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## Buccodental side effects of sunitinib in patients with metastatic renal cell carcinoma

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**Background:** Sunitinib is a tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma (RCC). Few data evaluated severe buccodental adverse events. The aim of this study was to evaluate sunitinib buccodental toxicity in patients with metastatic RCC and to compare it with that of standard chemotherapy in patients with other solid cancers.

**Methods:** Patients with RCC treated with sunitinib and patients with other solid tumours treated with chemotherapy were followed for 3 months. Data on dental appliances, oral hygiene/care practices before and during treatment were collected.

**Results:** A total of 116 patients were included (58 RCC treated by sunitinib: group S, and 58 treated by chemotherapy: group C). No differences in dental care habits were noted before treatment. In group S, patients reported significantly more frequent pain ( $P < 0.01$ ), teeth instability ( $P = 0.01$ ), gingival bleeding ( $P = 0.01$ ) and change in teeth colour ( $P = 0.02$ ). In all, 58% of patients in this group had to modify their diet ( $P < 0.01$ ). Frequency of dentist' visits for teeth removal was increased (25% vs 8%,  $P = 0.01$ ).

**Conclusion:** Sunitinib seems to increase buccodental toxicity as compared with chemotherapy. This finding emphasises the need for optimal dental care and standardised dental follow-up in patients treated with sunitinib.

Sunitinib is an inhibitor of tyrosine kinases receptors (TKIs), including vascular endothelial growth factor receptors type 1 and 2, platelet-derived growth factor receptors (PDGFR- $\alpha$  and PDGFR- $\beta$ ), stem cell factor (c-KIT), FMS-like tyrosine kinase 3, colony-stimulating factor1 and RET (Mendel *et al*, 2003; Arora and Scholar, 2005; Chow and Eckhardt, 2007; Haas and Uzzo, 2007). Sunitinib was approved for the treatment of metastatic renal cell carcinoma (mRCC) and metastatic neuroendocrine tumours of the pancreas. The most common toxicities are diarrhoea and fatigue, but other adverse events have also been reported, including stomatitis, hand foot syndrome and hypertension, while long-term side effects are still under investigation (Wolter *et al*, 2007;

Roodhart *et al*, 2008; Suwattee *et al*, 2008). Recently, one case of sunitinib-related osteonecrosis of the jaw (ONJ), has been published in a patient who did not receive any bisphosphonate medication (Ayllon *et al*, 2009; Brunello *et al*, 2009). This kind of side effect becomes more common with other TKI and may suggest a specific buccodental toxicity of sunitinib (or antiangiogenics in general). Then we decided to investigate this question. For this purpose, we compared prospectively the type and frequency of buccodental side effects and their functional impact on daily life in patients treated with sunitinib for mRCC with those reported by patients treated with conventional chemotherapy for other malignancies.

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**PATIENTS AND METHODS**

The authors received approval of the local IRB and all patients gave written informed consent before the study. Each group of patient received clear information about the study and agreed to fill a self-administered questionnaire, based on 35 questions assessing buccodental status and oral hygiene/care. The questionnaire was designed by medical oncologists and dentists.

The questions included descriptive demographic criteria, such as age, sex, old or recent tobacco intoxication (heavy or former smokers) with number of cigarettes per day since x year and/or alcohol intoxication, and clinical criteria, such as site of the primary tumour, antitumour treatment duration, number of therapeutic settings and prior treatment by bevacizumab or sorafenib. Concomitant treatment with bisphosphonates and presence of calcium metabolism disorders were also documented. The rest of the questionnaire included questions before treatment: dental status, dental care, frequency of daily tooth brushing and during or after the end of treatment such as dental status, diet changes, pain, dental instability, eating difficulties, cold or sugar sensitivities, gingival bleeding, extraction, cavities, infections, treatment by antibiotics, number of visits to dentists and impact on daily life. These last 14 criteria are defined to secondary buccodental toxicities.

The questionnaire was completed only one time during a consultation visit.

Patients included in the group sunitinib (group S) were seen in outpatients, treated for mRCC, having already received or are being treated by sunitinib. Sunitinib was given at 50 mg day<sup>-1</sup> during 4 weeks, followed by a 2-week treatment-free interval. Exclusion criteria were patients unable to understand or complete the questionnaire alone, or non-autonomous.

Patients included in the group chemotherapy (group C) were patients taken randomly, also seen in outpatient in order to have the same performance status between the two groups, treated for

metastatic solid cancer in first- or second-line chemotherapy. Chemotherapy was given every week, every 15 days or every 3 weeks in function of protocols. The main drugs that patients received in this group were anthracyclines, taxanes, fluorouracil, platinates and gemcitabine. Exclusion criteria were patients unable to understand or complete the questionnaire alone, non-metastatic or non-autonomous.

During the study, clinical examination and biological analyses were performed every 4 weeks for patients in group S and every 3 weeks for patients in group C.

**Statistical analysis.** To compare the groups, we took consecutive patients treated or been treated with sunitinib at our Institute and took the same number of patients treated by conventional chemotherapies. The hypotheses were expecting to show greater toxicity of >25% with sunitinib. Statistical analyses were performed using the Statistical Package for Social Services (SPSS) for Windows Release 10.0 (SPSS, Inc., IBM, Chicago, IL, USA). T-tests and Pearson's  $\chi^2$  analyses with an alpha risk set at 0.05 were performed to compare each group.

**RESULTS**

**Patients' characteristics.** Between October and December 2011, 116 patients treated at the Paoli-Calmettes Institute, Marseille, France, were included in the study (58 in each group). Their characteristics are depicted in Table 1. Median age was 64 years (35–80) in group S and 63 years (28–84) in group C. In all, 80% of the patients had a good performance status (Karnofsky score above 80%) and all were treated on a outpatient basis. There was a significant male predominance in group S as compared with group C (43 males out of 58 vs 25 males out of 58, respectively,  $P = 0.05$ ).

**Disease and treatment characteristics.** Median duration of treatment was 22 months (2–62) and 19 months (1–135) for sunitinib and chemotherapy, respectively, ( $P = 0.18$ ). All patients

Table 1. Patients' characteristics

	Group S (n = 58)	Group C (n = 58)	P-value
Age, years median (range)	64 (35–80)	63 (28–84)	0.16
Sex: male/female (n)	43/15	25/33	0.05
Karnofsky score % (median (range))	80 (60–100)	80 (50–100)	0.07
History of smoking, n (%)	5 (8.6%)	13 (22%)	0.02
Tumour site, n (%)	Kidney = 58 (100%)	Colorectal = 20 (34%) Ovarian = 11 (21%) Breast = 9 (15%) Pancreas = 8 (13%) Other = 10 (16%)	
Median duration of antitumoural treatment, months (range)	22 (2–62)	19 (1–135)	0.18
<b>Treatment by bisphosphonates</b>			
Yes	9 (15.5%)	7 (12%)	0.16
Median duration of treatment, months (range)	16.8 (3–18)	16.2 (2–18)	0.7
Treatment by bevacizumab before sunitinib or during chemotherapy, n (%)	9 (15.5%)	8 (13.7%)	0.12
Prior treatment by sorafenib	5 (8.6%)	0 (0%)	0.01
<b>Number of lines in the metastatic setting</b>			
1	53 (91.4%)	22 (38%)	0.001
2	5 (8.6%)	26 (44%)	
3 or more	0	10 (18%)	

Abbreviations: Group C = group chemotherapy; Group S = group sunitinib.

had metastatic diseases. Bisphosphonates were administered for hypercalcaemia or bone metastasis, in 15.5% and 12% of patients in groups S and C, respectively, ( $P = 0.16$ ), with a median duration of 16 months in both groups ( $P = 0.7$ ). In group S, only five patients (8.6%) were on a second-line metastatic treatment and have been previously treated by sorafenib, the other patients being treated frontline. In group C, the most frequently used chemotherapies were anthracyclines, taxanes and fluorouracil while 38% of patients being treated for a first metastatic treatment, 44% for second metastatic course and 18% for third and above metastatic course, respectively. Nine and eight patients received antiangiogenic treatment by bevacizumab in groups S and C, respectively, ( $P = 0.12$ ).

**Pre-treatment dental status and care.** Pre-treatment buccodental status was average or bad for 30 patients in both groups ( $P = 0.2$ ). Patients had similar pre-treatment buccodental care (dental adhesive care: 18% and 17% in groups S and C, respectively, ( $P = 0.13$ ), dental prosthesis: four patients (6.9%) in both groups ( $P = 0.8$ ) and frequency of daily tooth brushing). However, frequency of dentist’s visits were different with significantly more patients in group S visiting their dentist less than once a year (58% vs 49%,  $P = 0.01$ ; Table 2).

**Buccodental toxicity during treatment.** Patients’ self-reports of dental and gingival toxicities during oncologic treatment are reported in Table 3. The following adverse events were reported with a significantly higher frequency in group S: teeth colour changes ( $P = 0.02$ ), pain ( $P < 0.01$ ), teeth instability ( $P = 0.01$ ) and gingival bleeding ( $P = 0.01$ ). More than 50% of patients in this group had to change their dietary habits (58% vs 25%,  $P < 0.001$ ) because of buccodental side effects. However, neither cold nor sugar sensitivity were significantly increased. The periodontal/gingival alterations translated into a higher frequency of dentists’ visits within the few months following treatment initiation (39% vs 32%,  $P = 0.04$ ), in order to receive antibiotics (25% vs 10%,  $P = 0.01$ ), to undergo teeth extraction (25% vs 8%,  $P = 0.01$ ) or to set up of a denture (15% vs 0%,  $P < 0.001$ ).

In each group, patients with a pre-treatment defective hygiene seem to present more complications than the others (data not shown) but no significant differences between the two groups were

found regarding general buccodental status assessment, frequency of tooth brushing, incidence of cavities. Moreover, no significant differences were observed in terms of functional impact in daily life between the two groups ( $P = 0.81$ ).

Statistical analyses were repeated exclusion of patients treated with bisphosphonates, and no significant changes in terms of differences were observed.

**Smoking habits and oral lesions.** A history of smoking was reported by 8.6% and 22% of patients in groups S and C, respectively, ( $P = 0.02$ ). Patients with poor hygienic habits and tobacco or alcohol exposure presented more dental complications, such as cavities and loosening teeth (data not shown).

**DISCUSSION**

As cancer treatment becomes more intense and prolonged, deleterious effects on normal tissues may increase. The effective management of expected side effects associated with anticancer therapy is a key point in patients’ global care. Buccodental toxicities are poorly known or reported for most anticancer therapies including targeted therapies (National Institutes of Health, 1989). Such toxicities may limit food intake, impair patient’s quality of life and finally, represent an efficacy-limiting factor (Zadik *et al*, 2010). Over the past 10 years, many studies focused on oropharyngeal mucositis (Elting *et al*, 2003; Lalla *et al*, 2008; Peterson *et al*, 2009) but data on treatment-related buccodental effects are limited. Toxicity in oral status could influence diet and patient’s nutrition, especially in elderly patients. Moreover, pain associated with these complications may result in dose reduction, which is often associated with increased cancer recurrence and decreased survival rates (Rosenthal, 2007).

Table 2. Buccodental status and oral/hygiene care before introduction of antitumour treatment

	Group S (n = 58)	Group C (n = 58)	P-value
<b>Buccodental status, n (%)</b>			
Good	28 (48%)	25 (44.2%)	0.12
Average or bad	30 (52%)	33 (56.8%)	0.2
<b>Pre-treatment buccodental, n (%)</b>			
Dental adhesive	11 (18%)	10 (17%)	0.13
Dental prosthesis	4 (6.9%)	4 (6.9%)	0.8
<b>Frequency of daily teeth brushing, n (%)</b>			
≤ 1	11 (18%)	9 (15%)	0.02
> 1	47 (82%)	43 (80%)	0.08
<b>Number of visits to dentist per year and dental check-up, n (%)</b>			
≤ 1 Visit/year	34 (58%)	28 (49%)	0.01
> 1 Visit/year	24 (42%)	24 (42%)	0.1

Abbreviations: Group C = group chemotherapy; Group S = group sunitinib.

Table 3. Comparison of the frequencies of dental and gingival toxicities between group S and group C during treatment

	Group S (n = 58)	Group C (n = 58)	P-value
<b>Frequency of daily teeth brushing, n (%)</b>			
≤ 1	11 (18%)	12 (20%)	0.06
> 1	47 (81%)	46 (79%)	0.09
<b>Buccodental status, n (%)</b>			
Good	18 (31%)	17 (29%)	0.20
Average or bad	40 (69%)	41 (70%)	0.40
Teeth colour changes, n (%)	23 (39%)	20 (34%)	0.02
Pain, n (%)	37 (63%)	23 (39%)	<0.01
Teeth instability, n (%)	25 (43%)	14 (24%)	0.01
Loosening of the teeth, n (%)	21 (36%)	20 (38%)	0.68
Eating difficulties, n (%)	34 (58%)	15 (26%)	0.04
Gingival cold sensitivity, n (%)	31 (53%)	29 (50%)	0.09
Gingival sugar sensitivity, n (%)	11 (18%)	10 (18%)	0.75
Gingival bleeding, n (%)	36 (62%)	23 (39%)	0.01
Diet changes, n (%)	34 (58%)	15 (25%)	<0.01
More visits to dentists, n (%)	23 (39%)	19 (32%)	0.04
Teeth extraction during treatment, n (%)	15 (25%)	5 (8%)	0.01
Denture set-up, n (%)	9 (15%)	0 (0%)	<0.01
Cavities, n (%)	10 (17%)	10 (17%)	0.2
Antibiotics during treatment, n (%)	15 (25%)	6 (10%)	0.01
<b>Quality of life impairment, n (%)</b>			
Yes	33 (57%)	34 (59%)	0.84

Abbreviations: Group C = group chemotherapy; Group S = group sunitinib.

The multiple toxicities of cancer therapy in general has become increasingly apparent and led to develop the concept of a 'symptom burden' for a given patient, in which both severity of symptoms and patient's perception of their impact are relevant (Cleeland, 2007). The risk of developing buccodental toxicities is determined by a complex set of interactions with a variety of factors (type of malignancy, prescribed forms of therapy, age, status of oral health, nutritional status and so on) as described in the literature (Heimdahl and Nord, 1990; Sonis and Fey, 2002).

Commonly reported toxicities for antiangiogenic agents in patients with mRCC include asthenia, diarrhoea, nausea, anorexia, rash, hypertension, myelosuppression, elevated levels of thyroid-stimulating hormone, hypothyroidism and hepatotoxicity including liver failure (Rini, 2009; Di Lorenzo *et al*, 2011). Across oncology trials with sunitinib, these toxicities occur in  $\geq 20\%$  of patients (Motzer *et al*, 2009) but only few studies described oral toxicities, with the exception of the recent case report of ONJ by Fleissig *et al* (2012). In the literature, it has been suggested that unadapted dentures and exposure to alcohol and tobacco may create the oral mucosa and may favour the risk of chemotherapy-induced oral mucositis (Sonis and Clark, 1993; Christoloudou *et al*, 2009). In our study, only few patients had chronic alcoholic exposure, but 8% in group S and 22% in group C were heavy smokers or had prior tobacco exposure. Surprisingly, the percentage of smokers in group S was lower than of group C, while it was expected to be higher.

Moreover, we could note that denture set up was more frequent in group S but this may be confounded (by indication) by the fact that subjects in group S more frequently visited their dentist at baseline. However, during treatment, difference was not significant between the two groups.

Some patients (15%) received bisphosphonates, a treatment known to be responsible for ONJ (Woo *et al*, 2006; Christoloudou *et al*, 2009). Although there is just one case of ONJ described with sunitinib (Fleissig *et al*, 2012), the recent case of bevacizumab-related ONJ suggests that antiangiogenic therapy may contribute to oral mucosal lesions or impair angiogenesis-dependent bone cell differentiation and formation (Estilo *et al*, 2008; Santos-Silva *et al*, 2013). By inhibiting growth factor receptors and affecting revascularisation, sunitinib could have been responsible for osteonecrosis and poor wound healing after tooth extraction (Roodhart *et al*, 2008). This could explain the differences in oral toxicities between the two groups, in particular pain, fall of the teeth and need to denture set up.

In our study, the challenge for the long survivors was to find conceptual issues to anticipate symptoms in order to preserve a correct dental capital as well as it has been proposed in the past (Miaskowski *et al*, 2007; Aprile *et al*, 2008). It has been suggested that patients should visit their dentist for evaluation and care before starting chemotherapy as well as during treatment, but this approach is not systematic. According to our results, the same recommendations should apply to patients who receive sunitinib, but further prospective studies are needed to identify patients at risk of buccodental toxicity and to describe more accurately the type of dental follow-up to be performed, based on the patient's dental status.

In our study, dental or parodontal lesions were more frequently observed in the group treated by sunitinib, suggesting first, that patients should be specifically informed about these side effects, in order to prevent them as far as possible. This information should be simple, adapted and reassuring, but should focus on symptoms indicating a serious side effect. The message can be emphasised by nurse consultation, transmission to patients of the individualised care plan or linkage notebook, such as other oral chemotherapies (capecitabine, imatinib). Comprehensive clinical examination (global health status, nutritional status and buccodental status) and review of relevant pathological, radiological and biological data

should be performed before any chemotherapy/targeted therapy prescription. As one could notice in our study, patients with a defective hygiene seem to present more complications than the others whatever pre-treatment dental care done. This should encourage us to develop patient's information and prescription of prophylactic supportive care, such as mouthwashes, tooth brushing and appropriate diet. As nutritional status may have an impact on the incidence of buccodental side effects, nutritional biological parameters should be measured and taken into account. Other biological parameters currently under investigation may become important in the future: Van Erp *et al* (2009) demonstrated that the risk for mucosal inflammation was increased in the presence of G allele in CYP1A1 2455A/G in patients receiving single-agent sunitinib. These findings are particularly noteworthy and could lead to genetic-based technology to analyse toxicity associated with a molecularly targeted cancer therapy.

Then, strategies could be subsequently developed and tested, such as, prescription of panoramic X-rays as far as necessary, for screening of periapical lesions of granuloma, infections or first occurrence of osseous lesions. This is very important because buccodental lesions can be responsible for very serious complications, such as ONJ, sepsis and infectious endocarditis. For all patients, and especially for elderly patients, life expectancy, comorbidities, level of dependency and comprehensive geriatric assessment should be taken into account before initiation of treatment and during follow-up.

In summary, this prospective study highlighted the frequency of buccodental side effects among sunitinib-treated patients, and stressed the need for adapted information, prevention and surveillance. The purpose of the study was to demonstrate the fact that mouth and dental examination is not really a systematic assessment in the follow-up of these patients but, should be, considering its major importance and role for the long-term side effect occurrences. Moreover, considering the long-term benefits of sunitinib exposure in mRCC patients, our study pleads for optimised supportive care (including oral pain control, nutritional support and prevention/treatment of infections) for patients experiencing buccodental side effects, in order to favour compliance to treatment.

More studies are needed to address the complex relationship among pathobiological mechanisms, risks for clinically relevant side effects, and response to preventive and therapeutic interventions. It is likely that further research on mucositis and oral lesions will allow predicting the risk of toxicity and develop customised prophylactic and therapeutic approaches. These advances could mark a new era in the management of oral injuries caused by cancer therapies.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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