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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