Random Allocated Study of Wrapping Oblate for Prevention of Everolimus-associated Stomatitis in Patients With Metastatic Renal Cell Carcinoma

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Abstract. *Background:* The study aim was to evaluate the efficacy of wrapping oblate for prevention of everolimus-associated stomatitis in metastatic renal cell carcinoma (mRCC). *Patients and Methods:* Patients with mRCC prescribed everolimus after failure of vascular endothelial growth factor-tyrosine kinase inhibitor were enrolled. Patients were consecutively assigned to take everolimus covered with or without oblate. The primary end-points were the incidence of and time to grade 2 or more stomatitis. Additionally, we assessed whether grade 2 or more stomatitis that occurred in the non-oblate group could be prevented with crossover application of oblate. *Results:* This study included 79 patients [oblate group: 42(53%); non-oblate group: 37(47%)]. Thirty (38%) patients developed grade 2 or more stomatitis [incidence: oblate group, 31% (13/42); non-oblate group, 46% (17/37), $p=0.245$; median time to grade 2 or more stomatitis: oblate group, not reached; non-oblate group, 6.0 months, $p=0.251$]. Among 10 patients who developed grade 2 or more stomatitis in the non-oblate group and received oblate-covered everolimus, nine (90%) showed complete recovery or improved to grade 1, which persisted until discontinuation of everolimus. *Conclusion:* Oblate-covered everolimus improved the incidence of and time to grade 2 or more stomatitis, although it was not statistically significantly different compared to the non-oblate group. Oblate wrapping prevented recurrence of grade 2 or more stomatitis in patients who took uncovered everolimus and developed significant stomatitis.

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Everolimus is an orally available of mammalian target of rapamycin (mTOR) that has shown significant prolongation of progression-free survival (PFS) in patients whose disease has progressed during or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy for the treatment of metastatic renal cell carcinoma (mRCC) (1) and has been approved by regulatory agencies. Recently, everolimus plus lenvatinib showed efficacy as a second-line treatment for mRCC (2), and alone has been used for the treatment of a wide range of malignancies, such as breast cancer and neuroendocrine tumors (3, 4). Everolimus is generally well tolerated, but can cause some adverse events (AEs), such as stomatitis, non-infectious pneumonitis, infection, hyperglycemia, and hyperlipidemia (5, 6).

Stomatitis associated with mTOR inhibitor use, including everolimus, presents as an entity distinct from classic chemotherapy-induced stomatitis and is similar to aphthous-like ulceration; it is characterized as having discrete, ovoid, superficial, well-demarcated affected areas surrounded by an erythematous halo, with rare involvement of other parts of the gastrointestinal tract (7, 8). Thus, this condition has been termed mTOR inhibitor-associated stomatitis. Everolimus-associated stomatitis is challenging to physicians because it can affect not only the quality of life, but also treatment efficacy by leading to dose interruption or dose reduction (6, 9-11). In a previous phase III trial of everolimus in mRCC, the incidence of stomatitis was 42%, and 3% of cases were grade 3 or more, and nearly 10% required interruption or dose modification (6). We also reported that stomatitis occurred in 44%, and grade 3 or more in 6% of our cohort dataset of Korean patients with mRCC treated with everolimus (5). In a systematic review of clinical trials of everolimus, stomatitis was shown to be the most frequent adverse event (AE) (73%) and the third most severe (21%), accounting for 27% of dose reductions, 13% of discontinuations, and 53% of the causes of dose-limiting toxicity (most frequent) (11).

Considering the high incidence rate of everolimus-associated stomatitis and its clinical significance in treatment efficacy, its prevention and treatment are critical in order to maintain drug adherence and reduce the need for drug interruption or dose reduction. However, the exact pathophysiology of everolimus-associated stomatitis is poorly understood and management experience is limited (6). Thus, current interventions for everolimus-associated stomatitis are mainly based on expert opinions and basic oral care similar to measures for conventional chemotherapy-associated stomatitis, such as avoidance of triggers and education in oral hygiene that include use of oral pastes or rinses and topical steroids (12). Because the presence of an immune-mediated inflammatory response has been suggested as an underlying factor for everolimus-associated stomatitis (11, 13), a growing body of clinical evidence has shown the benefits of adding steroid-based mouth rinses for prevention (14, 15). Recently, a phase II trial investigated the efficacy of dexamethasone mouthwash for prophylaxis of stomatitis in patients with breast cancer treated with everolimus and exemestane. The results showed that dexamethasone-based mouthwash was significantly effective for prophylaxis of everolimus-associated stomatitis (15). However, in order to prescribe dexamethasone mouthwashes, healthcare providers should check oral symptoms and signs to rule out potential fungal or viral infection and educate the patient about the risk of opportunistic infection (6), which might be accentuated by the immunosuppressive properties of everolimus (13). These findings indicate the need for a new preventive method against stomatitis in patients with mRCC treated with everolimus, which would be able to comply with physiological requirements, unlike steroid-based mouthwashes.

Oblate is a thin film composed of starch that enables slow or prolonged dissolution of drugs when wrapped around a capsule or tablet. When drugs were wrapped in oblate, dissolution was found to be delayed, and the dissolution rate remarkably decreased relative to that of the drug not wrapped in oblate (16). Although the preventive effect and mechanism of oblate wrapping for prevention of stomatitis have not been studied, some clinicians and patients have used anecdotally reported application of oblate for treatment of everolimus or other tyrosine kinase inhibitor (TKI)-related stomatitis with success. Considering the safety of oblate as a natural product and clinical impact of everolimus-associated stomatitis, we planned to conduct an explorative study to investigate the efficacy of oblate. The aim of this study was to evaluate the efficacy of oblate for prevention of everolimus-associated stomatitis in patients with mRCC patients who had previous exposures to VEGF-TKIs. Additionally, we assessed whether grade 2 or more everolimus-associated stomatitis could be improved by crossover application of oblate.

Materials and Methods

Study design and patients. Patients with mRCC who had received everolimus after failure of VEGF-TKI treatment were included in this study from March, 2013 to September, 2015. During the study period, eligible patients were registered and randomly allocated (1:1) by a computer-generated allocation table to oblate-covered everolimus (oblate group) or everolimus without oblate (non-oblate group). Randomization was stratified according to prior history of stomatitis during VEGF-TKI. There were no restrictions regarding previous treatments, except that patients with prior treatment-related AEs of grade 2 or more, including stomatitis, were started on everolimus only after improvement to grade 1 or less. Patients who were lost to follow-up during the first 2 weeks without evidence of disease progression or assessment of toxicity were excluded from the analysis. The study protocol was reviewed and approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (AMC 2013-0871).

Procedures. Everolimus was administered at an approved dose of 10 mg by mouth, once daily. Dose interruption and modification were performed in accordance with the package insert. In the oblate group, the patients were orally administered oblate-covered everolimus from day 1 of cycle 1. Patients in the non-oblate group were treated with everolimus without wrapping. The patients were followed-up every 2 weeks for the first 2 months and then every 4-6 weeks thereafter for physical examinations, laboratory testing, and assessments for AEs, including stomatitis. Severity of AEs, including stomatitis, was categorized according to the Common Terminology Criteria for Adverse Events version 4.0 (17). When stomatitis of any grade developed, basic stomatitis management, including mouth washes (0.9% saltwater solution, sodium bicarbonate, or chlorhexidine), was applied. In the case of grade 2 or more stomatitis, everolimus was stopped at the discretion of the clinician or patient and then restarted with the same or reduced dose after recovery to grade 1 or less. Patients in the non-oblate group, who developed grade 2 or more stomatitis continued oblate-covered everolimus at the same dose or stopped everolimus until it recovered to grade 1 or less and then were treated with everolimus at the same or reduced dose of oblate-covered everolimus (crossover subgroup). The tumor response was assessed every 6-8 weeks during follow-up according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 (18).

Statistical analysis. The primary end-points were the incidence and time to grade 2 or more stomatitis. The incidence of grade 2 or more stomatitis was reported as counts and percentages, and time to grade 2 or more stomatitis was defined as the time from starting date of everolimus to the first occurrence of grade 2 or more stomatitis. Secondary endpoints were: i) assessment of whether grade 2 or more stomatitis occurred in the non-oblate group could be improved by switching the patients to oblate-covered everolimus (cross-over application), and ii) comparison of overall survival (OS) and PFS between the two groups. PFS was defined as the time from everolimus initiation until either first documentation of RECIST-defined disease progression or death from any cause, whichever came first. OS was defined as the time from everolimus initiation until death from any cause or the date of last follow-up for patients still alive.

The baseline characteristics of patients are expressed as the median value with the range for continuous variables, or frequency

Figure 1. Trial profile.

with proportion (%) for categorical variables. The two groups were compared using Fisher's exact or chi-square test for categorical variables, and independent *t*-test or Mann-Whitney *U*-test for continuous variables. Kaplan-Meier estimates were used to analyze time-to-event data and the differences between the two groups were analyzed using the log-rank test. All statistical analyses were two-sided and performed using SPSS version 19.0 (SPSS Inc. Chicago, IL, USA); values of $p < 0.05$ were accepted as indicating statistical significance.

Results

Baseline characteristics. Between March 2013 and October 2015, 92 consecutive patients were started on treatment with everolimus; 42 patients and 50 patients were randomly allocated to the non-oblate oblate groups, respectively. Five patients in the non-oblate group and eight patients in the oblate group were excluded because of follow-up loss or discontinuation of everolimus irrelevant to stomatitis within 2 weeks. Finally, 79 patients were included in the efficacy analysis; 42 (53%) patients in the oblate group and 37 in the

non-oblate group (Figure 1). There were no significant differences in the baseline characteristics, including the international metastatic renal cell carcinoma database consortium (IMDC) criteria (19) between the two groups; however, there were more patients who had undergone two or more previous VEGF-TKI treatments in the oblate than non-oblate group [8/42 (19%) vs. 2/37 (5%), respectively; $p = 0.094$]. The incidence of stomatitis during the previous VEGF-TKI treatments did not significantly differ between the two groups [3/33 (4%) vs. 4/36 (9%), respectively; $p > 0.99$], but all three patients with a previous history of grade 2 or more stomatitis related to VEGF-TKI were assigned to the oblate group (Table I).

Everolimus-associated stomatitis and efficacy of warping oblate. Overall, stomatitis developed in 52 (66%) patients, and was grade 2 or more in 30 (38%). Among the 30 patients who developed grade 2 or more stomatitis, the median time to grade 2 or more stomatitis was 1.43 (range=0.2-6.6) months and most cases (25 patients, 84%) occurred within 2

Table I. Patient characteristics and previous treatment.

Characteristic	Total (n=79)	Non-oblate group (n=37)	Oblate group (n=42)	p-Value
Median age (range), years	62.4 (36-87)	62.0	62.9	0.725
Gender, n (%)				
Male	63 (80%)	30 (80%)	33 (79%)	>0.99
Female	16 (20%)	7 (20%)	9 (21%)	
Tumor histology, n (%)				
Clear cell type	73 (92%)	34 (92%)	39 (93%)	>0.99
Non-clear cell type	6 (8%)	3 (8%)	3 (7%)	
Sarcomatoid features, n (%)				
Yes	17 (22%)	9 (24%)	8 (19%)	0.595
No	62 (78%)	28 (76%)	34 (81%)	
Initial VEGF-TKI therapy				
Sunitinib	45 (57%)	20 (54%)	25 (60%)	0.253
Sorafenib	3 (4%)	3 (8%)	0	
Pazopanib	30 (38%)	14 (38%)	16 (38%)	
Axitinib	1 (1%)	0	1 (2%)	
Number of previous VEGF-TKI therapy				
1	69 (87%)	35 (95%)	34 (81%)	0.094
≥2	10 (13%)	2 (5%)	8 (19%)	
Karnofsky performance scale				
≥80	62 (78%)	30 (80%)	32 (76%)	0.785
40-70	17 (22%)	7 (20%)	10 (24%)	
Previous Immunotherapy				
Yes	10 (14%)	6 (16%)	4 (10%)	0.502
No	69 (86%)	31 (84%)	38 (90%)	
IMDC criteria _ Everolimus ^a				
Favorable	10 (14%)	6 (18%)	4 (11%)	0.393
Intermediate	45 (64%)	22 (67%)	23 (62%)	
Poor	15 (21%)	5 (15%)	10 (27%)	
History of Gr≥2 stomatitis during prior VEGF-TKI therapy	3 (4%)	0	3 (7%)	0.243
History of stomatitis (all grade) during prior VEGF-TKI therapy	7 (9%)	3 (8%)	4 (9%)	>0.99

Gr: Grade; IDCM: International Database Consortium Model; VEGF-TKI: vascular endothelial growth factor-tyrosine kinase inhibitor. ^a70 patients with available clinical data at the time of everolimus treatment.

months from initiation of everolimus. The treatments of grade 2 or more stomatitis consisted only of basic stomatitis management, crossover application of oblate-covered everolimus with or without interruption/or dose reduction, interruption/or dose reduction, or discontinuation of everolimus (Table II).

There were no statistically significant differences in the incidences of all-grade and grade 2 or more stomatitis between the two groups. However, there were numerically fewer incidences of stomatitis in the oblate group than in the non-oblate group (Table III). Regarding the time to grade 2 or more stomatitis, the median time was 6.0 months in the non-oblate group, while that of the oblate group was not reached. Although the difference was not statistically significant [hazard ratio=(HR)=1.51; 95% confidence interval (CI)=0.74-3.12; $p=0.251$; Figure 2], the two curves started to diverge after 8 weeks, which suggested that oblate was able to prevent everolimus-associated stomatitis after 8 weeks.

Efficacy of crossover to wrapping oblate. Among 17 patients who developed grade 2 or more stomatitis in the non-oblate group, 10 were crossed over to receive oblate-covered everolimus with or without interruption. The other seven patients were not crossed over because of immediate discontinuation of everolimus in five (loss to follow-up, $n=2$; simultaneous confirmation of disease progression, $n=1$; concomitant gastrointestinal bleeding, $n=1$; change to other therapy (axitinib), $n=1$), and lack of prepared oblate in two. Among the 10 patients who did crossover, nine (90%) were able to continue everolimus treatments without recurrence of grade 2 or more stomatitis, and all discontinued everolimus because of disease progression (Table IV).

Efficacy of everolimus with and without wrapping with oblate. At the time of analysis (October 2017), a total of 79 patients had discontinued everolimus treatment, with a median follow-up duration of 32.2 months (95% CI=22.2-42.2 months). Reasons for treatment discontinuation

Table II. Treatment of grade 2 or more stomatitis.

	Total (n=30)	Non-oblate (n=17)	Oblate (n=13)
Basic management only ^a	3	0	3
Crossover application of oblate	7	7	0
Crossover application of oblate plus interruption/dose modification	3	3	0
Interruption/dose modification	5	2	3
Discontinuation	12	5	7
Disease progression	2	1	2
Stomatitis	1	0	1
Other AEs	3	2 (GI bleeding, delirium)	3 (NIP, pneumonia, asthenia)
Lost to follow-up	1	1	1
Change to other treatment	1	1 (Axitinib)	0

AEs: Adverse events, GI: gastrointestinal, NIP: non-infectious pneumonitis. ^aBasic management included mouth washes (0.9% saltwater solution, sodium bicarbonate, or chlorhexidine).

Table III. Incidence [n (%)] of everolimus-associated stomatitis of grade 2 or more according to application of oblate.

Stomatitis	Total (n=79)	Non-oblate (n=37)	Oblate (n=42)	p-Value
Grade≥2	30 (38%)	17 (46%)	13 (31%)	0.245
None or grade 1	49 (62%)	20 (54%)	29 (69%)	

included disease progression (n=49), everolimus-related AEs (n=15), treatment refusal (n=4), follow-up loss (n=10), or change to other therapy (n=1) (Table V).

Considering the whole cohort, the median PFS was 5.0 months (95% CI=3.9-6.1 months) and the median OS was 9.0 months (95% CI=6.8-11.2 months). Clinical outcomes (PFS and OS) were compared according to the application of oblate. The PFS times in the non-oblate and oblate groups were 5.4 months and 4.5 months, respectively (HR=1.59, 95% CI=0.89-2.84; $p=0.121$), and the OS times were 11.0 months and 9.0 months, respectively (HR=1.08, 95% CI 0.64-1.81 $p=0.519$) (Figure 3).

Regarding response, two patients (3%) achieved response, 53 (67%) had stable disease, and 16 (20%) had progressive disease. There was no significant difference in response according to application of oblate ($p=0.222$).

Discussion

This study investigated the efficacy of wrapping everolimus in oblate to prevent everolimus-associated stomatitis. Although there was a lack of statistical significance, wrapping with oblate showed numerical trends in reduction in the incidence and time to grade 2 or more stomatitis.

Figure 2. Time to grade 2 or more (Gr ≥2) stomatitis according to oblate application.

Additionally, crossover application of the oblate in cases of grade 2 or more everolimus-associated stomatitis also showed favorable results consistent with the primary outcomes and further substantiated the efficacy of oblate. To date, dental/oral hygiene education, mouth rinse, or steroid-based mouthwash have been generally applied for prophylactic strategies for everolimus-associated stomatitis on the basis of expert opinions and previous study results (7, 15). To our knowledge, the current study is the first to investigate the efficacy of wrapping with oblate for prevention of everolimus-associated stomatitis, which is distinct from prior methods.

For acceptance of oblate as a preventive method for stomatitis based on our results, which only showed favorable

Figure 3. Efficacy outcomes of everolimus. Progression-free (A) and overall (B) survival according to wrapping with oblate.

Table IV. Results of patients after crossover application of oblate (n=10).

Patients	Gr	Time to Gr ≥ 2 stomatitis (months)	Interruption/dose modification due to stomatitis	Recovery (Gr)	Treatment duration after Gr ≥ 2 (months)	Cause of discontinuation
1	3	1.0	Interruption 1 week	O (Gr 0)	3.4	PD
2	2	3.2		O (Gr 1)	2.7	PD
3	3	2.0		O (Gr 1)	1.4	PD
4	2	6.0	Interruption 1 week, dose modification (7.5 mg)	O (Gr 0)	4.6	PD
5	3	1.3		O (Gr 0)	25.0	PD
6	2	6.6		O (Gr 0)	9.4	PD
7	3	0.2	Interruption 1 week, dose modification (5 mg)	X (Gr 2)	1.7	PD
8	2	0.5		O (Gr 0)	20.2	PD
9	2	1.4		O (Gr 1)	6.9	PD
10	2	0.4		O (Gr 1)	2.4	PD

Gr: Grade, PD: progressive disease.

numerical trends without statistical significance, the pathophysiology of everolimus-associated stomatitis and the exact mechanism of action of oblate should be clarified. However, it is regrettable that there have been few prior studies on the use of oblate and stomatitis, and the detailed pathophysiology of everolimus-associated stomatitis has not yet been elucidated. Immune dysregulation is thought to have a role, and several potential mechanisms have been proposed as the pathogenesis of everolimus-associated stomatitis (7, 8), considering the clinical resemblance with aphthous ulcer-like lesions. Regarding oblate, wrapping with oblates lowers and prolongs dissolution of tablets or capsule formulations by forming a mucous layer of gelatinized oblate that acts as a barrier and reduces the rate at which the solution permeates into the structural part of the drug and the rates of

disintegration, dispersion, and dissolution of the drug (16). Therefore, in order to reconcile those findings, we reason that taking everolimus without oblate would induce a sharp increase in the everolimus concentration up to C_{max} , and the excessively increased peak concentration might trigger the development of stomatitis. Thus, we speculate that wrapping everolimus in oblate leads to blunting of rapid absorption and a decrease of C_{max} , consequentially reduce the development of stomatitis. Ferte et al. reported that as the daily dose of everolimus increased, the median time to stomatitis shortened, the median duration of stomatitis increased, and a trend toward higher values of C_{min} and C_{max} was observed in cases of stomatitis (20). These findings support our postulation about the usefulness of oblate against everolimus-associated stomatitis. Further studies on pharmacokinetic changes in

Table V. *Reasons for discontinuation of everolimus treatment.*

Response	Total (n=79)	Non-oblate (n=37)	Oblate (n=42)
Disease progression	49	24	25
Treatment-related AEs	15	5	10
Stomatitis	1	0	1
Pneumonitis	3	1	2
Infection	4	0	4
Other AEs	7	4	3
Other	15	8	7
Refusal	4	3	1
Lost to follow-up	10	4	6
Change to other treatment	1	1	0

AEs: Adverse events.

Cmax and area under curve of everolimus and development of stomatitis according to wrapping with oblate are needed.

Additionally, the question of whether oblate influences oncological outcomes of everolimus or not should be determined before considering the usefulness of oblate in prevention or treatment of stomatitis. It is necessary to determine if application of oblate improves quality of life without a negative influence on oncological outcomes, and furthermore, whether oblate could lead to favorable outcomes by means of reducing dose interruptions and discontinuations. This study showed no statistically significant differences in PFS, OS, and frequency of dose interruption or discontinuation between the oblate and non-oblate groups. We found that the oblate group had numerically worse PFS and OS compared to those in the non-oblate group. However, there were more patients with poor risk factors in the oblate group, such as a greater number of previous VEGF-TKI treatments and poor risk scores according to IMDC criteria. These findings might have contributed to the poor outcomes in the oblate group. Thus, we cannot conclude that the oncological efficacies of everolimus might be affected by the application of oblate in the current study. In particular, considering the hypothesis that everolimus-associated stomatitis is prevented by the pharmacokinetic effect of oblate wrapping, the efficacy of this approach should be clarified in future studies with a larger sample size.

We applied crossover to wrapping with oblate in 10 patients who developed grade 2 or more stomatitis in the non-oblate group, most of whom (9/10, 90%) remained on everolimus without recurrence of grade 2 or more stomatitis. We showed that the use of oblate wrapping as a treatment strategy after development of stomatitis was efficacious on the basis of the results for the crossover subgroup.

This study had several limitations because of its retrospective design. Firstly, we did not know the characteristics of everolimus-associated stomatitis because of a lack of descriptive information about stomatitis lesions.

Above all, as a grading scale for stomatitis, this study used NCI-CTCAE version 4.0, which consists of pure symptoms and functional assessments driven without objective signs; thus, information about the specific/characteristic ulcerative lesion is lacking. However, NCI-CTCAE version 4.0 has an advantage in some aspects because some studies have reported that symptoms of everolimus-associated stomatitis, such as mouth pain, taste distortion, and swallowing difficulty, which can affect patients' daily lives, can occur in the absence of objective lesions and determine the necessity for management (14, 21). Secondly, we did not gather information regarding the compliance in taking oblate. Due to old age or poor performance, the patients in the oblate group might not have used oblate appropriately, which might have affected the outcomes. Lastly, the relatively small sample size might have led to insufficient statistical power, although oblate wrapping was associated with numerically better outcomes.

Thus, it is obvious that the present study was of an explorative nature. Nevertheless, the results do suggest that oblate has potential as an inexpensive, well-tolerated, physiological natural product and its use involves a completely distinctive approach from previous preventive management approaches. Thus, oblate wrapping might be suggested as a new option, at least for the treatment of everolimus-associated stomatitis. Further studies that acquire pharmacokinetic data in larger study populations are warranted to draw definitive conclusions.

In conclusion, wrapping everolimus in oblate showed favorable results in both the incidence of and time to grade 2 or more stomatitis, although the effects were not statistically significant. Oblate also prevented the recurrence of grade 2 stomatitis in patients who had developed significant stomatitis without oblate. The results of this study indicated that oblate has potential as a new option for prophylaxis or treatment of stomatitis in patients receiving everolimus.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Kwonoh Park contributed in data analysis, drafting the article and revising it. Youngae Baek contributed in data collection. Jae-Lyun Lee contributed in conception and design, and interpretation.

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