pain relief, xerostomia, and taste disturbances, has also been reported as promising. However, further evaluation through high-quality, multi-institutional randomized studies on a larger scale, preferably conducted outside of Japan, is needed to confirm polaprezinc's efficacy in preventing and managing OM.

Keywords: oral mucositis, polaprezinc, radiotherapy, chemotherapy, head and neck neoplasms

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Introduction

Head and neck cancers (HNCs) represent a growing global health challenge, characterized by high incidence and mortality rates. In 2022, approximately 1.8 million new cases of HNCs were diagnosed, with over 500,000 associated deaths [1]. Standard therapeutic approaches for HNCs include surgical resection, radiotherapy, and chemotherapy, either as standalone modalities or in combination [2]. However, these treatments are often associated with significant adverse effects. Oral mucositis (OM) is one of the most common and debilitating complications of radiotherapy and chemotherapy and is often associated with hematopoietic stem cell transplantation (HSCT). Clinically, OM is characterized by erythema and ulcerations of the oral mucosa [3]. Patients with oral mucositis often endure persistent and excruciating pain in the oral cavity, which significantly impairs their ability to eat, drink, and speak. This severe discomfort adversely affects their nutritional status and physical condition, leading to a cascade of consequences for mental health and overall quality of life [4, 5]. The incidence of OM varies depending on the treatment regimen. It affects approximately 20% to 40% of patients undergoing conventional chemotherapy and up to 80% of patients receiving high-dose chemotherapy as part of conditioning protocols for HSCT. Furthermore, nearly all patients undergoing

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head and neck radiation therapy (H&NRT) experience OM [6]. Oral mucositis increases healthcare costs by prolonging hospital stays and requiring additional medical resources, such as pain management and supportive care. This results in a significant economic burden to healthcare systems [7, 8]. In severe cases, the intensity of symptoms may necessitate premature interruption of radiotherapy or dose reduction in chemotherapy, which can compromise the efficacy of cancer treatment [3]. Such interruptions risk diminishing tumor control, as residual cancer cells that survive the cytotoxic effects of treatment may regrow and lead to recurrence [9].

Risk factors for oral mucositis include sex, with female patients often reported to have a higher risk. Genetic variations affecting drug metabolism, immune responses, and cell repair mechanisms may also contribute to susceptibility, although the evidence is inconsistent and limited. Additionally, tumor characteristics, such as its site and stage, influence the risk and severity of mucositis, particularly in head and neck cancer patients, as these factors determine the radiation plan, including field and dose [10].

The pathomechanism of oral mucositis is a complex process triggered by chemotherapy and radiotherapy, which cause DNA damage and generate reactive oxygen species (ROS). This activates transcription factors, such as nuclear factor kappa B (NF-κB) and p53, leading to the release of inflammatory mediators, such as cytokines and adhesion molecules. The cascade amplifies tumor necrosis factor-alpha (TNF-α) signaling, activating mitogen-activated protein kinase (MAPK) pathways and resulting in apoptosis. Once cell death exceeds a threshold, ulceration occurs, which can become infected, worsening inflammation. Healing follows, though its timing depends on the specific initiating factors [11].

The guidelines published by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISO) serve as a credible source of information about treatment of oral mucositis. Numerous drugs, supplements, and interventions have been investigated, but most have not demonstrated sufficient efficacy to establish comprehensive treatment guidelines. The existing guidelines emphasize the importance of oral hygiene in managing the condition. Even though compounds containing zinc, such as zinc sulfate and polaprezinc (PZ), have been explored, the guidelines were unable to make definitive recommendations.

However, during our research on OM, we encountered numerous studies, especially those published in recent years, investigating the effects of PZ on oral mucositis. Most of these studies highlighted the potential benefits of PZ in managing OM. Given the lack of a comprehensive review summarizing all publications on PZ and considering the debilitating nature of OM and the pressing need for effective treatments, we decided to make it the focus of our article. In our review, we included nine publications, involving mostly retrospective studies and three randomized controlled trials. Given the various forms in which polaprezinc was administered in these studies, we decided to categorize them based on this criterion to best describe their potential effects on OM treatment (Tab. 1).

Zinc

Zinc is the second most abundant trace mineral in the human body. Since the body cannot synthesize or store zinc, a regular daily intake is essential to maintain proper physiological function [12]. In the body, zinc is found in muscle, bone, and skin, while in the oral cavity, it is present in saliva, dental plaque, and dental enamel's hydroxyapatite [13]. Meat, poultry, and seafood are the richest sources of zinc. Consuming these foods with vegetables enhances zinc absorption, while vegetarians, relying on legumes for protein, are more prone to zinc deficiency [14]. Zinc is essential for proper bodily function as it is required for the activity of over 300 enzymes and the structural stability and DNA-binding ability of more than 2,000 transcription factors [15]. It plays a critical role in cell division, growth, differentiation, apoptosis, and function, with both stimulatory and inhibitory effects on immune cells, making it essential for effective wound healing [14]. Zinc is vital for DNA repair and p53 activation and induces metallothionein synthesis, which helps maintain metal homeostasis and protects cells from the cytotoxic effects of ROS [15, 16]. From an immunological perspective, zinc serves as a regulator of immune function by modulating the activity of key signaling molecules and cytokines, including interleukin-6 (IL-6), NF-κB, and TNF-α [17]. These functions are directly implicated in OM pathogenesis, which suggests that zinc may serve as an effective therapeutic agent for its management. There have been studies that investigated the correlation between serum zinc levels and the development of oral mucositis. The results of Rao et al.'s [18] prospective, observational study showed that serum zinc levels had a significant correlation ($r = 0.29$; $p < 0.038$) for mild oral mucositis. However, no significant correlation was found for more severe oral mucositis. These results indicate that the serum level of zinc has an inverse association with the development of mucositis in patients with head and neck cancer undergoing radiotherapy [18]. Another retrospective study conducted by Da Rocha et al. [19] found that severe mucositis was significantly related to zinc deficiency ($p = 0.01$) in patients undergoing allogenic HSCT. In contrast, in patients undergoing autologous HSCT, no statistically significant difference was observed between zinc deficiency and the occurrence of mucositis [19]. All of these findings suggest that zinc may serve as an effective therapeutic agent for OM management.

Table 1. Basic characteristics of reviewed studies involving polaprezinc

Study	Cancer treatment	No. of patients receiving PZ	Form of PZ with dose	Type of carcinoma	Outcomes of study
Watanabe et al. 2010 [26]	Radiation or Chemoradiation	16	PZ granule (0.5g) dissolved in 20 ml of 5% sodium alginate solution; 5 ml 4 times daily	Head and neck cancer	PZ reduces: — OM incidence — pain — xerostomia — taste disturbance — use of analgesics
Suzuki et al. 2016 [27]	Radiation or Chemoradiation	79	PZ granule (0.5g) dissolved in 20ml of 5% sodium alginate solution; 5 ml 4 times daily	Head and neck cancer	PZ reduces: — OM incidence — duration of radiotherapy — median time to discharge after completing radiotherapy
Hayashi et al. 2014 [28]	Chemoradiation	25	PZ granule (0.5g) dissolved in 20 ml of 5% sodium alginate solution; 5 ml 4 times daily	Hematological malignancies	PZ reduces: — OM incidence — OM average severity — pain — use of analgesics PZ does not reduce: — taste disturbances — terostomia
Tsubura et al. 2021 [23]	Chemoradiation	79	1500 mg polaprezinc dissolved in 250 ml of 0.2% polyacrylic acid solution; 5 ml 4 times daily	Hematological malignancies	PZ reduces: — OM incidence — pain — dysgeusia
Hayashi et al. 2016 [30]	Chemoradiation	16	Lozenge containing 18.75 mg of polaprezinc; 4 times daily	Hematological malignancies	PZ reduces: — OM incidence — OM severity — pain — use of analgesics
Funato et al. 2018 [29]	Chemotherapy	10	PZ granule (0.5g) dissolved in 20 ml of 5% sodium alginate solution; 5 ml 4 times daily	Hematological malignancies	PZ reduces: — OM incidence — OM severity — use of analgesic — duration of parenteral nutrition use
Kitagawa et al. 2021 [31]	Chemotherapy	41	Lozenge containing 18.75 mg of polaprezinc; 4 times daily	Hematological malignancies	PZ reduces: — OM incidence (grade ≥2) PZ does not reduce: — OM incidence (grade ≥3) — anorexia — xerostomia — taste disturbance — use of analgesics
Nakagaki et al. 2023 [20]	Chemoradiation	55	Normal Saline mouthwash 10 ml followed by polaprezinc mouthwash 5 ml; 4 times daily	Hematological malignancies	PZ does not reduce: — OM incidence — OM duration, — use of patient controlled analgesia — nutrition supplementation
Doi et al. 2015 [32]	Radiation	32	Oral rinse with a total amount of PZ at 150 mg/day; 4 times daily	Head and neck cancer	PZ reduces: — OM incidence

PZ — polaprezinc; OM — oral mucositis

Table 2. The World Health Organization (WHO) Oral Toxicity Scale [24] and the Common Terminology Criteria for Adverse Events (CTCAE) version 3 and 4 [25]

Grade	WHO	CTCAE version 3	CTCAE version 4
0	No findings	–	–
I	Erythema and soreness; no ulcers	Erythema of the mucosa	Asymptomatic or mild symptoms; intervention not indicated
II	Oral erythema, ulcers, solid diet tolerated	Patchy ulcerations or pseudomembranes	Moderate pain; not interfering with oral intake; modified diet indicated
III	Oral ulcers, liquid diet only	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Severe pain; interfering with oral intake
IV	Not able to tolerate a solid or liquid diet	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Life-threatening consequences; urgent intervention indicated
V	–	Death	Death

Polaprezinc is an anti-ulcer agent and a chelating compound composed of a zinc ion and L-carnosine, a dipeptide consisting of β-alanine and L-histidine. It is licensed in Japan, where it is approved for the treatment of peptic ulcers [20]. The beneficial effects of polaprezinc on metabolic regulation and its anti-inflammatory properties are similar to those of zinc alone but surpass them, probably because of its dual structure [21]. β-Alanyl-l-histidine is a dipeptide and metal ion chelator that supports wound healing and immune function, likely due to its buffering and antioxidant properties. The combination of zinc and carnosine in PZ provides better clinical outcomes because carnosine enhances zinc absorption and may promote a delayed or extended release to tissues [22]. PZ is not absorbed by intact epithelium; instead, it adheres to and penetrates ulcerated areas. This action triggers the activation of mesenchymal stem cells and stimulates the production of insulin-like growth factor-1 in vascular endothelial cells and, with this, protects and heals damaged gastric tissue and skin [23].

Polaprezinc suspension

Most of the research, including one of the first studies published on polaprezinc in OM management, evaluated its potential benefits when it is administered as a suspension. Among the five studies on polaprezinc suspension that we reviewed, four used PZ granules (0.5 g) dissolved in 20 ml of a 5% sodium alginate solution, while one utilized 1,500 mg of polaprezinc dissolved in 250 ml of a 0.2% polyacrylic acid (PPAA) solution.

One of the first studies that reported polaprezinc use in patients with oral mucositis was a study conducted by Watanabe et al. [26] The authors examined the application of a mouth rinse (swish and swallow) of PZ granules (0.5g) dissolved in 20 ml of 5% sodium alginate solution rinsed 4 times a day. The drug was administered to 16 head and neck cancer patients receiving radiotherapy or chemoradiation. The evaluation of the incidence of mucositis, pain, xerostomia, and taste disturbance was made with the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. (Tab. 2) They have found that treatment with PZ reduced the risk of oral mucositis by 56.7% (grade 2) and 90.6% (grade 3), pain by 73.9% (grade 2) and 81.2% (grade 3), xerostomia (grade 2) by 83% and, finally taste disturbance (grade 2) by 88.3%. Additionally, the study found that the use of analgesics was significantly lower in the PZ group (50% *vs*. 100%, p = 0.003), and food intake was notably higher in the PZ group (78.8% *vs.* 30.7%, p = 0.002). It is also important to note that the tumor response rate in patients with neoadjuvant radiochemotherapy was not significantly affected by polaprezinc use [26].

Another report that also involved administering polaprezinc-alginate (P-AG) to head and neck cancer patients undergoing radiotherapy or chemoradiotherapy, as in the Watanabe et al.'s [26] study, was a nonrandomized, single-center, retrospective study conducted by Suzuki et al. [27] The results showed that 5 ml of P-AG suspension administered 4 times daily is effective in reducing OM severity by significantly decreasing the incidence of grade 3 oral mucositis in the P-AG group (16.5% *vs.* 52.0% in the control group, p = 0.0003). Other important outcomes of this research were that P-AG also significantly reduced the median duration of radiotherapy [51.5 days *vs.* 56.0 days in the control group; hazard ratio (HR) = 0.557; 95% confidence interval (CI) 0.357–0.871; p = 0.0149] and median time to discharge after completing radiotherapy (5 days *vs.* 10 days in the control group; HR = 0.604; 95% CI 0.386–0.946; p = 0.028). Notably, overall survival did not significantly differ between the two groups (HR = 0.744; 95% CI 0.262–2.11; p = 0.579) [27].

Another study involving 36 patients with hematological malignancies receiving high-dose chemotherapy and radiotherapy followed by HSCT was conducted by

Hayashi et al. [28]. The patients were given the same dose of P-AG as in the Suzuki et al.'s [27] study and were evaluated according to CTCAE version 3.0. The results showed that P-AG significantly reduced the incidence of moderate-to-severe (grade 2 or higher) oral mucositis as compared to the control group treated with azulene gargle (20% *vs.* 82% for grade ≥ 2, $p < 0.01$; 0% *vs.* 45% for grade ≥ 3, $p < 0.01$). P-AG use resulted in significant ($p = 0.004$) pain relief associated with oral mucositis, which allowed a reduction in the use of all analgesic agents (28% *vs.* 73%, $p = 0.025$). Although P-AG tended to reduce the incidence of xerostomia and taste disturbances, the differences were not statistically significant. Other adverse events, tumor remission rate, and the survival rate were not affected by P-AG use. In conclusion, the study emphasized the need for larger, randomized trials to confirm these findings and address limitations of the study, such as its retrospective nature, different chemotherapeutic regimens between the two groups, and a small patient population enrolled at a single institution [28].

Funato et al. [29] performed a study on pediatric patients (1–18 years old) undergoing autologous stem cell transplantation. The patients were administered a daily dose of 75 mg of polaprezinc suspended in sodium alginate (P-AG). The administration involved rinsing with 5 ml of the P-AG suspension for 2 minutes, four times daily, starting before chemotherapy and continuing for a month post-transplantation. The results showed a significantly lower incidence of grade 3 or higher, measured with the WHO Oral Mucositis Grading Scale in patients receiving P-AG compared to the azulene group, as well as a lower average severity (Tab. 2). The research also showed that the administration of P-AG decreased the use of opioid analgesics (30% compared to 100% in the azulene gargle group, $p = 0.011$), as well as the average duration of total parenteral nutrition use (11.1 *vs.* 24.3 days, $p = 0.016$). Additionally, there were no significant differences reported in the incidence rates of other adverse events, time to engraftment, or rate of overall survival between the two groups. However, it should be noted that given the small sample size, the authors emphasized the need for larger randomized controlled trials to confirm their findings [29].

The latest research on polaprezinc investigating its potential benefits on preventing oral mucositis includes a retrospective cohort study conducted by Tsubura et al. [23] on patients with a hematopoietic neoplasm scheduled for HSCT. The study analyzed the effects of gargling with and then swallowing 1500 mg polaprezinc dissolved in 250 ml of 0.2% polyacrylic acid (PPAA), in addition to regular oral management. Oral damage was evaluated based on the CTCAE version 4.0 (Tab. 2). The results showed that the severity of oral mucositis ($p = 0.008$), oral pain ($p < 0.001$), and dysgeusia ($p = 0.004$) were significantly reduced in patients who were treated with 5 ml of PPAA four times daily. Notably, although the PPAA group had a higher survival rate (68.4%) compared to the control group (58.5%), the difference was not statistically significant ($p = 0.285$). Additionally, the study demonstrated that the severity of allograft-induced acute graft-versus-host disease (GVHD) was significantly lower in the PPAA group ($p = 0.011$) [23].

Polaprezinc lozenge

Following the success of polaprezinc suspension in reducing the severity of oral mucositis in patients receiving radiochemotherapy, as demonstrated by previous studies, researchers decided to develop a more practical formulation of polaprezinc — a lozenge. Hayashi et al. [30] evaluated the clinical effect of the lozenge containing 18.75 mg of polaprezinc for prevention of oral mucositis in patients who received conditioning high-dose chemotherapy for HSCT. The study found that the efficacy of the lozenge given four times a day was almost as good as polarizing suspension in sodium alginate The incidence rate of grade ≥ 2 (CTCAE version 3.0) oral mucositis in patients without premedication was 74%, whereas in patients receiving the suspension or lozenge of Polaprezinc, the rate was remarkably reduced (23% and 13%, respectively, $p < 0.01$). Both the lozenge and suspension significantly reduced the occurrence of accompanying oral pain. The use of non-opioid analgesic drugs such as anti-inflammatory agents and local anesthetics for oral pain was greatly reduced in patients receiving polaprezinc suspension and its lozenge (16% for suspension and 13% for lozenge, compared with 89% with no premedication, $p < 0.01$). In conclusion, the study found that polaprezinc in the form of a lozenge is an efficient alternative to the suspension [30].

All previous studies examining the potential benefits of polaprezinc in patients receiving high-dose chemotherapy for HSCT were limited to single-institutional retrospective studies [28–30]. To verify the accuracy of the prophylactic effect of PZ on the development of oral mucositis, a multi-institutional prospective randomized controlled study was conducted by Kitagawa et al. [31] PZ lozenges were prepared as specified by previous research [30]. They were administered in two groups: a prevention group, which started PZ treatment before chemotherapy, and a control group, where PZ lozenges were given after the onset of grade 2 oral mucositis. Oral damage was measured according to the CTCAE version 4. The results demonstrated a significant reduction in Grade ≥ 2 oral mucositis in the prevention group compared to the control group (22.0% *vs.* 44.7%, $p = 0.025$). Additionally, no significant differences were observed

between the two groups regarding the incidence of anorexia (89.4% *vs.* 92.7%, p = 0.589), xerostomia (27.7% *vs.* 31.7%, p = 0.678), or taste disturbances (59.6% *vs.* 51.2%, p = 0.431). These results indicate that PZ lozenges are effective in preventing grade ≥ 2 chemotherapy-induced oral mucositis in patients undergoing HSCT without affecting the overall outcome of the transplant [31].

Polaprezinc mouthwash

The last and, at the same time, most controversial form of polaprezinc reported is a mouthwash. We encountered two studies that evaluated its efficacy in OM, presenting contradictory results.

The first study that investigated the efficacy of oral rinses with PZ mouthwash was performed by Doi et al. [32] in 2015. In this study, a new polaprezinc oral rinse was developed using carboxyvinyl polymer as a base to enhance the drug's attachment to the oral and oropharyngeal mucosa. The rinse dose of polaprezinc 150 mg/day was given to head and neck cancer patients undergoing radiotherapy. Oral mucositis was assessed according to the CTCAE version 3.0. Of the patients who were treated with the rinse, 29% experienced grade 3 mucositis based on the mucosal evaluations, while 39.3% were diagnosed based on the self-reported symptoms. In contrast, 40% of the patients who did not receive the rinse developed grade 3 mucositis according to mucosal assessments, and 60.7% reported experiencing grade 3 symptoms. The results of the study indicated that PZ oral rinse was effective in reducing the incidence of severe oral mucositis [32].

Notably, all of the previously mentioned studies involving polaprezinc and its influence on oral mucositis were conducted solely in Japan. To assess polaprezinc efficacy on a broader scale, Nakagaki et al. [20] performed a study that included a non-Japanese patient population. The open-label randomized clinical trial evaluated the value of polaprezinc mouthwash in OM prevention in patients who underwent HSCT. A total of 108 patients (55 test arm, 53 control arm) were randomized. The control arm received standard care, which involved normal saline (N/S) mouthwash 10 ml followed by sodium bicarbonate mouthwash 10 ml four times daily. The test arm received N/S mouthwash 10 ml followed by polaprezinc mouthwash 5 ml four times daily. The results showed no significant difference in the incidence of grade 3–4 oral mucositis between the two groups, with 35% of patients in the test group and 36% in the control group developed these severe grades of OM. Other endpoints also showed no significant differences, suggesting that topical polaprezinc did not prevent OM in this HSCT patient cohort [20].

Discussion

Oral mucositis is a debilitating complication of cancer therapy, which affects mainly patients treated with radiation therapy to the head and neck cancer or myeloablative chemotherapy treatment [10]. It is associated with severe pain and dysphagia, which significantly reduce patients' quality of life [33]. Some studies have found that adverse events, such as OM, are significant factors contributing to longer hospital stays for head and neck cancer patients in otolaryngology wards [34]. Although there have been numerous agents and procedures proposed for OM management, most yield contradictory results and are suggested only for specific clinical scenarios. The most recent 2020 Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISO) Clinical Practice Recommendations emphasize the need for further research to explore more effective treatments for managing OM [3].

While preparing our review, we encountered an increasing number of recent studies highlighting polaprezinc as a promising new form of zinc in managing oral mucositis. The medication is an insoluble zinc complex of L-carnosine, and it was initially used for its protective effects on the gastric mucosa [26].

Although there is still a small number of research studies evaluating polaprezinc's efficacy in OM, it is important to note that most studies examining polaprezinc confirm its safety and lack of typical adverse events associated with zinc supplements, such as rash, nausea, vomiting, and diarrhea [29, 31, 32]. However, it has been reported that approximately 37.5% of children may find the taste and texture of one of the polaprezinc formulations, the PZ-AG suspension, to be unpleasant, which may be an obstacle in the pediatric population [29].

Most of the studies we reviewed confirmed polaprezinc's efficacy in decreasing the incidence and/or severity of OM [23, 26–32]. Only one of the reviewed studies reported no significant difference in the incidence of grade 3–4 OM or its duration in patients with hematological malignancies undergoing HSCT. However, it is worth mentioning that this study was the only one conducted on a non-Japanese population, and its findings may be linked to the role of zinc deficiency, which could be more prevalent in the Japanese population. Further studies are needed to evaluate polaprezinc's efficacy in non-Japanese populations, including the measurement of serum zinc levels in patients [20].

There have been contradictory findings on the effects of polaprezinc on patients' xerostomia and taste disturbances. Watanabe et al.'s [26] study reported a significant reduction in both side effects, while Kitagawa et al. [31] and Hayashi et al. [30] found no influence. Additionally, Watanabe et al. [26] observed a higher food intake in patients receiving polaprezinc [26].

One of the most challenging aspects of managing OM is the impact it has on patients' quality of life. Its decrease is mainly associated with severe pain associated with OM lesions. Watanabe et al.'s [26] study confirmed polaprezinc's benefit in reducing patients' pain and consequently in improving their quality of life. Both studies conducted by Hayashi et al. [28, 30] supported those findings. A significant reduction in the use of analgesics in patients receiving polaprezinc has been reported in four studies [26, 28–30].

It is also important to mention that polaprezinc appears to have no impact on patients' overall survival [27, 28]. Moreover, Suzuki et al. [27] found that it reduces both the median duration of radiotherapy and the median time to discharge after its completion.

As previously mentioned, most of the reviewed studies supporting polaprezinc's efficacy in OM management have examined its suspension form. However, we reviewed two studies that investigated polaprezinc lozenges. Hayashi et al. [30] and Kitagawa et al. [31] showed that this form may be an efficient alternative to the suspension in reducing OM incidence in patients with hematological malignancies. Polaprezinc's suspension may be inferior to the lozenge due to its time-consuming preparation, rapid separation of the ingredient from sodium alginate solution, difficulty in precise dosing, and unfavorable taste and texture. An additional advantage is that lozenge formulation is suitable for both hospitalized patients and those in ambulatory chemotherapy settings, providing flexibility in treatment and improving patient compliance. These advantages indicate the need for more research on the lozenge form of polaprezinc [30].

We reviewed two studies that examined polaprezinc as a mouthwash, and they showed contradictory results. Nakagaki et al. [20] did not confirm polaprezinc's benefits in reducing OM incidence. However, it should be emphasized that the formulation of polaprezinc used in Nakagaki et al.'s [20] study differed from other trials. Most of the studies utilized polaprezinc mouthwash containing sodium alginate or other thickeners to improve its adhesion to the oral mucosa, whereas this study used a simple suspension. This may explain why the study conducted by Doi et al. [21] demonstrated that the PZ oral rinse effectively reduced the incidence of severe radiation-induced oral mucositis. In this case, polaprezinc oral rinse was developed using carboxyvinyl polymer as a base, which enhanced the drug's attachment to the oral and oropharyngeal mucosa. There were also a few other limitations noted in Nakagaki et al.'s [20] study. Since polaprezinc is insoluble and requires shaking before use, a double-blind trial was not feasible, leading to potential bias. Additionally, OM was assessed using the WHO scale, which emphasizes mainly ulceration and the ability to eat. However, patients in this study reported more throat pain than mouth pain, a symptom that the WHO scale might underrepresent due to its focus on oral ulcers. As mentioned before, choosing a non-Japanese population may also be the reason for the infavourable results in that study [20].

There are several limitations in the studies we reviewed. Firstly, most of them were conducted on small sample sizes from single institutions. Secondly, only three of the reviewed studies were randomized controlled trials, while the rest were retrospective studies. Finally, the patients included were primarily of Japanese descent, and only one study involved a pediatric population. Although all five studies involving polaprezinc's suspension confirmed its efficacy in OM treatment, the small number of participants in these studies makes it difficult to draw definitive conclusions.

Conclusions

In recent years, some indications have been emerging that polaprezinc, an insoluble zinc complex of L-carnosine, may be a highly safe and inexpensive treatment option for oral mucositis. However, due to the various forms of polaprezinc that have been studied, it remains unclear whether its effects are due to topical or systemic actions. That is why further evaluation through high-quality, multi-institutional randomized studies on a larger scale, preferably conducted outside of Japan, is needed to confirm polaprezinc's efficacy in preventing oral mucositis.

Article Information and Declarations

Author contributions

G.B.: study conception and design, analysis and interpretation of the reviewed studies, draft manuscript preparation; M.Z.: study conception and design, analysis and interpretation of the reviewed studies, draft manuscript preparation; K.M.: data collection, draft manuscript preparation; A.B.: data collection, draft manuscript preparation.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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