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Natural history, management and pharmacokinetics of Everolimus-induced-oral ulcers: Insights into compliance issues

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ABSTRACT

Background: Oral Ulcers is a well-recognised adverse event (AE) of mTOR inhibitors. Paradoxically, little is known about its natural history, risk factors, and basic management.
Patients and methods: AEs of 79 patients prospectively enrolled in 6 phase I–II studies testing Everolimus were reviewed. The following parameters were analysed: incidence, severity, duration and associated AE. The association between OU and Everolimus dose, pharmacokinetics and the effectiveness of empiric treatments were explored.
Results: OU, grade 3–4 OU, prolonged time under OU and RCOU (recurrent and chronic oral ulcer) were observed in 72% 11%, 30% and 25% patients, respectively. Patients with antecedent of prior chemotherapy, with PS 1, or receiving Everolimus in combination tended to present higher rates of prolonged time under OU and of grade 3–4 OU. As Everolimus daily dose increased, the median time to OU was shorter, the median duration was longer and OU incidence tended to increase. Simultaneously, OU tended to be associated with higher Everolimus exposure. None of the empiric treatments appeared effective against OU (preventive or curative intent).
Conclusion: Everolimus-induced OU is a frequent, recurrent and sometimes harmful complication. A dose effect relationship is displayed. Its daily management remains challenging. OU represents a key issue in the compliance of mTOR inhibitors.

1. Introduction

Mucositis is a well-recognised adverse event following conventional chemotherapy and ionising radiation.[1] It is responsible for increases in both health complications and economic outcomes.[2] mTOR inhibitors have been recently approved for metastatic renal cancer, mantle cell lymphoma and are actively investigated in other solid tumours and haematological

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Table 1 – Description of the six phase I–II trials considered for analysis.

Code and type of trial	Total patients treated	Experimental regimen	Patient numbers according to Everolimus dose	Indication	Time in the study (days) median (range)
CRAD01C2116 (phase 1)	11	Cisplatin: 75 mg/m^2 (Day 1) Etoposide: 100 mg/m^2 (Day 1–3) Everolimus 21-day cycle; delivered until progression	20 mg qw: 2 pts 30 mg qw: 5 pts 2.5 mg qd: 2 pts 5 mg qd: 2 pts	SCLC (extended disease)	194 (44–952)
RAD RT (phase 1)	7	External Beam Radiotherapy (66 Gy during 6.5 weeks) followed by 2 cycles of: Cisplatin (100mg/m2; Day 1) – Vinorelbine (25 mg/m^2; Day 1, Day 8) (21-day cycle) Everolimus delivered during 11 weeks	10 mg qw: 3 pts 2.5 mg qd: 3 pts 5 mg qw: 1 pt	NSCLC (locally advanced)	141 (56–339)
CRAD001C2111 (phase 1)	10	Erlotinib 75–150 mg qd Everolimus delivered until progression	50 mg qw: 4 pts 2.5 mg qd: 2 pts 5 mg qd: 4 pts	NSCLC (metastatic disease)	84 (14–1054)
CRAD01J2101 (phase 1)	16	Paclitaxel: 80 mg/m^2 on Day 1, Day 8, and Day 15 Trastuzumab: 4 mg/kg (loading dose) then 2 mg/kg qw Everolimus 28-day cycle; delivered until progression	5 mg qd: 4 pts 10 mg qd: 9 pts 30 mg qw: 3 pts	Breast cancer (metastatic disease)	274 (127–883)
CRAD001C2235 (phase 2)	14	Everolimus (alone) delivered until progression	10 mg qd: 14 pts	NSCLC	83 (23–439)
CRAD001C2111 (phase 2)	21	Erlotinib 150 mg qd Everolimus delivered until progression	5 mg qd: 20 pts 2.5 mg qd: 1 pt	NSCLC	70 (56–339)

E: Everolimus ; qd: dayly ; qw: weekly ; pts: patients.

malignancies.[3] This class of agents has unravelled a particular subset of oral lesions named oral ulcers (OU), stomatitis or mouth sores, which contrast with the conventional cytotoxics induced mucositis.[4] OU are described as one of the most frequent side-effects in mTOR inhibitor phase III trials (up to 40%), whatever the mode of administration (per os, intravenous).[5–7] Paradoxically, little is known about their pathophysiology, natural history (time to event, number of episode, duration of episode), biological and clinical risk factors, associated clinical outcome, efficacy of empiric treatments (mouthwash, antifungics). This study was aimed to better describe Everolimus-induced OU.

2. Material and methods

2.1. Study population

We considered all consecutive patients treated with Everolimus (E) that were prospectively enrolled in dose–escalation phase I–II trials at Institut Gustave Roussy (Villejuif, France) from November 1, 2005 to October 1, 2009. A total of 79 patients received Everolimus according to the six different protocols (Table 1). The local ethics committee approved each study. Written informed consent was obtained from each patient.

2.2. Methods

All the patients had detailed baseline examinations and all adverse events were prospectively recorded according to the NCI-CTC AE v3.0 grading system.[8] As per protocol, a clinical and biological evaluation was performed at least once weekly. The primary end-point of this study was to describe the incidence and the severity of oral ulcer during the first 60 days after Everolimus onset. Secondary end-points were the number of episodes of OU, the time to OU, the duration of the episode of OU and the prevalence of associated adverse events concomitant to OU. Since E dose was susceptible to change during the study for a given patient (dosing delay, dose reduction), the duration of the episode of OU was correlated with Everolimus actual dose. On the opposite, the time to OU was analysed according to Everolimus intended dose. Further, we evaluated the proportions of patients with prolonged time under OU (defined as a time under OU $\geqslant$ 21 days within the first 60 days after Everolimus onset), and patients with RCOU (recurrent and chronic oral ulcer). RCOU was defined as any

OU occurring 60 days after Everolimus onset, at least once monthly for a minimum of two consecutive months. The association between OU and Everolimus dose and the effectiveness of empiric treatments delivered either in preventive intent (occurrence of OU versus no OU) or in curative intent (improvement of the symptoms within the 5 days after the prescription of the symptomatic treatment) was also evaluated. Finally, we correlated the occurrence of OU with pharmacokinetic data.

2.3. Statistical analysis

The description of the results was based on classical statistical methods: percentage and 95%-confidence intervals (CI-95%), median and range, mean and standard derivation. Comparisons used Fischer exact test for categorical variables and Kruskal–Wallis and Mann–Whitney tests for continuous variables. All statistical tests were two-sided and significance was assumed at <.05. The collected data were analysed using SPSS (version 18.0) statistical software.

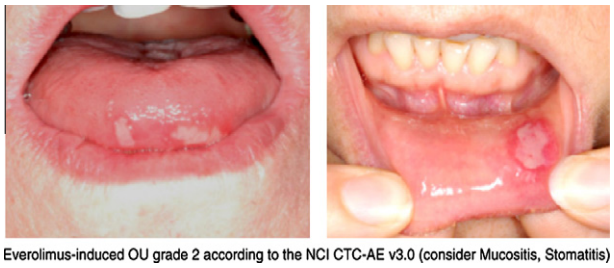

Fig. 1 – Everolimus-induced oral ulcers.

3. Results

3.1. Clinical description

Oral ulcers mostly affect the non-malphighian mucosa of the oral cavity and consist in painful aphtous ulcerations. Interestingly, they seem to be especially located on zones implicated with local friction, and mechanical trauma (e.g.: lateral side of the tongue, inner mucosae touching the teeth). Their size may reach up to 1–2 centimetres for the longest diameter, although there is an important intra and inter-patient variability. Oral ulcers are mostly ovoid-shaped lesions. Another common trait is the inflammatory halo surrounding the well-circumscribed white-coloured central area (Fig 1).

3.2. Incidence, severity, and associated AE

Baseline characteristics of the patients are described in Table 2. A total of 72%, 11%, 30% and 25% of patients presented OU; grade 3–4 OU, prolonged time under OU and RCOU, respectively. Patients with antecedent of prior chemotherapy (versus chemonaive) tended to have higher incidence of OU (80% versus 40%), grade 3–4 OU (15% versus 0%), prolonged time under OU (39% versus 0%) and RCOU (32% versus 6%). Patients delivered Everolimus in combination with other antineoplastics (versus in monotherapy) tended to have higher incidence of OU (78% versus 57%), grade 3–4 OU (16% versus 0%) but not with prolonged time under OU (29% versus 33%). Patients with PS 1 (versus PS 0) tended to exhibit higher rates of OU (73% versus 65%), grade 3–4 OU (13% versus 8%) and prolonged time under OU (35% versus 19%). Regarding other baseline characteristics (sex, age), no clear correlation was found between any

Table 2 – Baseline characteristics of patients.

	Patients with OU		Patients with grade 3–4 OU		Patients with prolonged time under OU[a]		Patients with RCOU		All patients	
	N	%, CI-95%	N	%, CI-95%	N	%, CI-95%	N	%, CI-95%	N	%
Median age, range	59 (28–74)		58 (39–73)		59 (33–74)		58 (33–74)		58 (25–74)	
Age <65 years old	44	75% (63–86)	6	10% (2–18)	16	27% (16–38)	14	24% (13–35)	59	75%
Age >65 years old	13	65% (44–86)	3	15% (0–31)	8	40% (19–61)	6	30% (10–50)	20	25%
Females	28	76% (62–90)	4	11% (1–21)	12	32% (17–47)	12	32% (17–47)	37	47%
Males	29	69% (55–83)	5	12% (2–22)	12	29% (15–42)	8	20% (7–32)	42	53%
PS 0	17	65% (47–84)	2	8% (0–18)	5	19% (4–34)	8	31% (13–49)	26	33%
PS 1	35	73% (60–85)	6	13% (3–22)	17	35% (22–49)	11	23% (11–36)	48	61%
Delivered weekly	10	56% (33–79)	0	0% (0–0)	1	6% (0–16)	4	22% (3–41)	18	23%
Delivered daily	47	77% (66–88)	9	15% (6–24)	23	38% (26–50)	16	27% (16–38)	61	77%
Delivered in monotherapy	12	57% (36–78)	0	0% (0–0)	7	33% (13–53)	4	19% (2–36)	21	27%
Delivered in combination[b]	45	78% (67–88)	9	16% (6–25)	17	29% (18–41)	16	28% (16–40)	58	73%
Chemonaive	8	44% (21–67)	0	0% (0–0)	0	0% (0–0)	1	6% (0–16)	18	23%
Antecedent of prior chemotherapy	49	80% (70–90)	9	15% (6–24)	24	39% (27–52)	19	32% (20–43)	61	77%
Total	57	72% (62–82)	9	11% (4–18)	24	30% (20–40)	20	25% (15–35)	79	100%

[a] Time under OU >21 days within the first 60 days after onset.
[b] Combined with other antineoplastics (radiotherapy excluded).

Table 3 – Frequency of OU, OU grade 3–4 and RCOU according to the Everolimus dose.

		Patients with OU		Patients with grade 3–4 OU		Patients with prolonged time under OU[a]		Patients with RCOU		All patients	
		N	%	N	%	N	%	N	%	N	%
Everolimus	2.5 mg qd	4	57	0	0	0	0	1	14	7	9
	5 mg qd	24	77	8	26	9	11	6	19	31	39
	10 mg qd	19	83	1	4	14	18	9	39	23	29
	Total Everolimus qd	47	77	9	15	23	29	16	26	61	77
	5 mg qw	0	0	0	0	0	0	0	0	1	1
	10 mg qw	0	0	0	0	0	0	0	0	3	4
	20 mg qw	2	100	0	0	0	0	0	0	2	3
	30 mg qw	4	50	0	0	0	0	2	25	8	10
	50 mg qw	4	100	0	0	0	0	2	50	4	5
	Total Everolimus qw	10	56	0	0	0	0	4	22	18	23
	Total Everolimus	57	72	9	11	23	29	20	25	79	100

[a] Time under OU >21 days within the first 60 days after onset; qd: daily dosing; qw: weekly dosing.

Table 4 – Median time to OU and median duration of the episode of OU according to the Everolimus daily dose (actual dose).

		Median time to OU Days	Kruskall–Wallis test P value	Median duration of OU episode Days	Kruskall–Wallis test P value
Everolimus daily dose (actual dose)	2.5 mg qd	22.5	0.043[b]	6.0	0.016[a]
	5 mg qd	7.0		17.0	
	10 mg qd	6.0		23.0	
	Total everolimus qd	7.0		15.0	

[a] Pairwise comparisons: 10 mg qd versus 2.5 mg qd: P = 0.036; 5 mg qd versus 2.5 mg qd: P = 0.046; 10 mg qd versus 5 mg qd :P = 1.00.
[b] Pairwise comparisons: 10 mg qd versus 2.5 mg qd: P = 0.008; 5 mg qd versus 2.5 mg qd: P = 0.011; 10 mg qd versus 5 mg qd :P = 0.962.

Table 5 – Effectiveness of preventive mouthwash on the occurrence of oral ulcer.

	No oral ulcer N (%)	Oral ulcer N	Fisher's exact test P value	No grade 3–4 oral ulcer N	Grade 3–4 oral ulcer N	Fisher's exact test P value
No preventive mouths wash	19 (29)	47 (71)	1.000	59 (89)	7 (11)	0.637
Preventive mouths wash	3 (23)	10 (77)		11 (85)	2 (15)	

Preventive mouth wash were always sodium bicarbonate based solutions.

of these parameters and OU, grade 3–4 OU or RCOU. At the 10 mg per day dosing scheme, 17% of the patients presented 2–3 episode of OU within the 60 fist days; whist 39% of them presented RCOU (Table 3). Concomitantly to OU, 10 patients (18%) and 18 patients (32%) presented severe neutropenia (grade 3–4) and digestive symptoms (all grade) (e.g.: oesophagitis, gastritis, and diarrhoea). A total of 8 (10%) and 7 (9%) patients necessitated dosing delay and dose reduction because of OU, respectively.

3.3. *Dose effect*

As the intended daily dose of Everolimus increased (2.5 mg qd; 5 mg qd; 10 mg qd), both the proportion of patients developing OU and RCOU tended to increase: 57% – 77% – 83% and 14% – 19% – 39%, respectively (Table 3). Given the small number of patients with weekly administration, we restricted the time to OU and duration of OU analyses to the patients with daily dosing only (61 pts). Simultaneously, the median time to OU was significantly reduced: 22.5 days – 7 days – 6 days (P = .003) and the median duration of the episode of OU was significantly prolonged: 6 days – 17 days – 23 days (P = .02) (Table 4).

3.4. *Effectiveness of empiric treatments*

When delivered in a preventive intent, sodium bicarbonate based mouthwash was not associated with a decrease of

Table 6 – Effectiveness of empiric treatments delivered in curative intent.

	Efficacy[a] N (%)	No efficacy[a] N (%)	Fisher's exact test P value
Sodium bicarbonate based mouthwash[b]	11 (24)	34 (76)	0.713
No sodium bicarbonate based mouth wash	4 (33)	8 (67)	
Oral fluconazole[b]	3 (19)	13 (81)	0.515
No oral fluconazole	11 (29)	27 (71)	
Total empiric treatment[b]	9 (22)	32 (78)	0.614
None empiric treatment	2 (33)	4 (67)	

[a] Efficacy was defined as any improvement in OU symptoms (NCI CTC v 3.0) within 5 days after onset of the empiric treatment.
[b] Each empiric treatment was at the investigator's discretion.

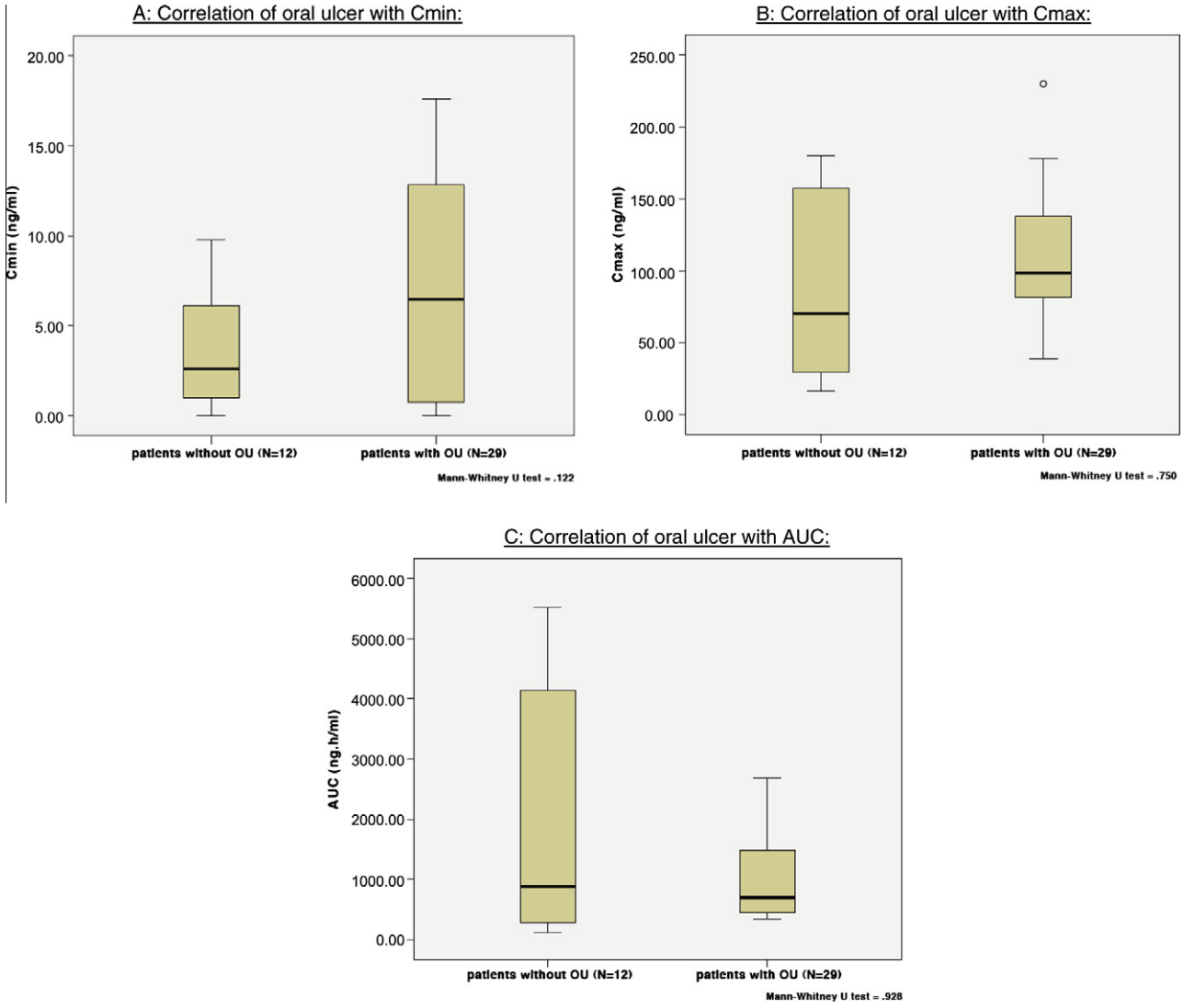

Fig. 2 – Correlations of oral ulcer with minimum concentration (C_{min}) (A), maximum concentration (C_{max}) (B), and area under the curve (AUC) (C).

the occurrence of OU (Table 5). The empiric treatments (sodium bicarbonate-based mouthwash, oral fluconazole) were not associated with improvement in OU symptoms within 5 days after their onset (Table 6).

3.5. *Correlations with pharmacokinetics*

Pharmacokinetic data were available for 41 patients. The minimum and maximum concentrations (C_{min}, C_{max}) as well as

the area under the curve (AUC) of Everolimus are described according to the OU status (OU vs no OU) in Table 7. We observed a trend towards higher value of C_{min} and C_{max} in case of oral ulcer (Fig. 2A, B). Nevertheless, no clear correlation was observed regarding the distribution of AUC between the patients presenting with OU or not (Fig. 2C).

4. Discussion

This is the first study to precisely describe natural history and management issues of mTOR inhibitor-induced OU in oncology. The fact that the patients' data were exclusively derived from prospective phase 1–2 trials led to a comprehensive record of adverse events and is an indicator of good quality of the generated model. We have observed that OU is a very frequent (72%) and often a recurrent and chronic adverse event following Everolimus (25%). Further, patients with antecedent of prior chemotherapy, with PS 1, or receiving Everolimus in combination tended to present higher rates of severe OU or prolonged time under OU. We demonstrated a dose effect relationship: as the Everolimus dose increases, the time to OU is reduced and the duration of OU is prolonged. When delivered at 10 mg daily dosing, which is the approval scheme, OU mostly occurs 6 days after onset, remains 23 days and is recurrent in up to 39% of patients. Finally, the empiric treatments (sodium bicarbonate-based mouthwash, oral fluconazole) delivered either in a preventive or curative intent appear useless.

In our opinion, the existing grading systems for the assessment of oral mucositis (WHO, WCCNR, OMAS, RTOG, NCI CTCAE v3.0 and v4.0)[8–12] appear as somewhat limited to describe OU in a detailed and quantitative manner. These scales have been developed in the conventional cytotoxics era and may not be adapted for targeted agents. mTOR inhibitor-induced oral mucositis consist in patchy ulcerations but rarely lead to pseudomembranes, confluent ulcerations, bleeding lesions or even tissue necrosis. Thus, investigators rather use the functional/symptomatic category grading of the NCI CTCAE v3.0 scale, which refers to pain (absent: G1; moderate: G2; severe: G3) and to reduction of oral intake (normal diet: G1, modified diet G2; unable to adequately aliment and hydrate orally: G3) than the clinical scale. Further, in NCI CTC v4.0, skin disorders (and notably rash) are also being categorised according to the affected body surface area. Such approach could be difficult to translate for mTOR inhibitor-induced oral ulcer given their particular clinical presentation: localised patchy ulcerations. Finally, conventional grading systems do not integrate the important time-related parameters such as the duration, the recurrency or the chronicity of AEs.[13] These traits could be especially important when defining the safety and the quality of life under mTOR inhibitors. Indeed, to experience grade 2 OU during more than 21 days may have a worse impact on the patient's quality of life than exhibiting grade 3 OU during a couple of days. Innovative scales incorporating both functional and time-related end-points (duration, recurrence) could be proposed to better assess mTOR inhibitor induced OU.

The high rate (72%) of patients with OU herein reported is concordant with the literature: in phase 1 trials, Temsirolimus, Deforolimus and Ridaforolimus induced OU in 54–89%[14,15]; 45–78%[16,17] and 79%[18] of patients, respectively. The fact that most of our population received Everolimus in combination with drugs sharing the same metabolism pathway could also have led to higher frequency of OU: Everolimus, Vinorelbine, Etoposide, Paclitaxel and Erlotinib are major substrates of CYP3A4. The lower frequencies of OU described in phase III trails are mostly explained by the fact that such studies are not primarily designed to detect AE (e.g.: 40% for Everolimus[5]; 35% Temsirolimus).[6,7]

Interestingly, patients with either antecedent of prior chemotherapy and or being delivered Everolimus in combination with other antineoplastics had higher rates of grade 3–4 OU and were more likely to present prolonged time under OU. This provides an insight towards a possible synergistic implication of conventional cytotoxics in the pathophysiology of mTOR inhibitor-induced oral ulcers. Such hypothesis is emphasised by the fact that conventional cytotoxics could provoke subclinical but long-term remaining sequels in the oral cavity epithelium.[1] The implication of the mTOR pathway in the wound healing process naturally emphasises this hypothesis.[19,20]

We described a dose effect relationship: the time to OU and the duration of OU increased with the dose escalation. Although not significant, the incidence of OU and the number of episode of OU also tended to increase at the same time. The trend towards higher Everolimus C_{min} and C_{max} for patients with OU also supports this hypothesis as well. The dose effect relationship might even be corroborated by the further indirect comparison: only 10–19% of patients present OU when Everolimus is delivered at much lower dose (e.g. 1.5 mg bid daily to prevent the acute rejection in renal transplantation),[21,22] whereas phase III oncology trials report up to 40% of patients with OU at the 10 mg qd dosing.

The management at bedside of such painful and recurrent lesions is challenging. By analogy to the conventional cytotoxics induced mucositis, physicians often treat OU with sodium bicarbonate-based mouthwash and oral fluconazole. Both of these treatments appear worthless either to prevent the occurrence of OU or to improve OU related symptoms. This retrospective analysis is however limited by the small number of patients. Interestingly, the presence of an inflammatory ring around the ulcer, has led some clinicians to prescribe anti-inflammatory based topical treatments. Such approaches have already been successfully implemented in nephrology where Everolimus is delivered at much lower dose.[23] Further prospective evaluation of these strategies is warranted for oncology patients. Another compelling issue is the 32% rate of patients who exhibited digestive symptoms concomitantly to OU. This raises the question about a possible extension of OU beyond the oral cavity. However, a definitive conclusion cannot be addressed since we did not explore the digestive tract of these patients during OU.

mTOR inhibitors have been recently introduced in oncology and often induce long lasting stable disease. In our series, OU are very frequent (72%), sometimes severe (11%) and often recurrent (25%) even two months after Everolimus onset. These lesions are very painful and remain for 17 to 23 days per episode at the usual dosing (i.e.: 5 mg qd, 10 mg qd). The bedside management of mTOR inhibitors-induced OU remains challenging. To our opinion, traditional mouthwashs are useless but dose delay or dose reduction appear to reduce OU symptoms. Although not yet validated, promising strategies

Table 7 – Pharmacokinetic parameters (Minimum concentration (C_{min}), maximum concentration (C_{max}) and area under the curve (AUC)) according to OU.

	C_{min} (ng/ml)			C_{max} (ng/ml)			AUC (ng h/ml)		
	Minimum	Maximum	Median	Minimum	Maximum	Median	Minimum	Maximum	Median
Patients with OU (29 pts)	0	33.90	12.86	14.30	230.00	95.60	335.00	2693.00	798.31
Patients without OU (12 pts)	0	25.50	4.60	16.00	180.00	70.10	124.00	5524.92	884.96
Total number of patients (41 pts)	0	33.90	9.45	14.30	230.00	94.80	124.00	5524.92	798.31

to improve symptoms could include anti-inflammatory topic treatments. Oncologists have to be aware that OU will undeniably be a key issue of the compliance to mTOR inhibitors.

Conflict of interest statement

Tarek Sahmoud is currently employed by Novartis, the industrial maker of Everolimus (investigated drug). No other author reported any conflict of interest.

Appendix A

See Table 7.

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