Phase II study of sunitinib as first-line treatment of urothelial cancer patients ineligible to receive cisplatin-based chemotherapy: baseline interleukin-8 and tumor contrast enhancement as potential predictive factors of activity

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Background: A strong rationale supports the role of antiangiogenic drugs in urothelial cancer. This trial was designed to assess the activity of sunitinib as first-line treatment in patients with metastatic urothelial cancer ineligible for cisplatin and to explore molecular and imaging variables predictive of clinical benefit.

Patients and methods: This was a multicenter phase II trial with sunitinib 50 mg daily in 4/2-week schedule. Eligibility criteria were as follows: creatinine clearance 30–60 ml/min, Eastern Cooperative Oncology Group performance status of one or less, and adequate hepatic and hematologic function. Twelve circulating cytokines were evaluated at baseline and sequentially using Luminex xMAP® (Austin, TX). Baseline and treatment-related changes in perfusion were evaluated in a patient subgroup using contrast-enhanced computed tomography.

Results: On intention-to-treat analysis, 38 patients showed 3 (8%) partial responses (PRs) and 19 (50%) presented with stable disease (SD), 17 (45%) of them >3 months. Clinical benefit (PR + SD) was 58%. Median time to progression (TTP) was 4.8 months and median overall survival 8.1 months. Toxicity was consistent with previous reports for sunitinib. Low interleukin-8 (IL-8) baseline levels were significantly associated with increased TTP. Baseline tumor contrast enhancement with >40 Hounsfield units was associated with clinical benefit.

Conclusions: This study highlights the potential role of the angiogenic pathway as a therapy target in urothelial cancer. Baseline IL-8 serum levels and contrast enhancement of lesions warrant further study.

Key words: biomarkers, interleukin-8, sunitinib, urothelial carcinoma

introduction

Urothelial cancer is one of the most common malignancies worldwide, with >140 000 deaths every year [1]. In advanced disease, cisplatin-based chemotherapy is the standard treatment as first-line therapy [2]. Up to 50% of patients presenting advanced urothelial cancer are unfit to receive cisplatin due to poor performance status, impaired renal function, and concomitant comorbidities [3–6]. For this patient subset, few therapeutic options are available. Although carboplatin-based combinations are used in this setting [7], they produce inferior results when compared with cisplatin-based regimens [8–10].

Recently, vinflunine has been granted approval for the second-line treatment of metastatic urothelial cancer [11]. However, in the first-line setting, the number of new drugs that are being evaluated for this disease is relatively low in comparison with other cancer types, and therefore, the development of new therapeutic alternatives for metastatic urothelial cancer is a priority.

Sunitinib (Sutent; Pfizer Inc., New York, NY) is a low-molecular weight, orally administered molecule that inhibits the tyrosine kinase domain activity of the receptors of vascular endothelial growth factor (VEGF)-1, -2, and -3; platelet-derived growth factor-α and -β; KIT; fms-like tyrosine kinase-3; receptor tyrosine kinase class XIV; and colony-stimulating factor-IR [12]. It has shown efficacy through phase III trials in metastatic renal cell carcinoma (mRCC) [13] and...
gastrointestinal stromal tumors refractory to imatinib [14]. VEGF and its receptors are overexpressed in urothelial carcinomas [15–17] and tumor angiogenesis has been identified as a negative prognostic factor in this disease [18–22]. Furthermore, sunitinib has shown activity against urothelial carcinoma cell lines and a synergistic effect when associated with cisplatin [23, 24]. A recent trial evaluated the clinical efficacy of sunitinib as second-line treatment of urothelial cancer patients, showing some clinical benefit warranting further investigation [25]. To improve current understanding of potential predictive markers of sunitinib activity as well as to identify alternative mechanisms of action and of drug resistance, we carried out correlative studies to determine sequential levels of serum-soluble proteins. We also assessed the potential role of contrast enhancement in tumor lesions as a way of measuring tumor vascularization using computed tomography (CT) scans to predict clinical activity of sunitinib and its correlation with time to tumor progression (TTP).

**patients and methods**

**study design**

This was an open-label phase II study conducted at four hospitals in Spain. The protocol was approved by the clinical research ethics committee at each participating site and registered in www.clinicaltrials.gov (NCT01118039). Study procedures were carried out in accordance with the Declaration of Helsinki of 1975, as revised in 2000. Written informed consent was obtained from all patients before enrollment.

**eligibility**

Eligible patients were required to have a diagnosis of locally advanced or metastatic transitional carcinoma of the urinary tract, previously untreated and nonamenable to potentially curative treatment. Patients were considered unfit to receive cisplatin-based therapy when they presented creatinine clearance <60 ml/min, according to the Cockcroft–Gault formula but were required to have a minimum clearance of 30 ml/min to be selected. In addition, patients had to present adequate hematologic and hepatic function, Eastern Cooperative Oncology Group performance status (ECOG PS) of zero or one, and a life expectancy beyond 12 weeks.

Patients were excluded in the event of relevant concomitant diseases, including other tumors, cardiac failure, coronary events in the previous 12 months, or uncontrolled arrhythmia or hypertension.

**treatment plan**

Sunitinib was administered orally at a dose of 50 mg/day over 28 days, followed by a rest period of 14 days before starting a new cycle. Doses were adjusted using standard recommendations in the event of toxicity. Because of the uncertainty of sunitinib activity, patients were closely assessed and evaluated after the first cycle of therapy with appropriate imaging to allow patients not obtaining benefit to switch to a carboplatin-based regimen. Otherwise, in patients deriving benefit, treatment was maintained until progression or unacceptable toxicity that could not be controlled by dose adjustment and adequate supportive treatment. The use of other concomitant antitumor treatment as well as of medication that is known to interact with sunitinib was not allowed.

**patient evaluation**

Baseline clinical evaluation, complete blood tests, electrocardiogram, and imaging studies were carried out. Clinical evaluation and blood tests were repeated on days 15 and 29 of each cycle during the first two cycles and every 6 weeks thereafter. Imaging tests were done at baseline and at week 6 (or earlier if clinically indicated), and repeated every 12 weeks. Quality of life was assessed on day 1 of each cycle. Follow-up after treatment discontinuation was carried out every 3 months.

**multiplex analysis of serum biomarkers**

Blood samples for pharmacodynamic studies were collected from 20 patients at baseline and on day 15 of the first cycle. Serum was obtained after blood centrifugation at 1500 rpm (.36 g) for 10 min at 4°C. Samples were aliquoted and stored at −80°C until use. Defrosted serum samples were analyzed using an xMAP multiplex immunobead assay (Luminex Corp., Austin, TX), a technology platform that has been previously validated [26] to simultaneously quantify 12 potential biomarkers. Twenty-five microliters of each serum sample was assayed in duplicate in 96-well microtiter filter plates (Milliplex™ MAP human panels; Millipore, Billerica, MA) for interleukin (IL)-8, IL-15, IL-17, granulocyte colony-stimulating factor, tumour necrosis factor-α (TNF-α), stromal cell derived factor-1 (SDF-1) alpha-beta, intercellular adhesion molecule-1, soluble (s)VEGFR1, sVEGFR2, sVEGFR3, Shhoblast growth factor type-2, and matrix metalloproteinase type 9 (MMP-9), according to the manufacturer’s instructions. The potential biomarkers were selected according to previous publications involving such molecules in sunitinib activity in other types of tumors or for their potential role in urothelial cancer development. VEGF was not selected as a biomarker because previous studies have shown that levels of this cytokine have no clinical value in predicting sunitinib clinical efficacy [27]. Concentrations of each protein were assessed according to standard calibration curves, analyzing the median fluorescent intensity data with the five-parameter logistic curve fitting method.

**assessment of tumor vascularization by contrast-enhanced computerized tomography**

In those patients treated in one of the participating institutions, baseline tumor enhancement in contrast-enhanced computed tomography (CECT) was assessed, as well as its variations in at least the first tumor evaluation. Tumor enhancement was quantified by measuring the differences between enhanced and nonevaluated phases in the CECTs, determined in Hounsfield units (HU), and the changes were correlated with tumor response. A radiologist, blinded to study participants, calculated the attenuation values in selected lesions.

**statistical methods**

The primary end point of this study was to determine TTP. Secondary objectives were response rate (assessed by RECIST criteria), progression-free survival (PFS), time to treatment failure (TTF), overall survival (OS), and toxicity. Serum levels of biomarkers and imaging analyses were correlated with TTP and clinical benefit, respectively.

Sample size was calculated using Simon’s optimal two-stage method for \( P_0 = 0.10 \) and \( P_1 = 0.30 \), using error probability limits \( \alpha = 0.05 \) and \( \beta = 0.10 \). It was estimated that at least 29 assessable patients were required. An interim analysis was planned to stop the trial in case less than one response was observed among the first 10 treated patients.

Safety analyses were carried out in all patients who received at least one dose of sunitinib (safety population). All toxic effects recorded were documented and graded according to the National Cancer Institute—Common Toxicity Criteria version 3.0.

Efficacy analyses were conducted on the intention-to-treat population (efficacy population). Times-to-event variables were described using the Kaplan–Meier method. Descriptive statistics were used to present response rate, clinical characteristics, and toxicity. Differences in serum protein levels between groups were examined with the Student’s \( t \)-test for unpaired and paired data for parametric variables, and the Mann–Whitney \( U \) test for unpaired nonparametric variables. The Wilcoxon signed rank test was used.
to study paired nonparametric variables. Normality was analyzed with the Shapiro–Wilks’ test. Log-rank test and Cox regression analysis were used to compare survival curves. *P* values <0.05 were considered significant and 95% confidence intervals (CIs) were calculated. Following the methodology of other exploratory studies [28, 29], we did not adjust for multiple statistical tests for the cytokine analysis.

**results**

**patient characteristics at baseline**

From July 2006 to September 2009, 38 patients were enrolled in the study. Median age was 75 years (range 70–80 years). The primary tumor was localized in the bladder in 85% of the patients. Visceral metastases were present in 47% of the patient population, specifically in lung (29%), liver (10%), and bone (8%). Median creatinine clearance at baseline was 48 ml/min (range 23–69 ml/min). One patient had an ECOG PS of 2, and two patients presented a baseline creatinine clearance <30 ml/min, but all of them were included in the efficacy and safety analyses. Additional patient characteristics are described in Table 1.

**efficacy**

On an intention-to-treat analysis, 3 patients (8%) achieved a partial response (PR) and 19 patients (50%) presented with stable disease (SD), whereas 12 patients (32%) showed disease progression (Table 2). Four patients were considered not assessable for efficacy. The first patient had a creatinine clearance <30 ml/min and a short life expectancy at baseline. This patient died on day 17 after starting treatment. A second patient withdrew consent and was lost to follow-up after 18 days of treatment. The third patient received only 16 days of treatment and was excluded due to a serious adverse event (renal failure) not related to the investigational drug as defined by the investigator. The last patient presented a baseline creatinine clearance <30 ml/min, withdrew consent, and was lost to follow-up after receiving 28 days of treatment, without being evaluated for efficacy.

Out of the 19 patients who achieved SD, 6 patients had SD for at least 3 months (16%); 4 patients over 6 months, 2 patients over 9 months, and 5 patients achieved SD over 12 months. Two patients presented a short stabilization period (<3 months). Clinical benefit rate (PR + SD) was 58%.

Median TTP was 4.8 months (95% CI 0.7–8.9) (Figure 1A), median PFS was 4.3 months (95% CI 2.3–6.3), median TTF was 2.9 months (95% CI 1.9–3.8), and median OS was 8.1 months (95% CI 4.0–12.2) (Figure 1B).

**safety and tolerability**

The main toxic effects observed are presented in Table 3. There were no grade 4 non-hematologic toxic effects and only one patient (3%) presented grade 4 thrombocytopenia. Four patients (11%) had grade 3 asthenia, and the following grade 3 episodes were observed in one patient each: hypertension, abdominal pain, and thrombocytopenia.

Two patients died during the study due to adverse events. One patient suffered ischemic heart disease and heart failure, probably complicated by a previous mitral stenosis and pulmonary embolism. This patient had a history of debilitating illness as chronic obstructive pulmonary disease and goiter that contributed to his poor general condition. The other patient suffered an ischemic stroke, complicated with pneumonia and sepsis that led to the patient’s death. This patient’s medical history included asthmatic bronchitis, toxic syndrome, gouty arthritis, hypertension, and acute pain treated with morphine. Although both adverse events were considered not related to the investigational drug, based on the recently recognized side-effects of tyrosine kinase inhibitors, a possible contributory effect of sunitinib cannot be completely ruled out.

Treatment was well tolerated with a toxicity profile consistent with previously published observations with sunitinib.

**analysis of biomarkers**

To explore the potential predictive role of our set of biomarkers, the relationship between sunitinib efficacy and baseline levels of the biomarkers was first analyzed. Analysis by

**Table 1. Patient characteristics at baseline (N = 38)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>75 (70–80)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (79)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (21)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (39)</td>
</tr>
<tr>
<td>1</td>
<td>22 (58)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Primary site of diseasea</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>30 (85)</td>
</tr>
<tr>
<td>Urethra</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Predominant sites of disease</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>19 (50)</td>
</tr>
<tr>
<td>Lung</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Bone</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Liver</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Other metastases</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

aData from three patients were missing.

ECOG PS, Eastern Cooperative Oncology Group performance status.

**Table 2. Best response by RECIST on the intention-to-treat population (N = 38)**

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>0.0–0.0</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (8)</td>
<td>1.7–21.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19 (50)</td>
<td>32.8–67.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (32)</td>
<td>15.5–47.7</td>
</tr>
<tr>
<td>Not assessable</td>
<td>4 (10)</td>
<td>2.9–24.8</td>
</tr>
<tr>
<td>Overall clinical benefita</td>
<td>22 (58)</td>
<td>40.9–74.9</td>
</tr>
</tbody>
</table>

*aClinical benefit rate = complete response + partial response + stable disease.
the Cox regression model using the best-fit cut-off value for each marker showed that IL-8 levels ≤17 pg/ml were significantly associated with an increased TTP (hazard ratio = 5.37, P < 0.05) (Figure 2). No significant association was found with the other cytokines analyzed.

Changes in biomarker levels during the study, which could serve to monitor sunitinib activity, were investigated. To this end, basal levels of the proteins studied were compared with those found after 15 days of treatment (Table 4). sVEGFR2 levels were significantly reduced after sunitinib administration (P = 0.0039), whereas SDF-1 levels were significantly increased (P = 0.0117). In patients with clinical benefit, the average increase in SDF-1 levels was 25.2% ± 12.6%, whereas patients with no clinical benefit showed only a moderate increase.

Figure 1. Kaplan–Meier plots representing time to tumor progression (A) and overall survival (B).
Average decrease in sVEGFR2 levels was similar between the two groups (35.5% ± 5.5% for patients with response to sunitinib and 38.7% ± 5.8% for patients without benefit). Levels of the rest of the cytokines analyzed, including IL-8, did not change significantly on day 15 after commencement of treatment.

**Assessment of tumor vasculature by CECT**

Twelve patients presenting evaluable lesions >15 mm in baseline CTs were included in this pilot study. Attenuation values of metastatic lesions at baseline and at the first evaluation were assessed. These patients showed 33 lesions evaluable at baseline but only 29 of them had subsequent follow-up (first evaluation). The median change between baseline evaluation and the first evaluation by CECT was statistically significant for the total evaluable lesions ($P = 0.0131$). In a descriptive analysis of these patients, enhanced lesions (>40 HU) in basal scans were predictive of clinical benefit (three presented PR and eight showed SD). In addition, attenuation in HU in at least one measurable lesion was observed in early assessments (6–12 weeks) and attenuation of HU >15% in at least one target lesion was observed in 10 patients.

**Discussion**

Our results show that sunitinib produces a 8% response rate and a 58% clinical benefit rate when used as first-line treatment of urothelial cancer patients unfit to receive cisplatin, with a median OS of 8.1 months and median TTP of 4.8 months. Moreover, sunitinib produced prolonged disease stabilization in some patients. The toxicity profile associated with sunitinib was moderate and similar to those previously reported for this drug. Although the response rates were lower than those reported with carboplatin-based chemotherapy [9, 10, 30], the proportion of patients presenting clinical benefit supports further evaluation of sunitinib in this setting. Our trial, which to our knowledge is the first one to evaluate sunitinib activity as first-line treatment of urothelial cancer patients unfit for cisplatin, also supports further investigation on the angiogenic pathway as a valuable target in this disease.

Gallagher et al. [25] recently reported a phase II trial that evaluated sunitinib activity in patients with urothelial carcinoma previously treated with chemotherapy. In addition...
Table 4. Comparison of biomarker levels at baseline and after 15 days of treatment (n = 20)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline* (mean ± SD)</th>
<th>Post-treatment* (mean ± SD)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>33.3 ± 7.5</td>
<td>48.4 ± 14</td>
<td>0.25</td>
</tr>
<tr>
<td>IL-15</td>
<td>5.8 ± 1.27</td>
<td>4.1 ± 0.9</td>
<td>0.10</td>
</tr>
<tr>
<td>IL-17</td>
<td>24.1 ± 12.1</td>
<td>45.8 ± 20.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor</td>
<td>30.7 ± 4.1</td>
<td>46.4 ± 9.2</td>
<td>0.14</td>
</tr>
<tr>
<td>Tumour necrosis factor-α</td>
<td>16.5 ± 6.3</td>
<td>19.6 ± 6.3</td>
<td>0.31</td>
</tr>
<tr>
<td>SDF-1 alpha-beta</td>
<td>2354.4 ± 255.9</td>
<td>2996.0 ± 435.8</td>
<td>0.0017*</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>221.7 ± 13.8</td>
<td>198.3 ± 19.9</td>
<td>0.12</td>
</tr>
<tr>
<td>sVEGFR1</td>
<td>1632.1 ± 473.5</td>
<td>1929.4 ± 413.5</td>
<td>0.37</td>
</tr>
<tr>
<td>sVEGFR2</td>
<td>10382.0 ± 771.1</td>
<td>6542.6 ± 659.1</td>
<td>0.0039*</td>
</tr>
<tr>
<td>sVEGFR3</td>
<td>1286.1 ± 1008</td>
<td>590.6 ± 441.8</td>
<td>0.50</td>
</tr>
<tr>
<td>FGF-2</td>
<td>40.5 ± 6.0</td>
<td>46.2 ± 9.2</td>
<td>0.61</td>
</tr>
<tr>
<td>MMP-9</td>
<td>456.6 ± 195.6</td>
<td>269.9 ± 76.9</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Units of biomarkers are given in pg/ml, except for MMP-9 and I-CAM, which are given in ng/ml.

**Statistically significant.

SD, standard deviation; IL, interleukin; ICAM-1, intercellular adhesion molecule-1; sVEGFR1, soluble (s)VEGFR1; FGF-2, fibroblast growth factor type-2; MMP-9, matrix metalloproteinase type 9.

to the conventional sunitinib schedule, an alternative schedule of sunitinib 37.5 mg daily administered continuously was also studied. PRs were seen in 7% and 3%, respectively, for each sunitinib schedule, and clinical benefit was observed in 31% and 25%, respectively.

Although this activity seems to show potential in this group of patients with limited treatment alternatives, future strategies for development of antiangiogenic therapy in urothelial cancer might be in combination with chemotherapy or as a post-therapeutic maintenance strategy in patients with minimal residual disease [23, 31].

Recent reports have stressed the importance of evaluating biomarkers of activity for sunitinib and other inhibitors of angiogenesis [28]. The possibility of being able to determine which patients will benefit from these targeted agents is an urgent need and should be considered as a high priority in current drug development. In our trial, we explored the role of correlative clinical and biological markers as predictors of sunitinib activity. We found that baseline serum levels of IL-8 were significantly decreased in patients with clinical benefit and correlated with improved TTP. IL-8 is a proinflammatory chemokine, which belongs to the chemokine receptors family and which stimulates neutrophil chemotaxis and degranulation [32, 33]. IL-8 is a potent pro-angiogenic factor, which has been shown to initiate tumor angiogenesis in xenograft models in which VEGF signaling was regulated [34]. Its expression has been reported to enhance angiogenesis through the induction of MMP-9 and to induce metastases of human transitional cell cancer cell lines [35]. In animal models of urothelial cancer, high expression of IL-8 was associated with a significant increase in tumor growth and metastases [36]. A recent study has associated increased IL-8 plasma levels in xenograft renal cell carcinoma (RCC) models with resistance to sunitinib treatment [37]. In the same study, IL-8 was overexpressed in tumors from patients refractory to sunitinib. Increased expression of IL-8, MMP-9, and VEGF in non-small-cell lung cancer patients, treated with the oral inhibitor of VEGF2 tyrosine kinase vandetanib, correlated with a higher risk of progression [38]. In mRCC patients treated with pazopanib, baseline levels of IL-8 correlated with tumor burden [39], and different polymorphisms of the IL-8 gene were significantly associated with treatment activity [40]. These studies support the notion for the potential role for IL-8 baseline levels as a predictive serum biomarker of sunitinib activity in patients with urothelial cancer.

In RCC, high baseline TNF-α and MMP-9 levels were associated with lack of clinical benefit to sunitinib [41] and low baseline sVEGFR3 and vascular endothelial growth factor-C levels were correlated with longer TTP [27]. Increased baseline levels of VEGF and neutrophil gelatinase-associated lipocalin, a protein tightly correlated with MMP-9, have been shown to correlate with shorter TTP in mRCC patients treated with sunitinib [42]. In hepatocarcinoma patients treated with sunitinib, Zhu et al. [43] found that increased baseline levels of the proinflammatory cytokines IL-8, IL-6, SDF-1, and TNF-α were associated with rapid tumor progression and/or mortality. In addition, a decrease in sVEGFR2 and sVEGFR3 was found in these patients after sunitinib treatment, although no clinical correlation with time to event was found. Data obtained in the present study show that sunitinib decreases sVEGFR2 and increases SDF-1 levels in urothelial cancer patients soon after commencement of treatment (day 15). Reduced levels of sVEGFR2 have also been described in non-small-cell lung cancer patients treated with vandetanib [38]. Elevations of SDF-1 have been previously reported in normal non-tumor-bearing mice [44] as well as in mRCC patients treated with sunitinib [41].

Tumor vascularity is a potential predictor of treatment outcomes in highly vascularized tumors such as mRCC, and contrast enhancement of tumors in CT is significantly correlated with microvessel density. A recent study in patients with mRCC receiving antiangiogenic therapy demonstrated...
a positive correlation between tumor enhancement in CECT assessed in baseline scans, and tumor response and PFS [45]. Our results show that tumor enhancement >40 HU in basal CECT may be predictive of clinical benefit. These findings stress the point that it is through the combination of imaging, clinical, and molecular studies that further improvements in predicting the outcome of patients receiving new targeted treatment options may occur. This constitutes a relevant paradigm to be further investigated in clinical research trials.

In conclusion, this study highlights the potential role of angiogenic pathway as a new target for therapy in patients with advanced urothelial cancer and supports further evaluation of sunitinib in this setting. Baseline IL-8 levels and contrast enhancement of lesions in CECT seem to be potentially useful predictive markers of sunitinib activity and they should be implemented in future studies to further validate their role as biomarkers predicting the antiangiogenic therapeutic effect.

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disclosure

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