

Oral Care Evaluation to Prevent Oral Mucositis in Estrogen Receptor-Positive Metastatic Breast Cancer Patients Treated with Everolimus (Oral Care-BC): A Randomized Controlled Phase III Trial

NAOKI NIIKURA¹,^a KATSUHIKO NAKATUKASA,^c TAKESHI AMEMIYA,^d KEN-ICHI WATANABE,^e HIRONOBU HATA,^f YUICHIRO KIKAWA,^g NAOKI TANIKE,^h TAKASHI YAMANAKA,ⁱ SACHIYO MITSUNAGA,^j KAZUHIKO NAKAGAMI,^k MORIYASU ADACHI,^l NAOTO KONDO,^m YASUYUKI SHIBUYA,ⁿ NAOKI HAYASHI,^o MARIKO NAITO,^p KOSUKE KASHIWABARA,^q TOSHINARI YAMASHITA,ⁱ MASAHIRO UMEDA,^r HIROFUMI MUKAI,^s YOSHIHIDE OTA^b

Departments of ^aBreast and Endocrine Surgery and ^bDentistry and Oral and Maxillofacial Surgery, Tokai University School of Medicine, Tokyo, Japan; Departments of ^cBreast and Endocrine Surgery and ^dDentistry and Oral and Maxillofacial Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan; Departments of ^eBreast Surgery and ^fDentistry, Hokkaido Cancer Center, Sapporo, Japan; Departments of ^gBreast Surgery and ^hDentistry and Oral and Maxillofacial Surgery, Kobe City Medical Center General Hospital, Kobe, Japan; Departments of ⁱBreast and Endocrine Surgery and ^jDentistry and Oral and Maxillofacial Surgery, Kanagawa Cancer Center, Yokohama, Japan; Departments of ^kBreast and Endocrine Surgery and ^lOral and Maxillofacial Surgery, Shizuoka General Hospital, Shizuoka, Japan; Departments of ^mBreast and Endocrine Surgery and ⁿDentistry and Oral and Maxillofacial Surgery, Nagoya City University Hospital, Nagoya, Japan; ^oDepartment of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan; ^pDepartment of Oral Epidemiology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; ^qDepartment of Biostatistics, School of Public Health, the University of Tokyo, Tokyo, Japan; ^rDepartment of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; ^sDepartment of Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Oral care • Oral mucositis • Everolimus • Breast cancer

ABSTRACT

Background. The incidence of oral mucositis (any grade) after everolimus treatment is 58% in the general population and 81% in Asian patients. This study hypothesized that professional oral care (POC) before everolimus treatment could reduce the incidence of everolimus-induced oral mucositis.

Materials and Methods. This randomized, multicenter, open-label, phase III study evaluated the efficacy of POC in preventing everolimus-induced mucositis. Patients were randomized into POC and control groups (1:1 ratio) and received everolimus with exemestane. Patients in the POC group underwent teeth surface cleaning, scaling, and tongue cleaning before everolimus initiation and continued to receive weekly POC throughout the 8-week treatment period. Patients in the control group brushed their own teeth and gargled with 0.9% sodium chloride solution or water. The primary endpoint was the incidence of all grades of oral mucositis. We targeted acquisition of 200 patients with a 2-sided type I error rate of 5% and 80% power to detect 25% risk reduction.

Results. Between March 2015 and December 2017, we enrolled 175 women from 31 institutions, of which five did not receive the protocol treatment and were excluded. Over the 8 weeks, the incidence of grade 1 oral mucositis was significantly different between the POC group (76.5%, 62 of 82 patients) and control group (89.7%, 78 of 87 patients; $p = .034$). The incidence of grade 2 (severe) oral mucositis was also significantly different between the POC group (34.6%, 28 of 82 patients) and control group (54%, 47 of 87 patients; $p = .015$). As a result of oral mucositis, 18 (22.0%) patients in the POC group and 28 (32.2%) in the control group had to undergo everolimus dose reduction.

Conclusion. POC reduced the incidence and severity of oral mucositis in patients receiving everolimus and exemestane. This might be considered as a treatment option of oral care for patients undergoing this treatment. *Clinical trial identification number:* NCT 02069093. *The Oncologist* 2020;25:e223–e230

Correspondence: Naoki Niikura, M.D., Ph.D., Department of Breast and Endocrine Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. Telephone: 463-93-1121; e-mail: niikura@is.icc.u-tokai.ac.jp. Received May 20, 2019; accepted for publication August 23, 2019; published Online First on October 8, 2019. <http://dx.doi.org/10.1634/theoncologist.2019-0382>

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Implications for Practice: The Oral Care-BC trial that prophylactically used professional oral care (POC), available worldwide, did not show a greater than 25% difference in mucositis. The 12% difference in grade 1 or higher mucositis and especially the ~20% difference in grade 2 mucositis are likely clinically meaningful to patients. POC before treatment should be considered as a treatment option of oral care for postmenopausal patients who are receiving everolimus and exemestane for treatment of hormone receptor-positive, HER2-negative advanced breast cancer and metastatic breast cancer. However, POC was not adequate for prophylactic oral mucositis in these patients, and dexamethasone mouthwash prophylaxis is standard treatment before everolimus.

INTRODUCTION

Oral mucositis is a clinically significant complication of mucotoxic cancer therapy that affects 5%–40% of patients receiving standard-dose chemotherapy and more than 75% of patients receiving either high-dose chemotherapy with stem cell transplantation or radiation therapy for head and neck cancer [1–3]. Molecularly targeted therapeutic drugs and chemotherapy drugs used for cancer treatment can cause oral mucositis, resulting in pain and other symptoms. The pain makes it difficult for the patient to ingest orally and can result in malnutrition. Difficulties with oral ingestion and poor oral cleaning can also result in an increase of bacteria inside the mouth, which is associated with systemic risks due to an increased risk of aspiration pneumonitis. Oral mucositis can also result in postponement of changes in treatment, discontinuation of treatment, and prolongation of hospitalization [4, 5].

Although guidelines on oral mucositis [2, 3] state that dental intervention is preferred when implementing cancer treatment, such interventions are not strongly recommended. A retrospective study of 495 patients with nonhead and non-neck cancers showed that commencement of oral care reduced the incidence of complicating oral mucositis from 38.5% to 10.5% [6], but this is the only such study, and there is insufficient evidence for a strong recommendation. Saito et al. demonstrated that prophylactic professional oral health care reduced the risk of oral mucositis in a small prospective study to assess the usefulness of such care in preventing mucositis in patients undergoing adjuvant chemotherapy [7].

In a randomized phase III study of the treatment of hormone receptor-positive, hormone therapy-resistant refractory breast cancer, the progression-free survival was significantly longer in a concomitant everolimus group compared with an exemestane monotherapy group [8]. The incidence of oral mucositis of any grade as an adverse drug reaction of everolimus was 58%, and an analysis of Asian patients showed that the corresponding value in these patients was 81% [9], with an incidence of 91% in Japanese patients [10]. However, the mechanism underlying the occurrence of everolimus-induced oral mucositis has not yet been elucidated.

Oral care is recommended with an evidence level of 3 by The Mucositis Study Group of Multinational Association for Supportive Care in Cancer and International Society of Oral Oncology [2, 3]. However, there is a dearth of evidence for recommending oral care, with no data from large-scale randomized studies. Thus, it is unknown whether the occurrence of oral mucositis can be reduced by implementation of professional oral care (POC) in the form of tooth surface cleaning, scaling, and oral hygiene instruction from a dental

and oral surgeon or a dental hygienist before everolimus treatment. Therefore, this study hypothesized that the occurrence of oral mucositis will be reduced by the implementation of dental intervention in the form of tooth surface cleaning, scaling, and oral hygiene instruction from a dentist and oral surgeon and use of Neostelin Green mouthwash before everolimus treatment.

DIGEST OF THE STUDY PROTOCOL

Oral Care-BC was a Japan-based, phase III, multicenter randomized clinical trial that assessed the effectiveness of POC in preventing oral mucositis in patients treated with everolimus and exemestane for hormone receptor-positive, human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer. This trial concept was already showed in Japanese journal of clinical oncology [11]. This study was a multicenter phase III trial, and patients were randomly assigned in a 1:1 ratio (stratified according to center, use of bone-modifying agent, age, and history of receiving chemotherapy within 3 months). Eligible patients were enrolled at 31 investigation sites from academic and community settings in Japan on the basis of the following key inclusion criteria: women aged 20 years or older who were postmenopausal and had metastatic histologically or cytologically confirmed hormone receptor-positive, HER2-negative breast cancer; were newly prescribed everolimus 10 mg and exemestane 25 mg; had Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and showed adequate renal function (serum creatinine level $\leq 1.5 \times$ upper limit of normal). Patients with an edentulous jaw, oral mucositis within 1 month, chemotherapy administered within 1 month prior to randomization (except bisphosphonates or denosumab), and severe or uncontrolled medical conditions were excluded. The institutional review boards at each of the 31 study sites approved the study protocol; all patients gave written informed consent before all study-related procedures.

Procedures

Using a dynamic allocation method that minimizes the effects of the allocation adjustment factors discussed below, the Comprehensive Support Project for Oncology Research (CSPOR) Data Center randomly allocated treatment protocols to participants who were then categorized into the POC and control (C) groups in a ratio of approximately 1:1. The allocation algorithm was employed by the person responsible for biostatistical analysis and considered the following factors: age at enrollment (<65 years vs. ≥ 65 years), use of bone-modifying

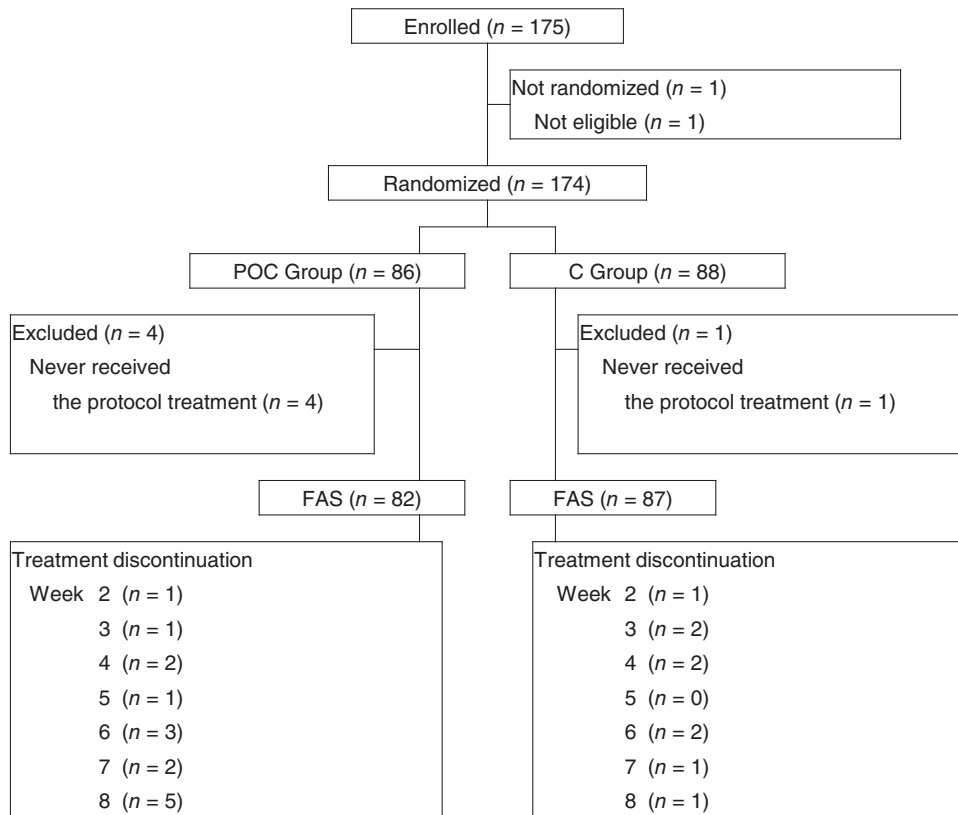


Figure 1. Consort diagram.

Abbreviations: C, control; FAS, full analysis set; POC, professional oral care.

agents (yes vs. no), chemotherapy within the last 3 months (yes vs. no), and facility (facility name).

Patients were randomly allocated to the two groups at enrollment, and the protocol treatment (everolimus 10 mg once a day and exemestane 25 mg once a day) was initiated within 3 weeks from the date of enrollment. "Protocol treatment completion" was defined as oral management for a period of 8 weeks in the C and POC groups.

In the POC group, patients received scaling, crown polishing, brushing instruction, tongue plaque removal instruction, gargling instruction (with Neostelin Green 0.2% mouthwash solution, which is an antiseptic mouthwash containing benzethonium chloride as an active ingredient), and dexamethasone ointment that is steroidal ointment for the oral cavity containing 0.1% dexamethasone use when grade 1 oral mucositis occurred. In the C group (brushing instruction only group), patients received instructions for gargling (with physiological saline) and brushing and were prohibited from using ointments for oral mucositis up to the appearance of grade 2 oral mucositis. The duration of the oral management protocols was 8 weeks in both groups. Dose modification or interruption of everolimus was allowed for management of adverse events. Everolimus use was paused in patients developing grade 2 or 3 stomatitis, and the treatment was resumed after recovery to a maximum severity of grade 1 stomatitis. Patients were discontinued from the study or from everolimus and exemestane treatment for the following reasons: diagnosis of grade 4 stomatitis and other nonhematologic toxicities, diagnosis of grade 3 noninfectious pneumonitis,

disease progression requiring a treatment change, or withdrawal of consent.

At each center, the oncologist and dentist or an oral surgeon assessed and documented oral mucositis separately. Each patient was assessed weekly for oral mucositis until 8 weeks. Safety assessments were performed according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0). Adverse events were monitored throughout the study duration, for 28 days after the last treatment dose (the last dose of everolimus and exemestane), or until study discontinuation. Laboratory assessments of complete blood count, biochemical profile, and liver function profile for adverse event monitoring were performed at screening or baseline and then at every week until 8 weeks.

Interventions were provided by a licensed dentist or a dental hygienist under the supervision of a dentist at 31 sites. Training manuals were prepared to standardize POC. The oncologist and dentist evaluated oral mucositis every week until 8 weeks by using CTCAE v3.0 for a comparison with BOLERO-2.

Outcomes

The primary endpoint was the incidence of grade 1 or worse oral mucositis evaluated by the oncologist over 8 weeks for comparisons between the POC and C groups. For better assessment of the clinical effect of Everolimus-associated stomatitis on patients, we evaluated the primary endpoint using a composite assessment. Oral mucositis was graded by the oncologist with the composite score of CTCAE 3.0.

Table 1. Patient characteristics

Characteristics	POC Group (n = 82)		C Group (n = 87)		p value
	n (%)	95% CI	n (%)	95% CI	
Age					.57 [†]
n, mean (SD)	82, 63.7 (7.4)		87, 62.9 (8.9)		
median (min, max)	64.0 (49, 84)		64.0 (42, 83)		
Age					.93*
<65 yr	42 (51.2)	39.9–62.4	44 (50.6)	39.6–61.5	
≥65 yr	40 (48.8)	37.6–60.1	43 (49.4)	38.5–60.4	
Bone-modifying agent					.84*
Not used	39 (47.6)	36.4–58.9	40 (46.0)	35.2–57	
Used	43 (52.4)	41.1–63.6	47 (54.0)	43–64.8	
Chemotherapy					.55*
Not used	74 (90.2)	81.7–95.7	76 (87.4)	78.5–93.5	
Used	8 (9.8)	4.3–18.3	11 (12.6)	6.5–21.5	
PS					.14*
0	63, (76.8)	66.2–85.4	72, (82.8)	73.2–90	
1	14, (17.1)	9.7–27	15 (17.2)	10–26.8	
2	1 (1.2)	0–6.6	0 (0.0)	0–4.2	
3	0 (0.0)	0–4.4	0 (0.0)	0–4.2	
4	0 (0.0)	0–4.4	0 (0.0)	0–4.2	
Missing	4 (4.9)	1.3–12	0 (0.0)	0–4.2	
BMI (kg/m ²)					.76 [†]
n, mean (SD)	78, 22.95 (3.84)		87, 22.77 (3.55)		
median (min, max)	22.52 (14.9, 35.9)		22.85 (16.4, 34.2)		
BMI					.07 [†]
<25	54, (65.9)	54.6–76	66 (75.9)	65.5–84.4	
≥25	24 (29.3)	19.7–40.4	21 (24.1)	15.6–34.5	
Missing	4 (4.9)	1.3–12	0 (0.0)	0–4.2	
Smoking					.50 [†]
Nonsmoker	75 (91.5)	83.2–96.5	83 (95.4)	88.6–98.7	
Smoker	4 (4.9)	1.3–12	3 (3.4)	0.7–9.7	
Missing	3 (3.7)	0.8–10.3	1 (1.1)	0–6.2	
Alcohol drinking					.90 [†]
Nondrinker	64 (78.0)	67.5–86.4	69 (79.3)	69.3–87.3	
Drinker	14 (17.1)	9.7–27	15 (17.2)	10–26.8	
Missing	4 (4.9)	1.3–12	3 (3.4)	0.7–9.7	

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; PgR, progesteron receptor; PS, performance status.

The following secondary endpoints were assessed throughout the 8-week period. Other endpoints included the incidence of oral mucositis grade greater than or equal to 2 evaluated by an oncologist, incidence of oral mucositis grade greater than or equal to 3 evaluated by an oncologist, incidence of oral mucositis grade greater than or equal to 1 evaluated by a dental and oral surgeon, incidence of oral mucositis grade greater than or equal to 2 evaluated by a dental and oral surgeon, incidence of oral mucositis grade greater than or equal to 3 evaluated by a dental and oral surgeon and time to the onset of oral mucositis, and the duration of each grade of oral mucositis, incidence of patients in suspension or dose reduction of everolimus treatment because of oral mucositis, Oral Assessment Guide (Revised)

[12], health-related quality of life, and time to treatment failure (TTF) were assessed.

Statistical Analysis

Main Analysis And Assessment Criteria

The incidence of oral mucositis of grade greater than or equal to 1 was calculated in the POC and C groups, and their difference was tested. The occurrence of oral mucositis was included if it occurred within 8 weeks from the initiation of protocol treatment, regardless of the completion of dental intervention or protocol treatment (everolimus and exemestane). Although Fisher's exact test was originally planned as the primary analysis, to overcome censoring

Table 2. Primary analysis: Incidence probability of oral mucositis

Oral mucositis grade 1 or worse (by oncologist)	POC group (n = 82), n (%)	C group (n = 87), n (%)	p value ^a
Overall			.034
Yes	62 (75.6)	78 (89.7)	
No	20 (24.4)	9 (10.3)	
Risk difference, % (95% CI) ^a	-11.88 (-22.82 to -0.95)		

^aWeighted analysis by inverse probability of censoring nonparametrically estimated by Kaplan-Meier method; the weight was also estimated nonparametrically stratified by the treatment assignment and the three factors used for minimization: use of bone-modifying agents (yes or no), age (<65 or ≥65 years), and use of chemotherapy within 3 months (yes or no).

Abbreviations: C, control; CI, confidence interval; POC, professional oral care.

prior to 8 weeks follow-up without incidence of oral mucositis, weighted chi-squared test was performed, in which participants were weighted by the inverse of censoring probability [13], which was nonparametrically estimated by the Kaplan-Meier method in each of the strata defined by treatment and stratification factors used for randomization. If the result of this test was statistically significant with a two-sided α -level of 5% and the incidence of oral mucositis was lower in the POC group than in the C group, the dental intervention was considered to have demonstrated some efficacy. The two-sided 95% confidence interval of the difference in incidence was also calculated for the purpose of analysis and interpretation.

The incidence of all grades of oral mucositis in Asian participants in the BOLERO-2 study was 80%, and the incidence of all grades of oral mucositis upon everolimus administration in Japanese participants was assumed to be 80%. The implementation of dental oral management was expected to reduce the relative risk by 25%, and for a two-sided α -level of 5% and statistical power of 80% with Fisher's test, the necessary sample size in the two groups was 182. Taking subject exclusions into account, the target sample size was set at 200. The actual sample size was 175 in total, but the trial still had the power of 77%.

The study protocol was registered at the Web site of the University Hospital Medical Information Network, Japan (protocol identifier 000016109), on January 5, 2015, and at clinicaltrials.gov (NCT02376985).

Role of the Funding Source

This study was funded by CSPOR of Public Health Research Foundation. The research fund was provided to CSPOR by Novartis Pharma K. K (Nishiazabu Minato-Ku, Japan). Novartis Pharma K. K. took no part in this study other than providing information relevant to proper use of the study drug. All decisions concerning the planning, implementation, and publication of this study were made by the steering committee

RESULTS

Between March 2015 and December 2017, 175 patients were screened and 174 eligible patients from 31 centers were

Table 3. Secondary analysis: Incidence probability of oral mucositis

Oral mucositis grade by oncologist or dentist	POC Group (n = 82), n (%)	C Group (n = 87), n (%)	p value ^a
Oral mucositis grade 2 or worse (by oncologist)			.013
Yes	28 (34.1)	47 (54.0)	
No	54 (65.9)	40 (46.0)	
Risk difference, % (95% CI) ^a	-19.00 (-33.71 to -4.28)		
Oral mucositis grade 3 or worse (by oncologist)			.281
Yes	5 (6.1)	10 (11.5)	
No	77 (93.9)	77 (88.5)	
Risk difference, % (95% CI) ^a	-4.78 (-13.40 to 3.83)		
Oral mucositis grade 1 or worse (by dental and oral surgeon)			.034
Yes	66 (80.5)	81 (93.1)	
No	16 (19.5)	6 (6.9)	
Risk difference, % (95% CI) ^a	-10.25 (-19.72 to -0.79)		
Oral mucositis grade 2 or worse (by dental and oral surgeon)			<.001
Yes	33 (40.2)	61 (70.1)	
No	49 (59.8)	26 (29.9)	
Risk difference, % (95% CI) ^a	-29.00 - 43.33 to -14.66)		
Oral mucositis grade 3 or worse (by dental and oral surgeon)			.117
Yes	1 (1.2)	5 (5.7)	
No	81 (98.8)	82 (94.3)	
Risk difference, % (95% CI) ^a	-4.51 (-10.00 to 0.98)		

^aWeighted analysis by inverse probability of censoring nonparametrically estimated by Kaplan-Meier method; the weight was also estimated nonparametrically stratified by the treatment assignment and the three factors used for minimization: use of bone-modifying agents (yes vs. no), age (<65 vs. ≥65 years), and use of chemotherapy within 3 months (yes vs. no).

Abbreviations: C, control; CI, confidence interval; POC, professional oral care.

enrolled in the Oral Care-BC trial (Fig. 1). Of the 174 women enrolled, 169 were evaluable for efficacy and safety; five women were unevaluable because they never received the protocol treatment. In the 169 evaluable patients, the median age was 64 years (range, 49–84) in the POC group and 64 years (range, 42–83) in the C group. Among these patients, 164 (97%) had an ECOG performance status of 0 or 1, and 19 (11%) received chemotherapy for metastatic disease before everolimus and exemestane treatment (Table 1).

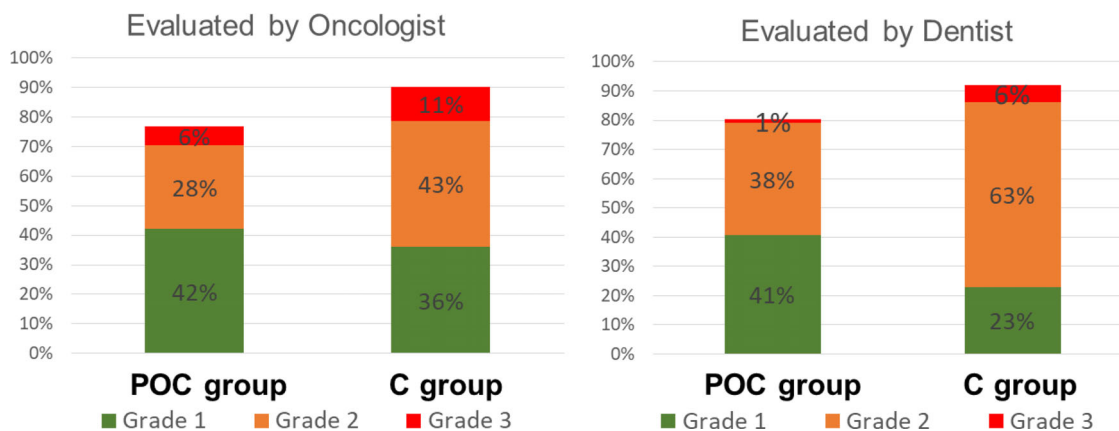


Figure 2. Incidence probability of oral mucositis. Incidence probability evaluated by oncologist (A) and evaluated by dentist (B). Abbreviations: C, control; POC, professional oral care.

Table 4. Delay or dose-reduction of everolimus

Event	POC group (n = 82), n (%)	C group (n = 87), n (%)	p value ^a
Treatment suspension			.079
Yes	37 (45.1)	51 (58.6)	
No	45 (54.9)	36 (41.4)	
Risk difference (95% CI)	-13.5 (-28.4 to 1.4)		
Dose reduction of everolimus treatment due to oral mucositis			.135
Yes	18 (22.0)	28 (32.2)	
No	64 (78.0)	59 (67.8)	
Risk difference (95% CI)	-10.2 (-23.5 to 3.1)		
Treatment suspension or dose reduction			.059
Yes	42 (51.2)	57 (65.5)	
No	40 (48.8)	30 (34.5)	
Risk difference (95% CI)	-14.3 (-29.0 to 0.4)		

^aChi-squared test.

Abbreviations: C, control; CI, confidence interval; POC, professional oral care.

In the full analysis set of 169 patients treated with everolimus and exemestane, the primary endpoint of grade 1 or worse oral mucositis evaluated by an oncologist within 8 weeks occurred in 62 of 82 patients (75.6%) in the POC group and 78 of 87 patients (89.7%) in the C group (Table 1; $p = .034$). The risk difference was -11.88 (95% confidence interval [CI], -22.80 to -0.85 ; Table 2).

The secondary endpoint of grade 2 or worse oral mucositis evaluated by an oncologist occurred in 28 of 82 patients (34.1%) in the POC group and in 47 of 87 patients (54%) in the C group (Table 3; $p = .013$). The risk difference was -19.00 (95% CI, -33.71 to -4.28). Grade 3 or worse oral mucositis evaluated by the oncologist occurred in 5 of 82 patients (6.1%) in the POC group and 10 of 87 patients (11.5%) in the C group (Table 3; $p = .281$). The risk difference was -4.78 (95% CI, -13.40 to 3.83).

The other secondary endpoint of grade 1 or worse oral mucositis evaluated by a dentist or oral surgeon occurred in

66 of 81 patients (80.5%) in the POC group and in 82 of 87 patients (93.1%) in the C group ($p = .034$). The risk difference was -10.25 (95% CI, -19.72 to -0.79). Grade 2 or worse oral mucositis evaluated by a dentist or oral surgeon occurred in 33 of 82 patients (40.2%) in the POC group and 61 of 87 patients (69%) in the C group (Table 3) ($p < .001$). The risk difference was -29.00 (95% CI, -43.33 to -14.66). Grade 3 or worse oral mucositis evaluated by a dentist or oral surgeon occurred in 1 of 82 patients (1.2%) in the POC group and 5 of 87 patients (5.7%) in the C group (Table 3; $p = .117$). The risk difference was -4.51 (95% CI, -10 to 0.98 ; Fig. 2).

During the entire study duration, treatment delays caused by a suspected treatment-related adverse event occurred in 37 patients (45.1%) in the POC group and 51 patients (58.6%) in the C group ($p = .079$) over the 8-week period, with the most common adverse event being stomatitis (Table 4). Dose reduction of everolimus treatment because of oral mucositis occurred in 18 patients (22%) in the POC group and 28 patients (32.2%) in the C group ($p = .135$) because of a suspected treatment-related adverse event, the most common of which was stomatitis.

Sixty-five (79%) of 82 patients in the POC group and 75 (86%) of 87 patients in the C group continued to receive treatment with protocol treatment after the 8-week study period. The median TTF was 6.75 months in the POC group and 5.74 months in the C group. This difference was not statistically significant ($p = .601$). A total of 148 of the 169 patients stopped everolimus and exemestane; 100 patients showed disease progression (median, 13.9 week follow-up; interquartile range, 6.9–23.9).

Overall, during the 8-week period, adverse events occurred in 71 (86%) of the 82 patients in the POC group and 82 (94%) of the 87 patients in the C group ($p = .059$). The most frequently reported adverse events, regardless of causality, were oral mucositis, appetite loss, dysgeusia, fatigue, and constipation (Table 5). The incidence of oral mucositis and peripheral edema differed significantly between the POC and C groups. The incidence of other oral-related events such as appetite loss and dysgeusia did not differ significantly between the two groups. No patient developed oral candidiasis during the study period.

DISCUSSION

This study is the first randomized trial to compare POC with a control group to evaluate its effectiveness in reducing oral mucositis. The results of the Oral Care-BC show that POC before everolimus treatment can prevent or reduce the incidence and severity of all-grade oral mucositis evaluated by oncologists and dentists, especially grade 2 or worse oral mucositis at 8 weeks in comparison with the incidence in a control group. No significant difference in the suspension or dose reduction of everolimus was noted between the POC and C groups. POC for early-onset disease and management of oral mucositis might have further improved tolerability and adherence.

Oral care is based on the following principles: prevention of infections, pain control, maintenance of oral function, and the interplay between managing oral complications of cancer treatment and improving quality of life [14]. The position paper for oral care described that oral and dental care must be recognized as a critical component of care prior to and during chemotherapy and hematopoietic stem cell transplantation and in survivorship. A multidisciplinary team approach is the key for success in the management of oral complications in hematology-oncology patients, including those undergoing hematopoietic stem cell transplantation [14]. In this context, POC can reduce early-onset oral mucositis during treatment with everolimus.

Oral Care-BC is a randomized control study because Asian patients show a higher incidence oral mucositis than western populations. Subgroup analyses in BOLERO-2 study showed that oral mucositis occurred in 81% of the Asian population [9], with the corresponding number in the Japanese being as high as 91% [10]. These findings could be attributable to the fact that the recommended dose of everolimus (10 mg) does not take weight and body mass index into account, and Asian individuals have a smaller body surface area.

The other study on prophylactic oral mucositis was the SWISH trial [15], which clearly showed that dexamethasone prophylaxis had a profound effect. In that trial, grade 2 or worse stomatitis was observed in only 2 (2%) of 85 patients by 8 weeks (95% CI, 0.29–8.24). The inclusion of video instructions about brushing the teeth at least twice daily with a soft-bristled toothbrush, daily flossing, and maintenance of good oral hygiene in the SWISH trial may have improved adherence and outcomes compared with those observed in a real-world situation.

In our study, POC had a profound effect on oral mucositis. However, 76.5% of the patients showed oral mucositis, indicating the need for other prophylactic approaches such as dexamethasone mouth wash. The POC might have prevented oral fungus infection, because dexamethasone mouth wash led to oral candidiasis in 2 of 85 patients.

These findings reinforce the importance of prophylaxis initiation concurrent with everolimus and exemestane treatment and the rationale for an early and short-term intervention. As such, the most oral mucositis events from the safety set occurred within the first 8 weeks of treatment, which is consistent with the findings from larger datasets [16]. In BOLERO-2, 83% of grade 2 or worse oral mucositis events occurred within 8 weeks, further supporting the rationale that the 8-week cutoff is sufficient to capture most events.

However, whether continuous preventive usage of POC over a longer period could further decrease the incidence of oral mucositis remains unknown.

The concurrent use of POC and an mTOR inhibitor during the period of highest risk for oral mucositis is an effective strategy. POC may allow broader use of everolimus with less toxicity in other indications with a higher incidence of oral mucositis, such as advanced renal cell carcinoma (incidence of oral mucositis, 59%) [16] or advanced neuroendocrine tumors (70%).

We recognize that our study has some limitations. Dexamethasone mouthwash prophylaxis has been a standard treatment before everolimus administration, but we did not evaluate the POC effect in the presence of dexamethasone mouthwash usage in our research. In addition, the duration of the follow-up was only 8 weeks. However, the patients from BOLERO-2 served as the benchmark for the 8-week incidence of oral mucositis, and this endpoint was considered to be valid because most events were observed within this time period [16]. A phase III, randomized trial design for Oral Care-BC was chosen because the Asian population shows a high incidence of oral mucositis. However, because our study was an open design with only a small difference between the POC and C groups observed, we cannot deny the possibility of bias in our assessment. Finally, our oral care protocol requires dental specialist consultation before everolimus treatment; however, oral health during cancer treatment is important to prevent not only stomatitis but also infection, osteonecrosis of the jaw.

CONCLUSION

The Oral Care-BC trial that prophylactically used POC, available worldwide, did not show a greater than 25% difference in mucositis. The 12% difference in grade 1 or higher mucositis and especially the ~20% difference in grade 2 mucositis are likely clinically meaningful to patients. POC before treatment should be considered a new treatment option of oral care for postmenopausal patients who are receiving everolimus and exemestane for treatment of hormone receptor-positive, HER2-negative advanced breast cancer and metastatic breast cancer, especially in the first 8 weeks of treatment and as needed thereafter. However, POC was not adequate for prophylactic oral mucositis in these patients, and steroid prophylaxis is standard treatment. In the future, POC may be considered as a treatment option in other diseases for which everolimus is indicated (advanced renal cell carcinoma, subependymal giant cell astrocytoma associated with tuberous sclerosis complex, and advanced neuroendocrine tumors).

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AUTHOR CONTRIBUTIONS

Conception/design: Naoki Niikura, Ken-ichi Watanabe, Naoki Hayashi, Mariko Naito, Kosuke Kashiwabara, Toshinari Yamashita, Masahiro Umeda, Yoshihide Ota

Provision of study material or patients: Naoki Niikura, Katsuhiko Nakatukasa, Takeshi Amemiya, Ken-ichi Watanabe, Hironobu Hata, Yuichiro Kikawa, Naoki Taniike, Takashi Yamanaka, Sachiyo Mitsunaga, Kazuhiko Nakagami, Moriyasu Adachi, Naoto Kondo, Yasuyuki Shibuya, Naoki Hayashi, Toshinari Yamashita, Masahiro Umeda, Hirofumi Mukai, Yoshihide Ota

Collection and/or assembly of data: Naoki Niikura, Katsuhiko Nakatukasa, Takeshi Amemiya, Ken-ichi Watanabe, Hironobu Hata, Yuichiro Kikawa, Naoki Taniike, Takashi Yamanaka, Sachiyo Mitsunaga, Kazuhiko Nakagami, Moriyasu Adachi, Naoto Kondo, Yasuyuki Shibuya, Naoki Hayashi, Mariko Naito, Kosuke Kashiwabara, Toshinari Yamashita, Masahiro Umeda, Hirofumi Mukai, Yoshihide Ota

Data analysis and interpretation: Naoki Niikura, Ken-ichi Watanabe, Naoki Hayashi, Mariko Naito, Kosuke Kashiwabara, Toshinari Yamashita, Masahiro Umeda, Hirofumi Mukai, Yoshihide Ota

Manuscript writing: Naoki Niikura, Yoshihide Ota

Final approval of manuscript: Naoki Niikura, Katsuhiko Nakatukasa, Takeshi Amemiya, Ken-ichi Watanabe, Hironobu Hata, Yuichiro Kikawa, Naoki Taniike, Takashi Yamanaka, Sachiyo Mitsunaga, Kazuhiko Nakagami, Moriyasu Adachi, Naoto Kondo, Yasuyuki Shibuya, Naoki Hayashi, Mariko Naito, Kosuke Kashiwabara, Toshinari Yamashita, Masahiro Umeda, Hirofumi Mukai, Yoshihide Ota

DISCLOSURES

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