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ORIGINAL ARTICLE

A single-arm, phase 2 study of steroid-containing mouthwash for the prevention of everolimus-associated stomatitis in multiple tumor types

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Abstract

Background Everolimus is a mammalian target of rapamycin inhibitor used in the treatment of multiple tumor types, and its most common toxicity, stomatitis, can affect patient quality of life. Recent studies in breast cancer have supported the efficacy of steroid mouthwash for the prevention of everolimus-associated stomatitis. However, a few studies have been reported to date, and none have examined this effect in other tumor types.

Methods This single-arm phase 2 study was designed to evaluate the efficacy of steroid-containing mouthwash for the prevention of stomatitis in patients with multiple tumor types receiving everolimus. The primary outcome was incidence of grade ≥ 2 stomatitis at 8 weeks of everolimus with steroid-containing mouthwash prophylaxis. We also assessed the stability of steroid-containing mouthwash components.

Results Twenty-nine patients were evaluated, of which 76% had breast cancer and 24% had neuroendocrine tumors originating in the lung, gastrointestinal tract, pancreas, or of unknown primary origin. Grade ≥ 2 stomatitis incidence at 8 weeks was 28.1% (90% CI 16.2–46.1); the higher confidence limit exceeded the prespecified threshold of 30%. No patients developed grade ≥ 3 stomatitis. Most stomatitis occurred behind the oral cavity, with no lesions observed on the lips or floor of the mouth.

Conclusions Our findings did not support a prophylactic effect of steroid-containing mouthwash on everolimus-associated stomatitis. Given the needs of prevention of everolimus-associated stomatitis in various tumor types, further studies in a larger population using a randomized controlled trial design are, therefore, required to confirm the efficacy of steroid-containing mouthwash.

Keywords Steroid-containing mouthwash · Breast cancer · Neuroendocrine tumors · Everolimus · Prophylaxis · Stomatitis

Introduction

Mammalian target of rapamycin (mTOR) is a serine–threonine protein kinase in the phosphoinositide 3 kinase/Akt signaling pathway. Everolimus, an oral mTOR inhibitor, has shown broad antitumor activity in many tumors [1–4].

Everolimus is widely used in the treatment of various tumors, including advanced renal cell carcinoma (RCC) [1]; advanced pancreatic neuroendocrine tumors (NETs) [2]; hormone receptor-positive (HR+) advanced breast cancer [3]; and advanced, non-functional NETs of the lung or gastrointestinal (GI) tract [4]. Stomatitis is the most common treatment-associated adverse event of everolimus [5], and can significantly affect nutritional intake and the quality of life of patients, leading to dose reductions and/or discontinuation of treatment [6]. In a previous meta-analysis, 67% of patients treated with everolimus developed stomatitis and 24% required dose interruptions or adjustments for stomatitis [6].

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As with other targeted drugs, optimal use of everolimus involves adequate prevention of adverse events to maximize treatment exposure and facilitate optimal outcomes. SWISH [7], a single-arm phase 2 study, recently demonstrated a significant reduction in the incidence of stomatitis by steroid mouthwash prophylaxis among 85 patients with HR+ advanced breast cancer receiving everolimus in combination with exemestane. At 8 weeks after starting everolimus, 79% of patients reported no stomatitis, compared with 39% in the BOLERO-2 study [3], and 21% of patients reported Grade 1 or 2 stomatitis, compared with 54% in BOLERO-2 study. Another randomized phase 2 study [8] also showed promising data supporting the prophylactic use of steroids and steroid-containing mouthwashes in 100 patients with HR+ advanced breast cancer. These studies provide support for the potential efficacy of steroid mouthwash for prevention of stomatitis. This promising new prophylactic method appears to be appropriate for all patients receiving everolimus. Further data are, therefore, required to support the adoption of this prophylactic method as standard of care for all tumors treated with everolimus.

To address this challenge, we conducted a single-arm phase 2 study to evaluate the efficacy of steroid-containing mouthwash for the prevention of stomatitis in patients receiving everolimus for the treatment with breast cancer and other tumor types. Based on previous findings [7, 8], we designed our study to evaluate the incidence of stomatitis at 8 weeks after starting everolimus treatment with steroid-containing mouthwash prophylaxis. We also assessed the stability of steroid-containing mouthwash to ascertain appropriate preservation methods.

Patients and methods

Study population

Patients were eligible for inclusion if they received 10 mg everolimus daily as treatment for HR+ advanced/metastatic breast cancer (MBC); advanced/metastatic NETs of the pancreas, lung, or GI tract, or of unknown primary origin; or advanced/metastatic RCC. Other key inclusion criteria were age ≥ 20 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 with adequate organ function. Patients were excluded if they had previous stomatitis within 30 days prior to participation, previous interstitial pneumonia or pulmonary fibrosis, detectable levels of HBV-DNA, uncontrolled diabetes mellitus or were currently receiving insulin therapy, or were currently receiving corticosteroids or other immunosuppressive therapy. Administration of everolimus in combination with bisphosphonates or denosumab was permitted. Written informed consent was obtained from all participants prior to their inclusion in the study.

Study design

This study was conducted as a prospective, single-arm, phase 2 study. Enrolled patients received 10 mg everolimus daily. Patients with HR+ breast cancer also received exemestane 25 mg daily with everolimus. Steroid-containing mouthwash was prescribed for 2 weeks in two bottles (280 ml each, for 1 week of use). The bottle for the first week was stored in a refrigerator while the second bottle was stored in a freezer until the second week. Patients were instructed to swish and expectorate 10 ml of steroid-containing mouthwash four times daily for 8 weeks starting on day 1 of everolimus therapy. Steroid-containing mouthwash prophylaxis was planned for an 8-week duration, even if everolimus therapy was continued beyond this period. Steroid-containing mouthwash prophylaxis was terminated if patients (1) were diagnosed with grade ≥ 2 stomatitis, (2) had dose modification or interruption (> 2 weeks) of everolimus, (3) had clinical disease progression, or (4) withdrew consent to participate. This study was reviewed and approved by the Ethics Committee of Aichi Cancer Center (Approval no. 2016-1-152).

Steroid-containing mouthwash

Each 280-ml bottle of steroid-containing mouthwash contained 50 mg of hydrocortisone sodium succinate, 300 mg of itraconazole, 1.2 g of tetracycline hydrochloride, 50 mg of *d*-chlorpheniramine maleate (oral solution), and saline. The quality of hydrocortisone sodium succinate was confirmed by stability testing. Patients were encouraged the use of a patient diary to check their adherence, but not mandatory.

Stability testing of steroid-containing mouthwash

The stability of hydrocortisone sodium succinate, itraconazole, tetracycline hydrochloride, and d-chlorpheniramine maleate in the steroid-containing mouthwash was investigated by high-performance liquid chromatography (HPLC) after optimization of analytical conditions (Online Appendix A1). Following quantification of these components, we examined their stability in the steroid-containing mouthwash. After preparation of the steroid-containing mouthwash, the admixture was immediately stored at 4 °C (home-use refrigerator) or at − 20 °C (home-use freezer). Hydrocortisone sodium succinate, itraconazole, and *d*-chlorpheniramine maleate were stable for 14 days at both temperatures. Tetracycline hydrochloride content was stable for 14 days at − 20 °C but was not stable at 4 °C; it gradually decreased to 84% of the initial content within 7 days, and then further decreased to 69% within 14 days. We, therefore,

prescribed steroid-containing mouthwash in two bottles (280 ml per bottle, for 1 week of use) and instructed the patients to store one bottle in a refrigerator for use during the first week and one bottle in a freezer for use during the second week.

Assessment

Oral status was assessed by an oral surgeon and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) v3.0 before study initiation and every 2 weeks during the study period. During the study period, the oral surgeon evaluated only the oral condition and did not perform prophylactic oral care (e.g., dental cleaning). Laboratory assessments including a chemistry panel, liver function testing, and complete blood count were performed to monitor for adverse events. After 8 weeks, patient oral condition was assessed by the clinician every 4 weeks or according to the individual patient schedule if everolimus therapy was continued.

Statistical methodology

The primary efficacy endpoint was the incidence of grade ≥ 2 stomatitis at 8 weeks. For this endpoint, we assumed an expected rate of 10% and threshold of 30%, based on the rate of historical control without steroid-containing mouthwash of around 30% [4, 9–11]. A sample size of 30 was determined to have a statistical power of 80% and a one-sided alpha of 0.05 based on binomial distribution. Incidence rate was calculated using the Kaplan–Meier method. Binomial test was performed using confidence interval corresponding to the significance level of the test. Secondary endpoints were the safety of everolimus with steroid-containing mouthwash prophylaxis, occurrence of stomatitis according to tumor type, and location of grade ≥ 2 stomatitis. Statistical analysis was performed using STATA ver. 12 software (StataCorp, College Station, TX).

Results

Patients

From December 2016 to September 2017, 30 patients were enrolled, and 1 patient was subsequently excluded because of PS 2. The characteristics of the 29 patients are summarized in Table 1. All patients were of Japanese ethnicity, and the median age was 63 years (range 44–78). Among the included patients, 76% had breast cancer and 24% had NETs. No patients with RCC were included. All breast cancer was HR+ metastatic breast cancer, and the origins of NETs were lung (10%), GI tract (7%), pancreas (3%), and unknown primary origin (3%). The median number of previous metastatic regimens was 2.5 (range 0–11), and 59% of patients had previously received chemotherapy for their metastatic or advanced disease, with 31% having received chemotherapy within the 3 months prior to enrollment. The majority of patients (97%) had no smoking history, and three patients (10%) used dentures.

Table 1 Baseline patient characteristics

	All patients ($n = 29$)
Age, median (range)	63 (44–78)
ECOG performance status	
0	26 (90)
1	3 (10)
Sex	
Men	1 (3)
Women	28 (97)
Primary tumor site	
Breast	22 (76)
Lung	3 (10)
Pancreas	1 (3)
Ileum	1 (3)
Jejunum	1 (3)
Unknown primary origin	1 (3)
Number of previous metastatic regimens	
0	4 (14)
1	8 (28)
2	3 (10)
3	4 (14)
≥ 4	11 (38)
Previous chemotherapy for metastatic disease	
Yes	17 (59)
No	12 (41)
Smoking history	
Never	28 (97)
Former/current	1 (3)
Dentures	
Yes	3 (10)
No	26 (90)

ECOG Eastern Cooperative Oncology Group

Efficacy and safety

Incidence of grade ≥ 2 stomatitis at 8 weeks, the primary endpoint of this study, was 28.1% (90% CI 16.2–46.1; Fig. 1), and the higher confidence limit exceeded the prespecified threshold of 30%. Four patients (13.7%), one with lung NETs, one with GI tract NETs, and two with breast cancer, developed grade 1 stomatitis. Eight patients, all with breast cancer, developed grade 2 stomatitis. No patients developed grade 3 or 4 stomatitis in the 8 weeks of the study

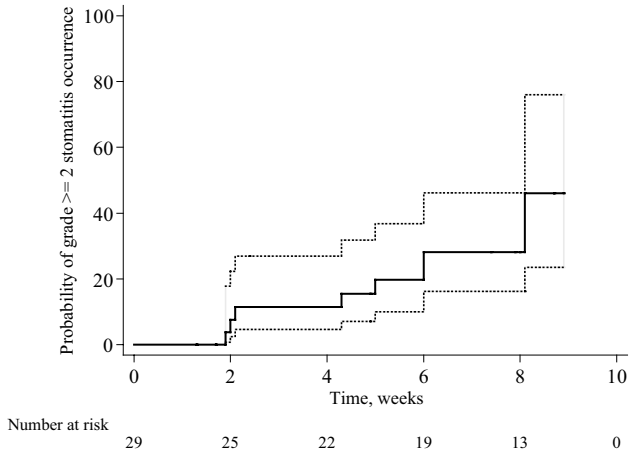

Fig. 1 Cumulative incidence of grade ≥2 stomatitis at 8 weeks. Dotted lines represent 90% CI

Table 2 Adverse events during everolimus therapy with steroid-containing mouthwash prophylaxis ($n=29$)

	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis	4 (14)	8 (28)	0	0
Hyperpigmentation of the tongue	12 (41)	0	0	0
Rash	5 (17)	1 (3)	0	0
Dysgeusia	5 (17)	0	0	0
Hyperglycemia	0	2 (7)	2 (7)	0
Pyrexia	2 (7)	2 (7)	0	0
Nausea	2 (7)	1 (3)	1 (3)	0
Paronychia	1 (3)	0	1 (3)	0
Fatigue	1 (3)	1 (3)	0	0
Cough	2 (7)	0	0	0
Sepsis	0	0	0	1 (3)
Neutropenia	0	0	1 (3)	0
Pneumonitis	0	1 (3)	0	0

period. Of the 29 patients included, six discontinued everolimus therapy by 8 weeks: four because of adverse events (excluding stomatitis), one because of disease progression, and one according to the patient's decision. Adherence to the use of steroid-containing mouthwash was generally good. The median adherence rate of eight patients for whom adherence to the four daily doses could be confirmed from the patients' diaries was 94.6% (only one case of an adherence rate of 53.0%; all others were 90% or more).

Frequent adverse events in 8 weeks were stomatitis, hyperpigmentation of the tongue, and rash (Table 2). Although no patients discontinued steroid-containing mouthwash because of related toxicity, 12 patients reported tongue discoloration that appeared to be related to the use of steroid-containing mouthwash (Online Appendix A2). However, this effect disappeared after the use of steroid-containing mouthwash was discontinued. No patients developed oral candidiasis during the use of steroid-containing mouthwash.

Of the 15 patients who continued everolimus treatment after 8 weeks, four (26.7%) developed stomatitis during subsequent treatment with a median duration of 10 weeks. Three patients developed stomatitis within 1 month, but all stomatitises were assessed as grade 1.

Locations of grade ≥ 2 stomatitis

All the locations and lesion sizes of grade ≥2 stomatitis reported during steroid-containing mouthwash prophylaxis are shown in Fig. 2. Stomatitis occurred as solitary or multiple lesions on the lateral edges of the tongue in four cases and on the hard palate in three cases, soft palate in three cases, and buccal mucosa in two cases. Most stomatitis occurred behind the oral cavity, and no patients developed this condition on the lips or floor of the mouth.

Discussion

To the best of our knowledge, this is the first report of the use of steroid-containing mouthwash for the prevention of everolimus-associated stomatitis in multiple tumor types. We created and used the steroid mouthwash containing antifungal drugs, based on the recipe reported by Jones et al. [8], to prevent the development of oral candidiasis during the steroid prophylaxis. We also evaluated the stability of the mouthwash components, which allowed us to develop a protocol for maintaining the steroid concentration. Tolerability of our steroid-containing mouthwash was good, as reported previously [7, 8], and adherence also appeared favorable. Tongue discoloration, which appears to be caused by chlorpheniramine contained in the mouthwash, was observed in some patients, but resolved after discontinuation of steroid-containing mouthwash prophylaxis. Despite a grade ≥2 stomatitis occurrence at 8 weeks of 28.1%, the study did not meet its prespecified primary endpoint, as the higher confidence limit for this value exceeded the threshold value of 30%.

The SWISH trial [7] showed substantial efficacy for the daily use of steroid mouthwash, with a reduction in the incidence of grade ≥2 everolimus-associated stomatitis at 8 weeks to only 2% (2/85), compared with 33% (159/482) in the BOLERO-2 study [3] in patients with breast cancer. Similarly, incidence of all grade stomatitises was 27% vs. 56%, respectively. These became rationale for informal recommendation of steroid mouthwash for the prevention of stomatitis. However, we have to keep in mind that this is based on cross trial comparison and SWISH trial is a

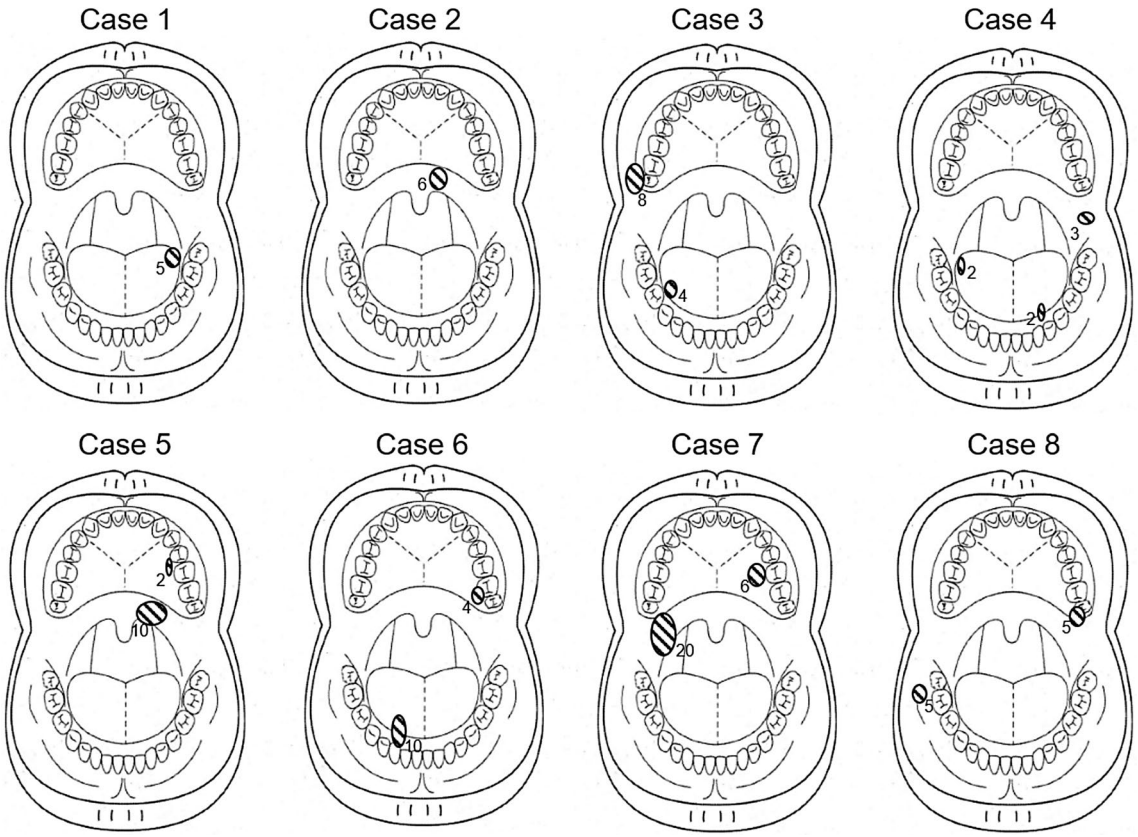

Fig. 2 Locations and sizes of stomatitis lesions in the eight patients who developed grade ≥ 2 stomatitis

single-arm study. There may be several biases existing in this comparison. For example, in SWISH trial, some other side effects considered to be everolimus related, such as rash (9 vs. 36%) and fatigue (17 vs. 33%), are also reduced by steroid mouthwash. Meanwhile, 28% of our patients, who received everolimus for either breast cancer or advanced NETs, experienced grade ≥ 2 everolimus-associated stomatitis by 8 weeks despite using steroid-containing mouthwash. This higher incidence compared to 2% in SWISH trial might be attributable to our study population. The incidence of stomatitis in Asian subsets of everolimus studies [10, 12–14] tends to be higher than in non-Asian subsets. In the BOLERO-2 study, the incidence of all grades of stomatitis was 80% in the Asian subset but 54% in the non-Asian subset [10]. In the recent phase 3 Oral Care-BC study [15], which examined the efficacy of pretreatment professional oral care (POC) on the incidence of everolimus-associated stomatitis in Japanese patients, a 39.5% incidence of grade ≥ 2 stomatitis was reported, despite the patients receiving POC. Although the mechanism of everolimus-associated stomatitis has not yet been elucidated, ethnic differences might have contributed to the higher incidence of stomatitis observed in our study compared with the SWISH trial. The inclusion of more heavily pretreated patients might also have caused the higher incidence in our study, as cytotoxic agents are known to affect the oral epithelial mucosa cells [16] and to be a risk factor for stomatitis [17]. In our study, 59% of patients had a previous history of chemotherapy for advanced or metastatic disease and 31% had received chemotherapy within the 3 months prior to starting everolimus therapy. In addition, oral assessment by the oral surgeon according to CTCAE 3.0 criteria, which have an objective grading scale, might also explain the higher incidence we observed. The Oral Care-BC study reported a higher incidence of stomatitis in evaluations by oral surgeons compared with evaluations by oncologists. The incidence of grade ≥ 2 stomatitis in the POC and control groups evaluated by oral surgeons was 39.5% and 69.0%, respectively, compared with 34.6% and 54.0% for evaluations by oncologists.

Our steroid mouthwash contained hydrocortisone at 1.8 mg per 10 ml, a concentration approximately equivalent to 0.07 mg of dexamethasone per 10 ml [18]. This steroid concentration was lower than that in the SWISH trial, which used dexamethasone at 1.0 mg per 10 ml [7]. However, mouthwash with a low steroid concentration has been shown to be effective for the prevention of everolimus-associated stomatitis: Jones et al. reported a similar efficacy for mouthwash containing hydrocortisone at 1.7 mg per 10 ml and

mouthwash containing prednisolone at 30 mg per 10 ml^2. In addition, mTOR inhibitor-associated stomatitis is typically observed on the lower lips, the lateral tongue, and the soft palate [19–22]. However, the majority of lesions in our study were located behind the oral cavity, with no lesions on the lower lips and the floor of the mouth, which are considered to be covered with mouthwash using the swish method. These results suggest that our lower concentration steroid-containing mouthwash had some efficacy for the prevention of everolimus-associated stomatitis, but only in the areas covered by the swish method.

Limitations of this study include the small sample size; the non-randomized, single-arm study design; and the proportions of tumor types included. Unfortunately, a comparison of the incidence of stomatitis with a control group was not included because of the study design. It is also important to include a design in future studies to allow ethnic differences to be evaluated between the subjects and with historical controls. Although our trial inclusion criteria permitted the enrollment of patients with breast cancer, advanced NETs, or advanced RCC, most participants were patients with breast cancer, and no patients with RCC patients were enrolled. Along with our small sample size, we were thus unable to compare the occurrence of stomatitis between the tumor types.

In conclusion, the results of our study did not demonstrate the efficacy of steroid-containing mouthwash for the prevention of everolimus-associated stomatitis. It does, however, provide useful information regarding potential risks lying in studies for the prevention of stomatitis. Further investigation of steroid-containing mouthwash prophylaxis, including the consideration of ethnic differences, steroid concentration, and optimized mouthwash methods (e.g., swish, gargle, volume of mouthwash), may clarify the potential of steroid-containing mouthwash for the prevention of everolimus-associated stomatitis, allowing for improved patient care in everolimus therapy for multiple tumor types.

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Compliance with ethical standards

Conflict of interest Masaya Hattori received honoraria from Chugai Pharmaceutical, Eli Lilly Japan, Novartis Pharma, AstraZeneca, Pfizer Japan, and Eisai for work performed outside of the current study. Susumu Hijioka received honoraria from Novel Pharma, Novartis Pharma, and Tenjin Pharma for work performed outside of the current study. Hiroji Iwata received research funding from Chugai Pharmaceutical, MSD K.K, Eli Lilly Japan, and Novartis Pharma for work performed outside of the current study; received honoraria from Chugai Pharmaceutical, Daiichi Sankyo, and AstraZeneca for work performed outside of the current study; and is a member of scientific advisory board of Daiichi Sankyo, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Pfizer Japan, Novartis Pharma, and AstraZeneca for work performed outside of the current study. The other authors have no conflicts of interest to declare.

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