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A Real-World Assessment of Palatability and Acceptability of Rebamipide Mouthwash in Patients with Head and Neck Cancer

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Oral mucositis frequently occurs in patients undergoing chemoradiotherapy. Oral care and cryotherapy are recommended for its prevention. Rebamipide mouthwash is clinically used as a hospital-compounded formulation because of its reactive oxygen species scavenging activity. However, patient-reported palatability and acceptability of this formulation remain unclear. This study aimed to assess the palatability and acceptability of rebamipide mouthwash in patients with head and neck cancer. The analysis included 43 patients newly prescribed this formulation (91% received cisplatin-based chemoradiotherapy). At initial use, palatability and overall acceptability were evaluated using 5-point scales, and taste attributes using a 100-mm visual analog scale (VAS). Three weeks later, patients completed a questionnaire regarding adherence and perceived need for formulation improvement. Receiver operating characteristic (ROC) curve analysis determined the bitterness VAS cut-off score for predicting favorable palatability and acceptability. Based on this cut-off, outcomes were compared between groups. Favorable ratings for palatability and acceptability were reported by 42% of patients. The median bitterness VAS score immediately after use was 34.0, the highest among all attributes, and persisted 5 min after use. ROC curve analysis identified a bitterness VAS cut-off of 29. Compared with the low-VAS group (<29), the high-VAS group showed significantly lower proportions of favorable ratings and a significantly higher perceived need for formulation improvement. Adherence to prescribed use did not differ significantly between groups. These findings suggest persistent bitterness may reduce the palatability and acceptability of rebamipide mouthwash in these patients. Improving formulation taste, particularly addressing persistent bitterness, may enhance acceptability and support consistent use.

Key words rebamipide, mouthwash, oral mucositis, palatability, taste attributes, medication adherence

INTRODUCTION

Oral mucositis is one of the most common adverse events associated with chemotherapy, affecting approximately 40–76% of patients.¹⁾ It is particularly prevalent and severe in patients receiving radiotherapy or chemoradiotherapy for head and neck cancers, with up to 91% developing mucositis and 66% experiencing severe (Grade 3–4) mucositis.²⁾ Oral mucositis is often accompanied by substantial pain, leading to difficulties in oral intake and subsequent malnutrition, which can impair patients' quality of life (QOL). It may also disrupt the continuity of cancer therapy, thereby adversely affecting treatment efficacy and prognosis.

Basic oral care and cryotherapy are widely used preventive strategies for cancer therapy-induced oral mucositis.³⁾ It is well established that the immediate generation of reactive oxygen species (ROS) serves as a primary driver in the pathogenesis of oral mucositis.⁴⁾ Treatment for head and neck can-

cer, including cisplatin (CDDP)-based chemotherapy and radiotherapy (RT), is known to trigger substantial ROS production and mitochondrial damage, leading to direct cytotoxicity.^{5,6)}

Rebamipide, which has antioxidant and anti-inflammatory properties, has been investigated for the prevention of oral mucositis. Originally developed for gastric mucosal protection,⁷⁾ it is expected to exert protective effects by scavenging free radicals⁸⁾ and has been used as a hospital-compounded mouthwash. Clinical studies have shown that topical rebamipide reduces both the incidence and severity of oral mucositis.^{9,10)} A randomized controlled trial (RCT) demonstrated its efficacy in preventing and managing oral mucositis compared with placebo,¹¹⁾ and another RCT reported comparable efficacy to benzydamine mouthwash, in patients with head and neck cancer undergoing radiotherapy.¹²⁾ Furthermore, a meta-analysis of several RCTs confirmed that rebamipide significantly reduces the risk of severe oral mucositis (Grade ≥ 3).¹³⁾

Despite its efficacy, rebamipide has a strong and persis-

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tent bitter taste,^{7,14)} which may reduce adherence to its use as a mouthwash. However, its palatability and impact on adherence have not been fully elucidated, particularly in patients with head and neck cancer, for whom data remain limited. Improving adherence may enhance the preventive efficacy of oral mucositis management and contribute to better QOL and continuity of cancer treatment.

The aim of this study was to evaluate the palatability and acceptability of rebamipide mouthwash. In patients with head and neck cancer newly prescribed rebamipide mouthwash, taste and acceptability were assessed, with additional assessment of medication adherence and oral mucositis symptoms.

MATERIALS AND METHODS

Preparation of Rebamipide Mouthwash The hospital-compounded rebamipide mouthwash was prepared at a standard concentration of 0.1% with reference to previous reports.^{10,11)} Briefly, 3.0 g of polyethylene oxide (Alcox E-30G; Meisei Chemical Co., Ltd.) and 1.2 g of carrageenan (Inagel F-13; Ina Food Industry Co., Ltd.) were sequentially added to warmed sterile water for injection and stirred until completely dissolved. Finally, three rebamipide tablets (100 mg, Rebamipide Tablets “Otsuka”; Otsuka Pharmaceutical Co., Ltd.) were powdered, and then added, followed by preservatives (80 mg of methyl p-hydroxybenzoate and 40 mg of propyl p-hydroxybenzoate; FUJIFILM Wako Pure Chemical Corp.). The volume was adjusted to 300 mL with sterile water for injection to obtain a uniform suspension.

Study Population This study enrolled patients with head and neck cancer who were newly prescribed rebamipide mouthwash at Yamanashi University Hospital. Eligible patients were aged between 18 and 79 years and received their first prescription of rebamipide mouthwash during their hospitalization between September 2023 and December 2025. Patients with preexisting oral mucositis at the time of enrollment, cognitive impairment, communication difficulties (including an inability to read or understand Japanese), or other conditions that precluded reliable completion of the questionnaire were excluded.

Schedule of Assessments This study was approved by the

Ethics Committee of Yamanashi University Hospital (Approval No. CS0033). Patient characteristics, including age, sex, height, weight, and anticancer treatment, were obtained from electronic medical records. Patients received standardized medication counseling from a pharmacist and were instructed to rinse with approximately 50 mL of rebamipide mouthwash six times daily (after breakfast, at 10:00, after lunch, at 15:00, after dinner, and before bedtime), ensuring that the mouthwash spread throughout the oral cavity. Written informed consent was obtained prior to participation.

The complete schedule of treatments, clinical evaluations, assessment methodologies, and observation time points across the 21-day treatment period is summarized in Fig. 1. Prior to the administration of chemotherapy and radiotherapy, patients completed a self-administered visual analog scale (VAS) immediately (0 min) and 5 min after the first use of rebamipide mouthwash on day 1, based on a previous study¹⁴⁾ (Fig. 2B). Palatability and overall acceptability were assessed after the VAS assessment (Fig. 2A). On day 21, patients completed a 4-item self-administered questionnaire, which was administered only to those who continued rebamipide mouthwash use (Fig. 2C). During the study period through day 21, the onset and severity of oral mucositis were evaluated by pharmacists according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for oral mucositis.

Outcome Measures The primary endpoints were the palatability and overall acceptability of rebamipide mouthwash. Palatability was rated on a 5-point scale from 1 (very pleasant) to 5 (very unpleasant), and overall acceptability from 1 (very good) to 5 (very poor) (Fig. 2A).

Secondary endpoints included taste attributes, treatment adherence, and the incidence of oral mucositis. Taste attributes (bitterness, sourness, sweetness, and astringency) were assessed using a 100-mm visual analog scale (VAS) ranging from 0 (no sensation) to 100 (maximal intensity) (Fig. 2B).

Adherence was assessed using a 4-item self-administered questionnaire. Adherence to the prescribed use of the mouthwash was evaluated (Q1). Patients who answered “no” were asked to report the frequency of missed use (Q2-1) and the main reason for non-adherence (Q2-2). In addition, the perceived need for improvement of the rebamipide mouthwash

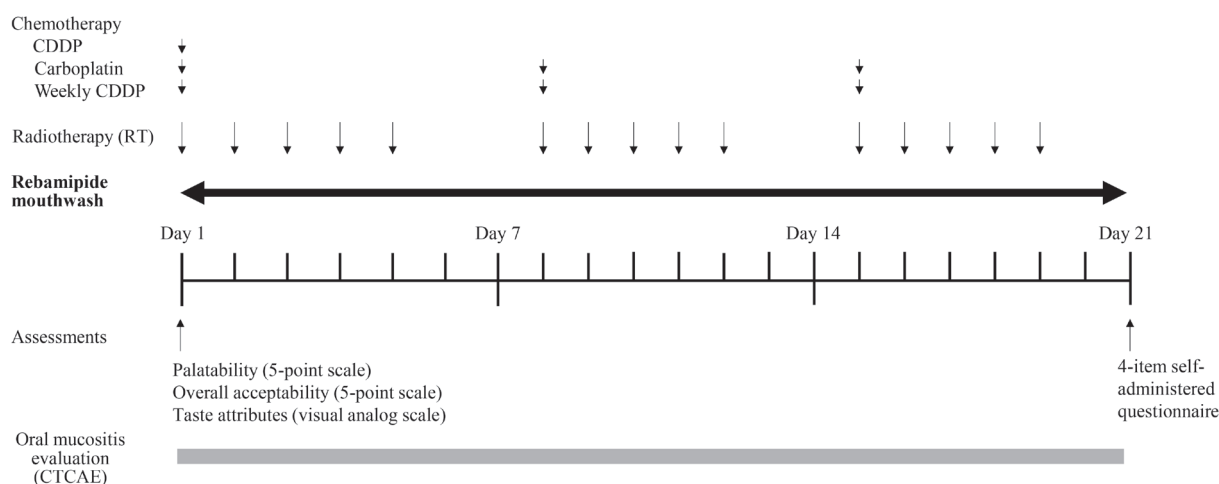


Fig. 1. Study Protocol and Assessment Schedule.

CDDP, Cisplatin; RT, Radiotherapy; CTCAE, Common Terminology Criteria for Adverse Events.

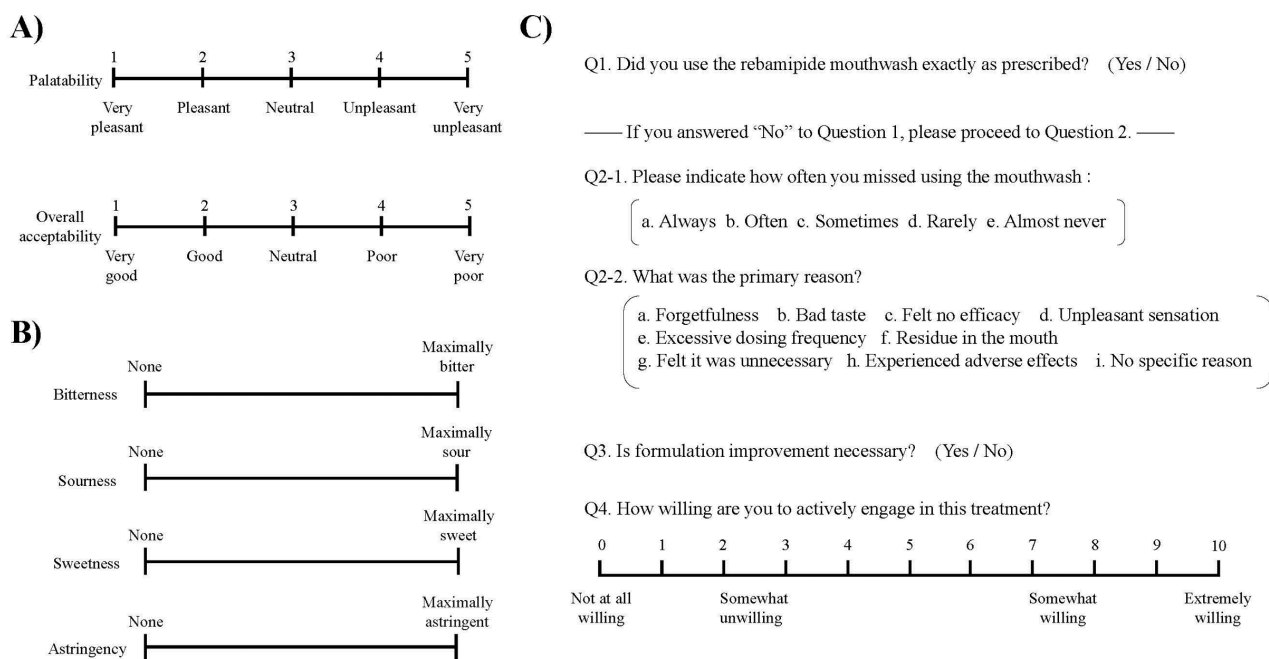


Fig. 2. Assessment Tools Used in This Study.

Five-point rating scales used to assess palatability and overall acceptability (A), visual analog scales (VAS) used to assess taste attributes (bitterness, sourness, sweetness, and astringency) (B), and a four-item self-administered questionnaire completed on day 21 (C).

Table 1. Patient Characteristics According to the Bitterness Visual Analog Scale (VAS) Score Cut-Off Value

	All patients	Bitterness VAS score group		p value
		< 29	≥ 29	
Number of patients	43	20	23	
Age (years)	65.0 (44–78)	66 (44–78)	64 (49–77)	0.751
Male	33 (77)	13 (65)	20 (87)	0.148
Height (cm)	163.6 (150.4–178.0)	162.4 (150.4–177.8)	165.8 (153.0–178.0)	0.268
Weight (kg)	58.9 (42.8–87.9)	58.7 (45.2–87.9)	59.9 (42.8–78.2)	0.644
Cancer type				1.000
Pharyngeal cancer	37 (86)	17 (85)	20 (87)	
Laryngeal cancer	6 (14)	3 (15)	3 (13)	

Patients were divided into two groups according to the cut-off value of 29 identified by receiver operating characteristic (ROC) curve analysis (Fig. 4). Data are presented as median (range) or number (%). P values between the groups were calculated using the Mann-Whitney U test or Fisher's exact test. Forty-four patients were enrolled; however, one patient died during the observation period, leaving 43 patients for the final analysis.

formulation was assessed (Q3). Willingness to actively engage in treatment with rebamipide mouthwash was evaluated using a numeric rating scale (NRS) ranging from 0 (not at all willing) to 10 (extremely willing) (Q4) (Fig. 2C).

Statistical Analysis Data are presented as medians (range) for continuous variables and numbers (percentages) for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the bitterness VAS score immediately after the rebamipide mouthwash use for predicting palatability and overall acceptability scores of 1 or 2. Based on this cut-off value, patients were divided into two groups. Differences between groups were analyzed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Statistical analyses were performed using EZR¹⁵⁾ (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statisti-

cal Computing, Vienna, Austria). A P value < 0.05 was considered statistically significant.

RESULTS

Study Participants A total of 44 patients were enrolled. One patient was excluded because of death on day 5, and 43 patients were included in the analysis. Baseline characteristics are summarized in Table 1. Regarding the primary disease, the cohort consisted of patients with pharyngeal cancer (n = 37) and laryngeal cancer (n = 6). Treatment regimens included CDDP plus RT (100 mg/m² every 3 weeks for 3 cycles; n = 38), carboplatin plus RT (AUC 1.5 weekly for 7 cycles; n = 4), and weekly CDDP plus RT (40 mg/m² weekly for 7 cycles; n = 1), with standard and comparable radiation schedules across all groups. During the 21-day treatment period, 11 patients switched from lidocaine-free to lidocaine-

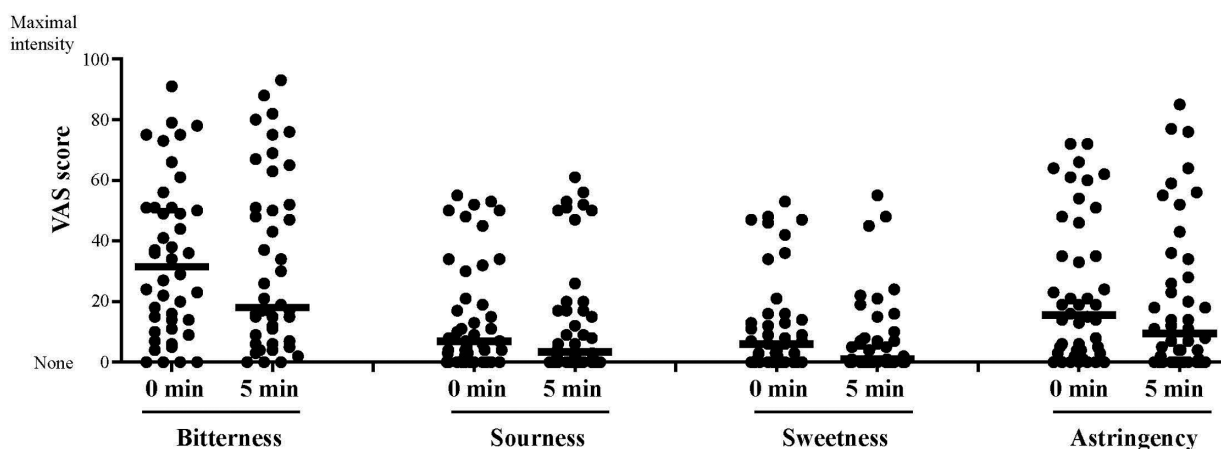


Fig. 3. Visual Analog Scale (VAS) Scores for Bitterness, Sourness, Sweetness, and Astringency Measured Immediately (0 min) and 5 min after Rebamipide Mouthwash Use on Day 1

Each point represents the value for an individual patient, and the horizontal line indicates the median value among the 43 patients.

Table 2. Outcomes According to the Bitterness Visual Analog Scale (VAS) Score Cut-Off Value

	All patients	Bitterness VAS score group		<i>p</i> value
		< 29	≥ 29	
Primary outcomes (Day 1)				
Favorable palatability (score 1–2)	18 (42)	13 (65)	5 (22)	0.018
Favorable overall acceptability (score 1–2)	18 (42)	14 (70)	4 (17)	0.001
Secondary outcomes (Day 21)				
Adherence to prescribed use	20 (47)	9 (45)	11 (49)	1.000
Need for formulation improvement	37 (86)	14 (70)	23 (100)	0.006
Willingness to actively engage in treatment	5 (1–10)	6.5 (1–10)	4.0 (1–10)	0.037
Low willingness (score < 6)	24 (56)	8 (40)	16 (70)	0.069
Oral mucositis during the study period through day 21				
CTCAE grade ≥ 2	17 (40)	8 (40)	9 (39)	1.000

Patients were divided into two groups according to the cut-off value of 29 identified by receiver operating characteristic (ROC) curve analysis (Fig. 4). Data are presented as median (range) or number (%). *P* values between the groups were calculated using the Mann-Whitney U test or Fisher's exact test. The number of patients with a willingness score < 6 is also presented to evaluate the proportion of patients with low willingness to actively engage in treatment. CTCAE, Common Terminology Criteria for Adverse Events.

Table 3. Palatability and Overall Acceptability Scores for Rebamipide Mouthwash on Day 1

Score	Palatability	Overall acceptability
1	0 (0)	0 (0)
2	18 (42)	18 (42)
3	16 (37)	22 (51)
4	9 (21)	3 (7)
5	0 (0)	0 (0)

Data are presented as number (%). Palatability and overall acceptability were evaluated using 5-point scales as follows: palatability (1, very pleasant; 2, pleasant; 3, neutral; 4, unpleasant; 5, very unpleasant) and overall acceptability (1, very good; 2, good; 3, neutral; 4, poor; 5, very poor).

containing mouthwash due to stomatitis-related pain (*n* = 6) or pharyngeal pain (*n* = 5). The median time to switching was day 18 (range, days 15–21). All 43 patients continued using either formulation throughout the study.

Palatability, Overall Acceptability, and Taste Profile of Rebamipide Mouthwash At the initial assessment on day 1, no patients rated palatability or overall acceptability as score 1, and 18 patients (42%) rated both as score 2 (Table 3),

whereas 9 (21%) and 3 (7%) patients rated palatability and overall acceptability as score 4, respectively. Taste attributes including bitterness, sourness, sweetness, and astringency were assessed using VAS scores on day 1 immediately (0 min) and 5 min after rebamipide mouthwash use (Fig. 3). Bitterness showed the highest median VAS scores (34.0 [0–91] immediately after use and 19.0 [0–93] after 5 min), followed by astringency (15.0 [0–72] and 8.0 [0–85], respectively), whereas sourness (7.0 [0–55] and 3.0 [0–61]) and sweetness (6.0 [0–53] and 1.0 [0–55]) were relatively low.

As bitterness showed the highest VAS scores, ROC curve analysis was performed to evaluate its ability to predict favorable palatability and overall acceptability (scores of 1 or 2) (Fig. 4). The optimal cut-off value of the bitterness VAS score for predicting scores of 1 or 2 was 29 for both palatability and overall acceptability. The area under the curve (AUC) was 0.724 (95% confidence interval [CI] 0.564–0.883) for palatability and 0.773 (95% CI 0.625–0.921) for overall acceptability, with sensitivities of 0.778 and 0.833 and specificities of 0.720 and 0.760, respectively.

Medication Adherence to Rebamipide Mouthwash For adherence to the prescribed use (Q1), 20 patients (47%) reported using the mouthwash as prescribed (Table 2). For the fre-

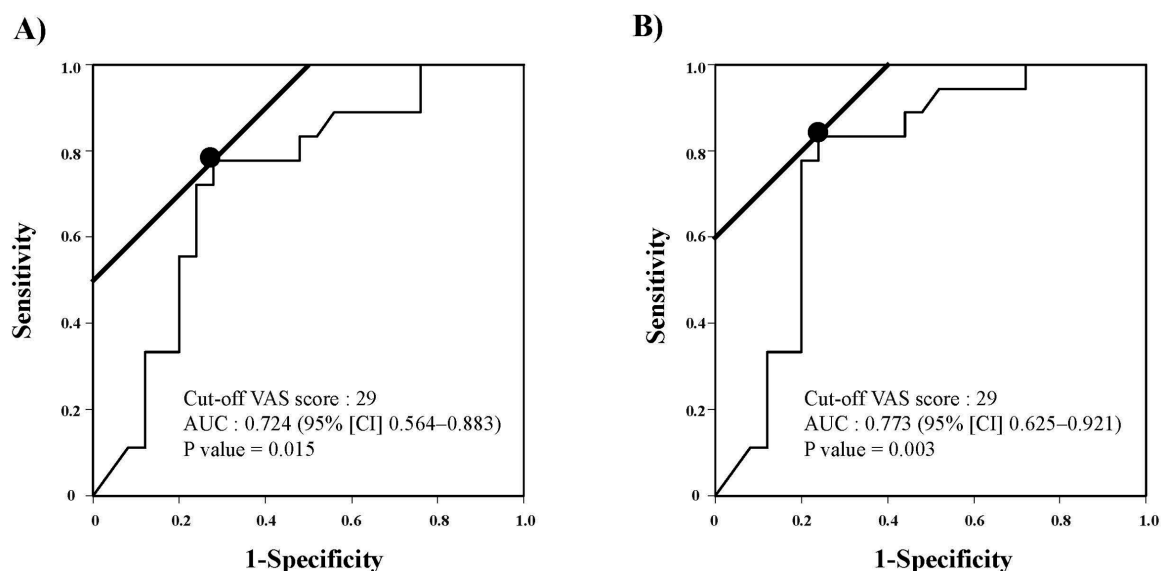


Fig. 4. Receiver Operating Characteristic (ROC) Curves, Cut-Off Visual Analog Scale (VAS) Scores, and Area under the Curve (AUC) Values for Palatability (A) and Overall Acceptability (B).

ROC curve analysis was performed using bitterness VAS scores measured immediately after rebamipide mouthwash use and favorable ratings on the 5-point scales. Scores of 1 or 2 for palatability and overall acceptability were defined as favorable ratings. The cut-off value was determined from the point closest to the upper left corner of the ROC curve. AUC values are presented with 95% confidence intervals (CI).

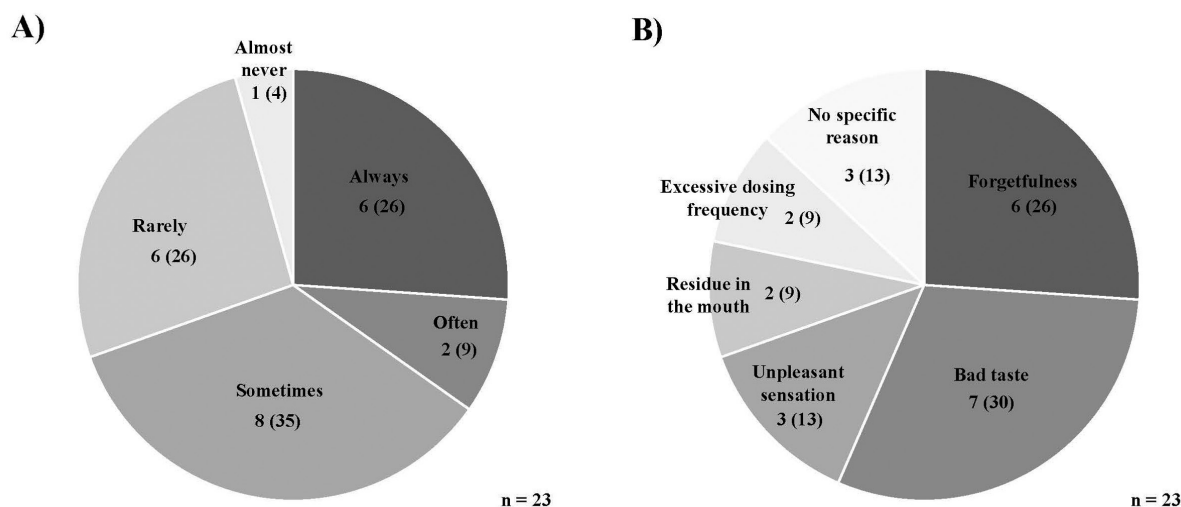


Fig. 5. Frequency of Missed Doses (Q2-1, A) and Reasons for Non-Adherence (Q2-2, B).

Patients reporting non-adherence were asked to report the frequency of missed doses using a 5-point scale and the main reason for non-adherence by selecting from predefined options. Data are presented as number (%) of 23 patients.

quency of missed use (Q2-1), “sometimes” was the most common response (35%) (Fig. 5A). The most frequently reported reason for missed use (Q2-2) was bad taste (30%) (Fig. 5B). Regarding the perceived need for formulation improvement (Q3), 37 patients (86%) answered “yes” (Table 2). Willingness to actively engage in treatment (Q4) had a median NRS score of 5 (range, 1–10) (Table 2). Scores < 6 were reported by 24 patients (56%), whereas 19 patients (44%) reported scores ≥ 6.

Incidence of Oral Mucositis Based on Pharmacist Assessment The distribution of oral mucositis severity

according to CTCAE grade during the 21 days after chemoradiotherapy initiation is presented in Table 4. The numbers of patients who developed grade ≥2 oral mucositis in the first, second, and third weeks were 1 (2%), 4 (9%), and 16 (37%), respectively. Severe oral mucositis (grade ≥3) was rare; by the third week, only 1 patient (2%) experienced difficulty with adequate oral intake.

Outcomes According to Bitterness VAS Score Patients were stratified into two groups based on a bitterness VAS score cut-off of 29, with a low-score group (<29, n = 20) and a

Table 4. Weekly Distribution of Oral Mucositis Severity according to CTCAE Grade during the Study Period through Day 21

	n	CTCAE Grade (%)			
		Grade 0-1	Grade 2	Grade 3	Grade 4-5
Day 1 - 7	44	43 (98)	1 (2)	0 (0)	0 (0)
Day 8 - 14	43	39 (91)	4 (9)	0 (0)	0 (0)
Day 15 - 21	43	27 (63)	15 (35)	1 (2)	0 (0)

Data are presented as number (%). Oral mucositis severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

high-score group (≥ 29 , $n = 23$). Baseline characteristics (age, male, height and weight) did not differ significantly between the groups (Table 1).

Significant differences were observed in ‘Favorable palatability’ and ‘Favorable overall acceptability’ (Table 2). Favorable ratings for palatability were more frequent in the low-score group than in the high-score group (65% vs. 22%, $P = 0.018$). Similarly, favorable ratings for overall acceptability were more frequent in the low-score group (70% vs. 17%, $P = 0.001$).

For secondary outcomes, adherence to the prescribed use did not differ between groups ($P = 1.000$, Table 2). In contrast, a perceived need for formulation improvement was more common in the high-score group (70% vs. 100%, $P = 0.006$). Willingness to engage in treatment was significantly lower in the high-score group (median score 6.5 vs. 4.0, $P = 0.037$). The incidence of CTCAE grade ≥ 2 oral mucositis did not differ between groups ($P = 1.000$, Table 2).

DISCUSSION

This study evaluated the real-world palatability, overall acceptability, and taste attributes of rebamipide mouthwash formulation in patients with head and neck cancer. Favorable ratings for palatability and overall acceptability were observed in only 42% of patients, and bitterness exhibited the highest VAS scores both immediately after use and 5 min later. These findings suggest limited palatability and overall acceptability, likely related to persistent bitterness. Patient responses varied considerably, with some rating the formulation as unpleasant or unacceptable and VAS scores for taste attributes showing a wide range. These findings indicate substantial inter-individual variability in the perception of the formulation.

ROC curve analyses showed that the bitterness VAS score predicted favorable ratings for both palatability and overall acceptability, with an identical optimal cut-off value of 29 for each. Patients in the high-score group (VAS ≥ 29) had lower ratings for palatability and overall acceptability, as well as a greater perceived need for formulation improvement. However, adherence did not differ significantly between groups, suggesting that patients may continue treatment despite dissatisfaction with the taste of the formulation.

Adherence to the prescribed use of rebamipide mouthwash was approximately 50%, with most non-adherent patients citing sensory discomfort as the primary reason. Moreover, most patients reported a need for formulation improvement. These findings suggest that taste-related factors may act as a barrier to consistent use. Because this mouthwash is used prophylactically, maintaining adherence may be more challenging than for symptomatic treatments.¹⁶ Over time, persistent taste discomfort may be associated with reduced adherence, potentially affecting efficacy and quality of life. Although taste-mask-

ing has been reported to improve adherence¹⁷) and has been applied to rebamipide orally disintegrating tablets,¹⁴) its application to mouthwash formulations remains limited. Therefore, addressing persistent bitterness may improve the acceptability of the formulation in patients with head and neck cancer.

The incidence of grade ≥ 2 oral mucositis at week 3 was 37%, whereas severe oral mucositis (grade ≥ 3) was observed in only 2% of patients. Given that grade 2 oral mucositis typically develops during the second or third week of chemoradiotherapy,¹⁸) these findings suggest that rebamipide mouthwash may delay the onset and progression of oral mucositis despite suboptimal adherence.

This study has several limitations, including its single-arm, non-blinded, single-center, and small-scale design, which may limit the generalizability of the findings. However, the patient population is broadly representative of typical head and neck cancer populations,¹⁹) with most patients receiving standard CDDP+RT.²⁰) In addition, the VAS-based evaluation of palatability encompassed not only basic taste but also mouthfeel and overall sensory perception, thereby capturing a broader sensory experience than assessments focused on taste alone. Although patients who switched to the lidocaine-containing formulation were instructed to complete the day 21 questionnaire based on their experience with the lidocaine-free formulation, their responses may have been subject to recall bias.

Conclusions This study demonstrates that persistent bitterness substantially impaired the palatability and overall acceptability of rebamipide mouthwash in patients with head and neck cancer. Taste-related factors were frequently reported as reasons for non-adherence and may act as a barrier to consistent use. Improving the taste of this formulation, particularly by addressing persistent bitterness, may enhance acceptability and support consistent use.

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Ethics Approval and Consent to Participate This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Yamanashi University Hospital (Approval No. CS0033). Written informed consent was obtained from all patients prior to their participation in the study. This study is a prospective observational study and does not require registration as a clinical trial.

Consent for Publication Not applicable. The manuscript does not contain any individual person's data in any form (including any individual details, images or videos).

Availability of Data and Materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests The authors declare that they have no competing interests.

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Authors' Contributions AN contributed to conceptualization, data curation, investigation, and writing of the original draft. SK contributed to investigation, validation, and writing, review, and editing. OY contributed to writing, review, and editing. TS contributed to supervision and writing, review, and editing. SU contributed to conceptualization, project administration, supervision, and writing, review, and editing. All authors read and approved the final manuscript.

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