Oral care and oral assessment guide in breast cancer patients receiving everolimus and exemestane: Subanalysis of a randomized controlled trial (Oral Care-BC)

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Research article

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Abstract

Background

This randomized, controlled, multicenter, open-label, phase III study was conducted to determine whether professional oral care (POC) reduces oral mucositis in estrogen receptor-positive metastatic breast cancer patients treated with everolimus and exemestane.

Methods

One hundred seventy-four patients were randomized into the POC group (n = 86) or the control group (n = 88). Four patients in the POC group and one patient in the control group were excluded from the study because they did not receive the protocol treatment. Thus, 169 patients (POC group: 82 patients; control group: 87 patients) were evaluated for efficacy and safety. The POC group received oral health instruction (OHI), professional mechanical tooth and tongue cleaning, gargling with a benzethonium chloride mouthwash, and dexamethasone ointment when grade 1 mucositis manifested. The control group received OHI and gargling. Eight weeks after everolimus and exemestane were administered, the patients were evaluated for oral status (based on the Oral Assessment Guide [OAG] criteria) and oral mucositis status (assessed with Common Terminology Criteria for Adverse Events [CTCAE] functional and clinical examinations).

Results

The incidences of oral mucositis of any grade and severe mucositis of grade 2 were significantly lower in the POC group ($p = 0.034$ and $p = 0.013$, respectively), based on the CTCAE functional and CTCAE clinical examinations ($p = 0.034$ and $p < 0.001$, respectively). The longitudinal data of the total OAG score ($p = 0.012$), total OAG grade ($p = 0.014$), and the longitudinal data of the OAG score of teeth/dentures ($p = 0.026$) and mucous membranes ($p = 0.011$) were significantly different between the two groups. The grade of oral mucositis diagnosed with CTCAE functional/clinical examinations was significantly correlated with the OAG grade for swallow ($p = 0.04/p < 0.01$), lip ($p = < 0.01/p < 0.01$), teeth/dentures ($p = 0.04/p = 0.01$), mucous membrane ($p < 0.01/p < 0.01$), tongue ($p < 0.01/p < 0.01$), and saliva ($p < 0.01/p < 0.01$).

Conclusions

Professional oral care may prevent oral mucositis and improve the condition of teeth/dentures in patients receiving everolimus and exemestane treatment.

Trial registration:

The study protocol was registered on the website of the University Hospital Medical Information Network (Tokyo, Japan; protocol ID 000016109) on January 5, 2015, and was registered on the ClinicalTrials.gov website (ClinicalTrials.gov identifier: NCT02376985) on March 3, 2015.

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Background

Oral mucositis is a clinically significant adverse event of cancer therapy. Its incidence is 5–40% among patients receiving standard-dose chemotherapy, and 75% or greater among patients receiving high-dose chemotherapy with stem-cell transplantation or radiation therapy for head and neck cancer [1, 2]. When the oral cavity and the salivary glands are exposed to radiation therapy, hyposalivation, oral mucositis, taste loss, trismus, radiation-induced dental caries, and osteoradionecrosis are the most common adverse events. Therefore, early and active participation of dental professionals may be paramount in patients' quality of life during and after radiotherapy [3]. Oral mucositis reduces the quality of life of patients and may result in the discontinuation of treatment and a poorer prognosis. Molecularly targeted therapeutic drugs can also cause oral mucositis. In particular, among patients receiving everolimus treatment, the incidence of oral mucositis of any grade is as high as 58% and is 81% among Asian patients and 91% among Japanese patients, based on subgroup analyses in the BOLERO-2 study [4, 5]. These findings could be attributable to the fact that the recommended dose of everolimus (10 mg) does not take into account weight and body mass index, and Asian individuals have a smaller body surface area. Among Asians, people in East Asia, including Japan, are more likely to have strong adverse effects because of their lower weight than are people in West Asia and South Asia. However, the mechanisms and prevention of everolimus-induced oral mucositis have not been elucidated.

Based on an evidence level of 3, the Mucositis Study Group of Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) recommend oral care for all patients receiving cancer chemotherapy and radiotherapy [2], although no data from large-scaled randomized controlled trials support the efficacy of oral care in preventing oral mucositis. Therefore, we conducted a randomized controlled trial to determine whether professional oral care (POC)— consisting of professional mechanical tooth cleaning, scaling, gargling with an antiseptic mouthwash containing benzethonium chloride, oral hygiene instruction, and use of dexamethasone ointment when grade 1 mucositis manifests—truly reduces oral mucositis in estrogen receptor-positive metastatic breast cancer patients treated with everolimus and exemestane (i.e., the Oral Care Evaluation to Prevent Oral Mucositis in Estrogen Receptor-Positive Metastatic Breast Cancer Patients Treated with Everolimus [Oral Care-BC] trial). This subanalysis study focused on the relationship between POC and changes in the Oral Assessment Guide (OAG) score/grade [6, 7].

A summary of the study protocol and treatment in the Oral Care-BC trial

Oral Care-BC is a Japan-based, phase 3, 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 [8]. Patients were randomized into the POC group and the control group in a 1:1 ratio (stratified, based on the center, use of bone-modifying agents, patient's age, and history of receiving chemotherapy within 3 months). Patients in the POC group received oral hygiene instruction, professional mechanical tooth cleaning, scaling, gargling with antiseptic mouthwash containing benzethonium chloride (Neostelin Green 0.2% mouthwash solution; Nihon Shika Yakuhin, Co., Ltd., Osaka, Japan), and dexamethasone ointment (Dexaltin Oral Ointment, 1 mg/g; Nihon Kayaku Co., Ltd, Tokyo Japan) when grade 1 mucositis manifested. The primary endpoint was the incidence of oral mucositis of any grade after everolimus and exemestane treatment, as evaluated with functional examination.

The inclusion criteria were as follows: 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 an Eastern Cooperative Oncology Group performance status of 0–1 [9]; and had adequate renal function (serum creatinine level $\leq 1.5 \times$ the upper limit of normal). The exclusion criteria consisted of (1) edentulism; (2) oral mucositis within 1 month; (3) chemotherapy administered within 1 month before randomization (except for bisphosphonate drugs or denosumab); and (4) severe or uncontrolled medical conditions.

Methods

Patients

Patients treated with everolimus and exemestane for hormone receptor-positive, human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer were recruited into the study. The inclusion and exclusion criteria were described previously. Between May 2015 and December 2017, 175 patients were screened in Japan. Of these, 174 eligible patients from 31 centers were enrolled in the Oral Care-BC trial (Fig. 1). Among the enrolled patients, 86 patients were allocated to the POC group and 88 patient were allocated to the control group. Four patients in the POC group and one in the control group were excluded from the study because they did not receive the protocol treatment. Thus, 169 patients (82 in the POC group and 87 in the control group) were evaluated for efficacy and safety. This study was conducted in accordance with the 2013 Declaration of Helsinki criteria [10]. The institutional review boards at each of the 31 study sites approved the study protocol. Written informed consent was obtained from all participants included in the study.

Evaluation of intraoral findings

Before the administration of everolimus and exemestane, a dentist examined the oral status of each patient once weekly for 8 weeks by using the OAG criteria, which were modified by Anderson *et al*. [6] from the original guideline described by Eilers [7]. The OAG is used to evaluate the oral condition, and is based on eight factors: swallow, lip, tongue, saliva, mucous membrane, gingivae, teeth/dentures, and voice. Each factor is categorized as grade 1 (normal), grade 2 (mild to moderate change), or grade 3 (moderate to severe change). Furthermore, the oral status is evaluated as "normal" when the total OAG

score is ≤ 8, as “mild functional disturbance” when the total OAG score is 9–12, and as “moderate or severe functional disturbance” when the total OAG score is ≥ 13.

The patients were examined once weekly for oral mucositis by an oncologist, who used the functional examination of Common Terminology Criteria for Adverse Events (CTCAE) guidelines, version 4.0 [11], and by a dentist, who conducted clinical examination in accordance with CTCAE guidelines, version 3.0 [12]. The functional examination findings were “grade 1” for asymptomatic or mild symptoms for which an intervention was not indicated; “grade 2” for moderate pain that did not interfere with oral intake but was an indication for a modified diet; and “grade 3” for severe pain that interfered with oral intake. The clinical examination findings were “grade 1” for erythema of the mucosa; “grade 2” for patchy ulcerations or pseudomembranes; and “grade 3” for confluent ulcerations or pseudomembranes, and bleeding with minor trauma. Before the administration of everolimus and exemestane, periodontal disease was further classified by a dentist into three categories: “mild” for a pocket depth of ≤ 3.0 mm and mobility of grade 1 or less; “moderate” for a pocket depth 4–6 mm or one or more teeth with grade 2 mobility; and “severe” for a pocket depth ≥ 7 mm or one or more teeth with grade 3 mobility.

Outcome

The primary endpoint was to examine whether a difference would exist between the POC group and the control group in the total score of the OAG. The secondary endpoints were (1) to examine whether a difference existed in each OAG score between the POC group and the control group and (2) to examine whether a relationship existed between oral mucositis and the total OAG score, or between oral mucositis and each OAG score.

Statistical analysis

The differences in the incidence of oral mucositis in the POC group and in the control group were analyzed by using the Fisher test. The differences in periodontal disease and the OAG score between the POC and control groups were analyzed by using the chi-square test or the Wilcoxon rank-sum test. The longitudinal data of changes in the OAG score between the POC group and the control group were analyzed by using the linear mixed effect model. A two-tailed *p* value of 5% or less was significant.

Ethics and registration

The study was approved by Institutional Review Board for Clinical Research, Tokai University (approval no.: 14R-063). The study protocol was registered on the website of the University Hospital Medical Information Network (Tokyo, Japan; protocol ID 000016109) on January 5, 2015, and registered on the ClinicalTrials.gov website (ClinicalTrials.gov identifier: NCT02376985) on March 3, 2015. Details are available at the following addresses:

(1) https://upload.umin.ac . jp/cgi-open-bin/ctr/ctr.cgi?function = brows&action = brows&type = summary&recptno = R000018713&language = J
(2) https://clinicaltrials.gov/ct2/show/NCT02376985

Results

Main results of the Oral Care-BC trial

Tables 1 and 2 show the patients' characteristics and main results of Oral Care-BC, as reported previously [11]. Based on functional examinations, the incidence of grade 1 oral mucositis was significantly different between the POC group (75.6%) and the control group (89.7%) ($p = 0.034$). The incidence of grade 2 (i.e., severe) oral mucositis was also significantly different between the POC group (34.1%) and the control group (54.0%) ($p = 0.013$). Based on clinical examinations, grade 1 oral mucositis occurred in 80.5% of the POC group patients and in 93.1% of the control group patients ($p = 0.034$), and grade 2 oral mucositis occurred in 40.2% of the POC group patients and in 70.1% of the control group patients ($p < 0.001$).

Table 1
Patient characteristics

Characteristics	POC group (n=82)	Control group (n=87)	*p*-value
Age			0.57
mean (SD)	63.7 (7.4)	62.9 (8.9)	
median (min, max)	64.0 (49, 84)	64.0 (42, 83)	
Bone-modifying agent			0.84
Not used	39	40	
Used	43	47	
Chemotherapy			0.55
Not used	74	76	
Used	8	11	
PS			0.14
0	63	72	
1	14	15	
2	1	0	
3	0	0	
4	0	0	
Missing	4	0	
BMI (kg/m^2)			0.76
mean (SD)	22.95 (3.84)	22.77 (3.55)	
median (min, max)	22.52 (14.9, 35.9)	22.85 (16.4, 34.2)	
Smoking			0.50
Nonsmoker	75	83	
Smoker	4	4	
Missing	3	1	
Alcohol drinking			0.90
Nondrinker	64	69	
Drinker	14	15	
Missing	4	3	

Table 2

Incidence probability of oral mucositis

Oral mucositis	POC group (n=82)	Control group (n=87)	*p*-value
grade 1 or more (by functional examination)			0.034
Yes	62	78	
No	20	9	
grade 1 or more (by clinical examination)			
Yes	66	81	0.034
No	16	6	
grade 2 or more (by functional examination)			
Yes	28	47	0.013
No	54	40	
grade 2 or more (by clinical examination)			
Yes	33	61	<0.001
No	49	26	

Intraoral baseline findings in the POC and control groups

Table 3 shows the baseline OAG score and grade, and periodontal disease status in the POC and control groups. Before the administration of everolimus and exemestane, the POC group patients had significantly more severe periodontal disease than did the control group patients. The total OAG score, the OAG grade, and the OAG score of teeth/dentures were also worse in the POC group than in the control group.

Table 3
Background factors of baseline

	POC group (n=82)		Control group (n=87)		p-value
Periodontal disease, n, %, (95% CI)					<0.01 *
none	18	22.0 (13.,7-32.8)	36	41.4 (30.9-52.4)	
mild	63	76.8 (67.2-86.3)	51	58.6 (47.6-69.1)	
moderate	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
severe	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
OAG (total score)					<0.01 †
n, mean (SD)	80	9.4 (1.6)	87	8.9 (1.4)	
median (min, max)		9.0 (8, 14)		8.0 (8, 15)	
OAG (grade)					0.01 *
normal	30	36.6 (26.9-49.0)	52	59.8 (48.7-70.1)	
mild	45	54.9 (44.7-67.3)	33	37.9 (27.7-49.0)	
moderate / severe	5	6.1 (2.1-14.0)	2	2.3 (0.3-8.1)	
Voice, n, %, (95% CI)					0.33 *
grade 1	81	98.8 (95.5-100)	86	98.9 (93.8-100)	
grade 2	0	0.0 (0-4.5)	1	1.1 (0-6.2)	
grade 3	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
Swallowing, n, %, (95% CI)					□ *
grade 1	81	98.8 (95.5-100)	87	100.0 (95.8-100)	
grade 2	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
grade 3	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
Lip, n, %, (95% CI)					0.61 *
grade 1	76	92.7 (87.7-98.6)	81	93.1 (85.6-97.4)	
grade 2	4	4.9 (1.4-12.3)	6	6.9 (2.6-14.4)	
grade 3	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
Tooth, denture, n, %, (95% CI)					<0.01 *
grade 1	41	50.0 (39.3-61.9)	63	72.4 (61.8-81.5)	
grade 2	30	36.6 (26.6-48.5)	22	25.3 (16.6-35.7)	

grade 3	10	12.2 (6.1-21.5)	2	2.3 (0.3-8.1)	
Mucosa, n, %, (95% CI)					0.57 *
grade 1	73	89.0 (81.5-95.6)	82	94.3 (87.1-98.1)	
grade 2	7	8.5 (3.5-17)	4	4.6 (1.3-11.4)	
grade 3	1	1.2 (0-6.7)	1	1.1 (0-6.2)	
Gingiva, n, %, (95% CI)					0.26 *
grade 1	48	58.5 (47.8-70.1)	62	71.3 (60.6-80.5)	
grade 2	32	39.0 (28.8-51)	24	27.6 (18.5-38.2)	
grade 3	1	1.2 (0-6.7)	1	1.1 (0-6.2)	
Tongue, n, %, (95% CI)					0.30 *
grade 1	74	90.2 (83-96.5)	84	93.1 (85.6-97.4)	
grade 2	6	7.3 (2.8-15.4)	3	3.4 (0.7-9.7)	
grade 3	1	1.2 (0-6.7)	0	0.0 (0-4.2)	
Xerostomia, n, %, (95% CI)					0.15 *
grade 1	70	85.4 (77-93)	81	93.1 (85.6-97.4)	
grade 2	11	13.4 (7-23)	6	6.9 (2.6-14.4)	
grade 3	0	0.0 (0-4.5)	0	0.0 (0-4.2)	
† wilcoxon rank sum test					
* chi-square test					

Change in the OAG score in the POC and control groups

Total OAG score and grade in the control group increased in the first 2 weeks, whereas the total OAG score and grade in the POC group remained stable or decreased slightly during the whole study period. The longitudinal data of the total OAG score and total OAG grade were significantly different between the two groups (Fig. 2). An examination of each OAG score revealed significant differences between the POC and control groups in the longitudinal data of teeth/dentures and mucous membranes (Fig. 3).

Relationship between the OAG score and oral mucositis

The relationship between the total OAG score/grade and oral mucositis, based on clinical and functional examinations, is presented in Table 4. A significant correlation existed in that the total OAG score and grade increased as oral mucositis became more severe. With regard to the relationship between each

OAG grade and mucositis, the OAG grades for swallow, lip, teeth/dentures, mucous membranes, tongue, and saliva were significantly associated with the severity of oral mucositis (Table 5).

Table 4

Relationship between OAG total score/grade and oral mucositis

OAG	Grade of oral mucositis (by oncologist)					*p*-value	Grade of oral mucositis (by dentist)					*p*-value
	0	1	2	3	4		0	1	2	3	4	
Total score						<0.01						<0.01
3	0	0	0	0	0		0	0	0	0	0	
4	0	0	0	0	0		0	0	0	0	0	
5	0	0	0	0	0		0	0	0	0	0	
6	0	0	0	0	0		0	0	0	0	0	
7	0	0	0	0	0		0	0	0	0	0	
8	317	111	27	0	0		494	110	34	1	0	
9	195	97	28	4	0		260	94	45	0	0	
10	80	91	22	2	0		119	60	59	0	0	
11	43	42	13	1	0		65	36	28	1	0	
12	22	37	13	2	0		38	25	21	4	0	
13	12	17	13	1	0		17	16	15	1	0	
14	2	11	3	2	0		6	9	8	0	0	
15	0	2	0	2	0		2	1	2	1	0	
16	0	1	2	2	0		0	1	4	0	0	
17	1	0	0	0	0		0	0	1	0	0	
18	0	0	0	0	0		0	0	0	0	0	
19	0	0	1	0	0		0	0	1	0	0	
20	0	0	0	0	0		0	0	0	0	0	
21	0	0	0	0	0		0	0	0	0	0	
22	0	0	0	0	0		0	0	0	0	0	
23	0	0	0	0	0		0	0	0	0	0	
24	0	0	0	0	0		0	0	0	0	0	
Total grade						<0.01						<0.01
normal	317	111	27	0	0		494	110	34	1	0	

mild	340	267	76	9	0		482	215	153	5	0
moderate / severe	15	31	19	7	0		25	27	31	2	0

Table 5

Relationship between each OAG grade and oral mucositis

OAG		Grade of oral mucositis (by oncologist)					*p*-value	Grade of oral mucositis (by dentist)					*p*-value
		0	1	2	3	4		0	1	2	3	4	
Voice							0.64						0.89
	grade 1	645	391	116	11	0		973	341	205	5	0	
	grade 2	29	17	5	4	0		31	11	13	2	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Swallow							0.04						<0.01
	grade 1	658	390	105	8	0		991	334	194	4	0	
	grade 2	18	21	18	8	0		16	19	26	4	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Lips							<0.01						<0.01
	grade 1	556	291	78	7	0		883	246	137	3	0	
	grade 2	117	101	37	7	0		120	103	59	4	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Teeth/dentures							0.04						0.01
	grade 1	550	309	84	8	0		739	277	164	5	0	
	grade 2	120	101	38	8	0		240	75	54	3	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Mucous membrane							<0.01						<0.01
	grade 1	600	286	89	9	0		937	243	133	5	0	
	grade 2	71	104	23	6	0		66	97	64	3	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Gingivae							0.21						0.08
	grade 1	542	316	84	10	0		760	281	154	5	0	
	grade 2	133	94	38	6	0		244	71	65	3	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Tongue							<0.01						<0.01

	grade 1	617	302	84	7	0		936	269	142	2	0	
	grade 2	59	92	25	8	0		70	73	56	5	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	
Saliva							<0.01						<0.01
	grade 1	592	334	105	8	0		890	293	178	7	0	
	grade 2	84	74	17	7	0		118	57	40	1	0	
	grade 3	0	0	0	0	0		0	0	0	0	0	

Discussion

In this randomized controlled trial, we examined whether POC would truly reduce oral mucositis in estrogen receptor-positive metastatic breast cancer patients treated with everolimus and exemestane. We found that the incidences of oral mucositis of any grade and severe mucositis of grade 2 were significantly lower in patients in the POC group than in the control group, and the grade of oral mucositis was significantly correlated with OAG grade for swallow, lip, teeth/dentures, mucous membranes, tongue, and saliva. In this study, the functional examination classification of oral mucositis was determined by an oncologist, and the clinical examination classification was determined by a dentist familiar with findings in the oral cavity. Similar results were obtained by using any of the determination methods.

For patients with advanced breast cancer, the treatment aims are to delay disease progression while minimizing treatment-related adverse events. Oral mucositis associated with mammalian target of rapamycin (mTOR) inhibitor drug use reduces the oral food intake, drug adherence, and quality of life of patients [13]. On account of the clinical benefits and potential long-term use of everolimus and exemestane, establishing an effective strategy is desirable to prevent and reduce oral mucositis associated with these drugs.

Rugo *et al*. [14] reported that the prophylactic use of dexamethasone mouthwash reduced the incidence of severe oral mucositis in women with hormone receptor-positive, HER2-negative metastatic breast cancer (i.e., the SWISH trial). However, their study was a single-arm, phase 2 trial with a historical control.

To the best of our knowledge, the Oral Care-BC trial is the first randomized controlled trial that has clarified the efficacy of POC in preventing chemotherapy-related oral mucositis. Furthermore, the use of mouthwash containing steroids has not been allowed in Japanese insurance practice, and only dexamethasone- or triamcinolone-containing ointment has been approved for use on the oral mucosa.

Several assessment methods of the oral cavity have been used during chemotherapy or radiotherapy. Among these methods, Eilers OAG [7] is the most relevant method used in daily clinical practice [15]. The revised OAG is a revision of Eilers' OAG that can be applied to young people and to the elderly [7]. The relationship between the use of everolimus and exemestane and the change in the OAG score/grade has

not been reported. Our study revealed that the OAG score was increased in the control group, whereas it was not increased in the POC group, and that the OAG score was increased because of an increase in the scores for mucous membranes and for teeth/dentures. However, other scores for voice, swallow, lip, gingivae, tongue, and saliva were not increased in either group.

With regard to the relationship between oral mucositis and the OAG score, the severity of mucositis was associated with the total OAG score and with the score of mucous membranes and swallow, lip, tongue, and saliva. These findings suggested that POC can prevent oral mucositis and improve the condition of teeth/dentures in patients receiving everolimus and exemestane treatment, and that preventing severe oral mucositis may improve swallow, lip, tongue, and saliva scores, although no significant difference existed in the current study.

This study has some limitations. First, our study was an open-label study with a small number of patients. Thus, the possibility of bias in the assessments cannot be denied. Second, the control group consisted of patients who did not receive POC and who were not intended for being treated with a steroid mouthwash, which is standard in some countries, because steroid mouthwash products are not available in Japan. Third, detailed data on oral hygiene and periodontal disease in both groups were not investigated in this study. Therefore, the mechanism by which POC suppresses the incidence of mucositis or the increase in the OAG score was not possible to elucidate.

Conclusions

The Oral Care-BC trial showed that POC is effective in suppressing oral mucositis in breast cancer patients receiving everolims and exemestane therapy [16]. Oral care is a method that can be easily administered globally and should be considered a new standard before administering these drugs, especially in the first 8 weeks of treatment. Furthermore, POC may also be helpful in reducing oral mucositis when using everolimus for other diseases such as renal cell carcinoma, subependymal giant cell astrocytoma associated with tuberous sclerosis complex, and advanced neuroendocrine tumors.

Abbreviations

CTCAE, Common Terminology Criteria for Adverse Events; OAG, Oral Assessment Guide; POC, professional oral care

Declarations

Ethics approval and consent to participate:

The study was approved by Institutional Review Board for Clinical Research, Tokai University (approval no.: 14R-063). In addition, the institutional review boards at each of the 31 study sites approved the study protocol. Written informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

Competing interests:

NN has received research funding to Tokai University (Tokyo, Japan) from Novartis (Basel, Switzerland), Bristol-Myers Squibb (New York, NY, USA), Chugai Pharmaceutical Co. (Tokyo, Japan), Nihon Medi-Physics Co. Ltd. MSD (Tokyo, Japan), and Daiichi-Sankyo (Tokyo, Japan), and has received honoraria, consultancy, and speaker fees from AstraZeneca (Cambridge, United Kingdom), Novartis, Eisai (Tokyo, Japan), and Pfizer (New York, NY, USA) outside of the submitted work. T.Yamashita has received research grants and honoraria from Novartis, AstraZeneca, Eisai, Chugai, Taiho, Kyowa Kirin Pfizer, and Eli Lilly (Indianapolis, IN, USA). T.Yamanaka has received lecture fees from Novartis, Eisai, Chugai, Taiho (Tokyo, Japan), and Pfizer. NH has received personal fees from Chugai-pharma, Novartis, AstraZeneca, Pfizer, Kirin Pharma (Tokyo, Japan), Genomic Health, Inc. (Redwood City, CA, USA), Devicor Japan (Tokyo, Japan), and Allergan Japan (Tokyo, Japan) outside of the submitted work. HM received a grant from the Japanese government; honoraria from AstraZeneca, Pfizer, and Taiho; and grants from Daiichi Sankyo, Eisai, Nippon Kayaku (Tokyo, Japan), and Pfizer outside of the submitted work. The other authors declare no competing interests.

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Authors' contributions:

All authors contributed to the study conception and design. Materials were prepared by T.Yamashita, T.Yamanaka, and K.Nakatsukasa. Data were collected by SM, HM, TA, HH, NT, MA, KW, YK, K.Nakagami, NK, and YS. Analyses were conducted by KK, MN, and NH. The first draft of the manuscript was written by

MU, YO, and NN, and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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Figures

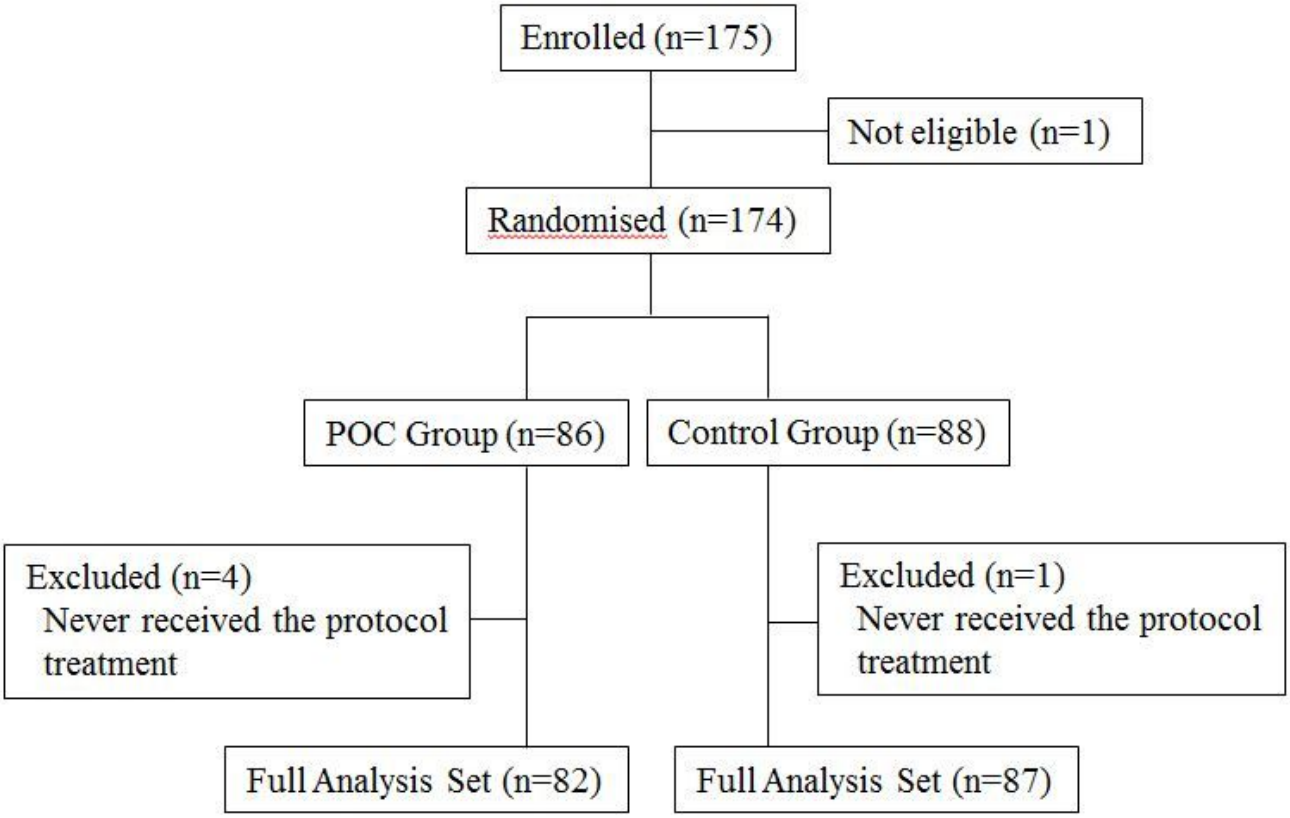
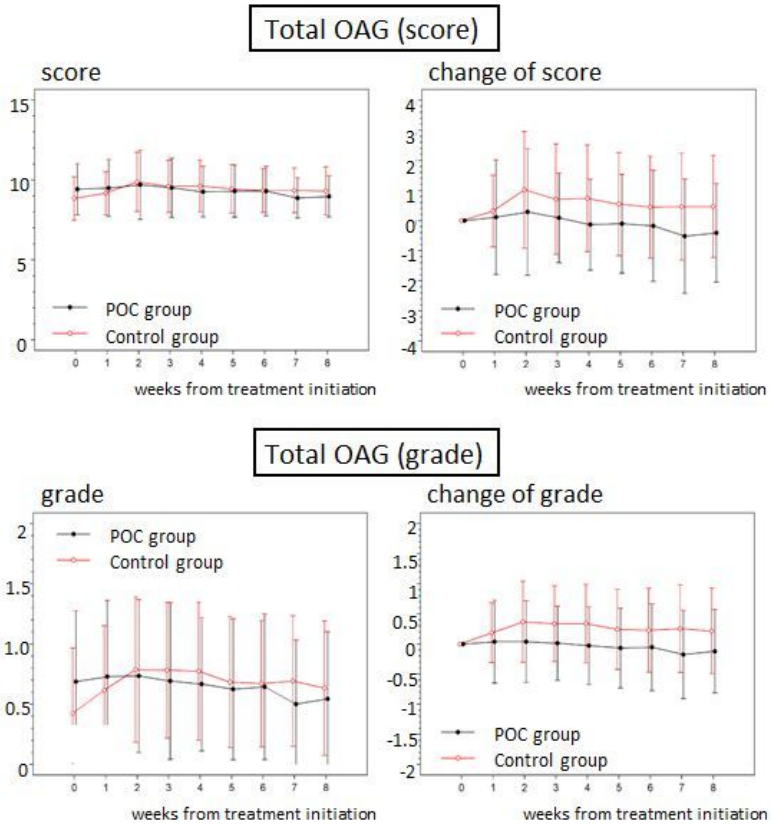


Figure 1

The CONSORT diagram POC, professional oral care; FAS, full analysis set; CONSORT, Consolidated Standards of Reporting Trials



OAG (score)

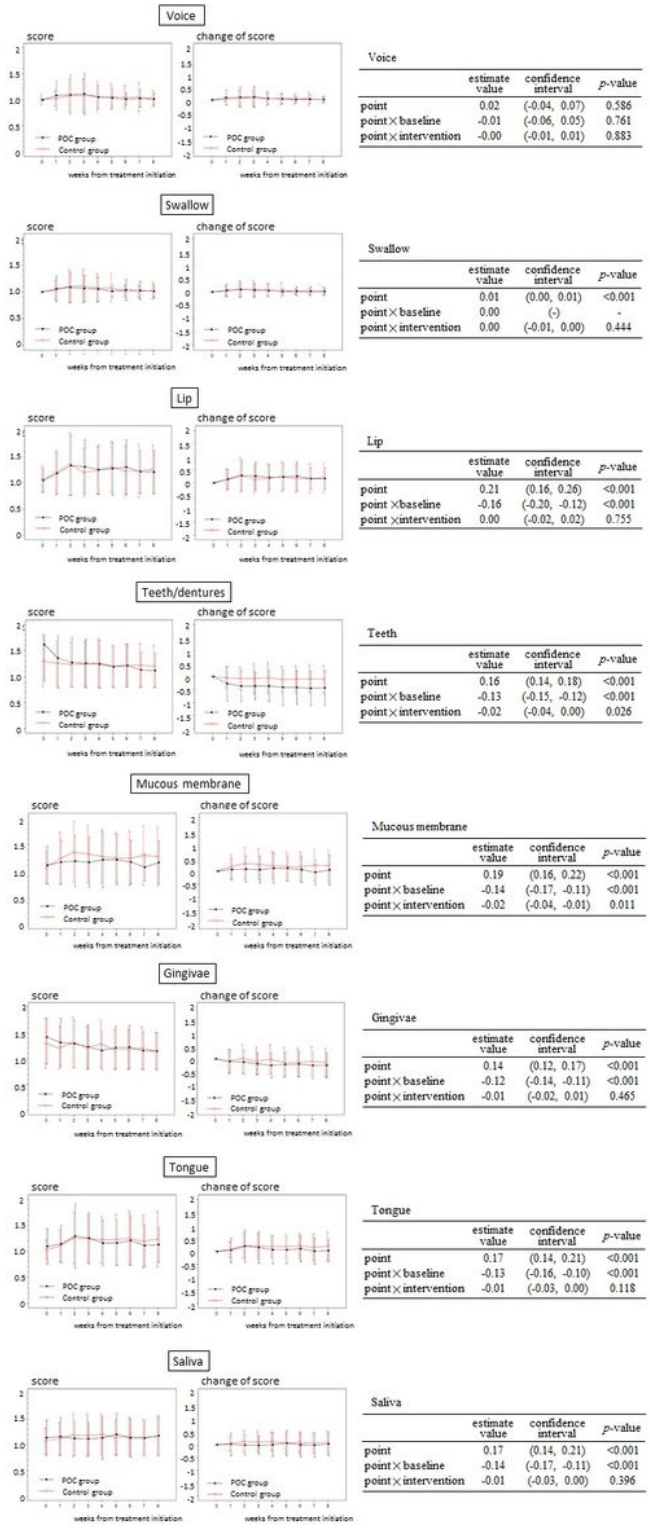
	estimate value	confidence interval	*p*-value
point	1.14	(0.95, 1.34)	<0.001
point × baseline	-0.12	(-0.14, -0.09)	<0.001
point × intervention	-0.08	(-0.15, -0.02)	0.012

OAG (grade)

	estimate value	confidence interval	*p*-value
point	0.11	(0.09, 0.12)	<0.001
point × baseline	-0.13	(-0.15, -0.11)	<0.001
point × intervention	-0.03	(-0.05, -0.01)	0.014

Figure 2

Longitudinal data of the total OAG score/grade in the POC group and the control group OAG, Oral Assessment Guide; POC, professional oral care



Voice

	estimate value	confidence interval	*p*-value
point	0.02	(-0.04, 0.07)	0.586
point × baseline	-0.01	(-0.06, 0.05)	0.761
point × intervention	-0.00	(-0.01, 0.01)	0.883

Swallow

	estimate value	confidence interval	*p*-value
point	0.01	(0.00, 0.01)	<0.001
point × baseline	0.00	(-)	-
point × intervention	0.00	(-0.01, 0.00)	0.444

Lip

	estimate value	confidence interval	*p*-value
point	0.21	(0.16, 0.26)	<0.001
point ×baseline	-0.16	(-0.20, -0.12)	<0.001
point ×intervention	0.00	(-0.02, 0.02)	0.755

Teeth

	estimate value	confidence interval	*p*-value
point	0.16	(0.14, 0.18)	<0.001
point × baseline	-0.13	(-0.15, -0.12)	<0.001
point × intervention	-0.02	(-0.04, 0.00)	0.026

Mucous membrane

	estimate value	confidence interval	*p*-value
point	0.19	(0.16, 0.22)	<0.001
point × baseline	-0.14	(-0.17, -0.11)	<0.001
point × intervention	-0.02	(-0.04, -0.01)	0.011

Gingivae

	estimate value	confidence interval	*p*-value
point	0.14	(0.12, 0.17)	<0.001
point × baseline	-0.12	(-0.14, -0.11)	<0.001
point × intervention	-0.01	(-0.02, 0.01)	0.465

Tongue

	estimate value	confidence interval	*p*-value
point	0.17	(0.14, 0.21)	<0.001
point × baseline	-0.13	(-0.16, -0.10)	<0.001
point × intervention	-0.01	(-0.03, 0.00)	0.118

Saliva

	estimate value	confidence interval	*p*-value
point	0.17	(0.14, 0.21)	<0.001
point × baseline	-0.14	(-0.17, -0.11)	<0.001
point × intervention	-0.01	(-0.03, 0.00)	0.396

Figure 3

Longitudinal data of each OAG score in the POC group and the control group OAG, Oral Assessment Guide; POC, professional oral care

Supplementary Files

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