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Optimizing the Sequencial Treatment of Metastatic Renal Cell Carcinoma (MRCC) − a Retrospective, Multicenter, Analysis of 40 Patients Treated With Either Sorafenib, an mTOR Inhibitor (mTORI) and Sunitinib, or Sunitinib, an mTORI and Sorafenib

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Background: Since the approval of 3 multikinase and 2 mTOR inhibitors (mTORI), an increasing number of mRCC patients have been empirically treated with a sequential treatment approach. However, the optimal sequential use of all these agents has yet to be estabilished. The purpose of this retrospective analysis was to assess the clinical benefit of 2 different sequential approaches, i.e., sorafenib, an mTORI and sunitinib, or sunitinib, an mTORI and sorafenib.
Material and Methods: This study was a retrospective analysis of 40 patients with mRCC treated between September 2005 and October 2010 at 6 European Centers. All patients were treated first-line with either sunitinib or sorafenib, followed by a second-line treatment with an mTORI (everolimus or temsirolimus), and, upon further progression, with the other multikinase inhibitor (sorafenib or sunitinib).
Results: 26 patients were treated with the sequence sorafenib-mTORI-sunitinib and 14 with the sequence sunitinib-mTORI-sorafenib. Baseline patient characteristics were similar between both populations in terms of age, ECOG Performance Status, Motzer's score, Fuhrman's grade, and presence of liver metastases. In the sunitinib-mTORI-sorafenib group, an higher incidence of non-clear cell mRCC were observed (5/14 *vs.* 0/26 in the sorafenib-mTORI-sunitinib group). The actuarial overall median PFS (not including inter-treatment periods) in the sorafenib-mTORI-sunitinib group and in the sunitinib-mTORI-sorafenib group were 21.9 and 22.8 months, respectively (Log-rank test: $p = 0.928$). In the sorafenib-mTORI-sunitinib group patient experienced a median PFS of 11.7 months at first-line, 5.1 months at second-line, and 9.1 months at third-line, while in the sunitinib-mTORI-sorafenib group the first-, second- and third-line PFS were 14.4, 4.3 and 3.9 months, respectively.
Conclusions: Even though biased by its retrospective nature and small sample size, this study suggests the absence of significant differences, in terms of median PFS, between patients treated with the two sequential modality considered. In particular, it is possible to assume that patients may be sensitive again to a multikinase inhibitor after a second-line treatment with an mTORI. The results of ongoing prospective studies will help us defining the best treatment sequence.
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Impairment of Cognitive Functioning During Sunitinib or Sorafenib Treatment − a Cross Sectional Study

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Background: Impairment of cognitive functioning has been reported in several studies in patients (pts) treated with chemotherapy. So far, no studies have been published on the effects of the vascular endothelial growth factor receptor (VEGFR) inhibitors on cognitive functioning. We investigated the objective and subjective cognitive function of patients during treatment with VEGFR tyrosine kinase inhibitors (VEGFR TKI).
Material and Methods: Three groups of participants, matched on age, sex and education, were enrolled; 1. metastatic renal cell cancer (mRCC) or GIST pts treated with sunitinib or sorafenib for $\geqslant$ 8 weeks (n = 29); 2. not-systemically-treated mRCC pts (n = 19); 3. healthy controls (n = 30). Sixteen neuropsychological tests examining the main cognitive domains (intelligence, memory, attention and concentration, executive functioning and abstract reasoning) were administered by a neuropsychologist. Four questionnaires were used to assess subjective cognitive complaints, mood, fatigue and psychological wellbeing.
Results: No significant differences in mean age, sex distribution, education level or IQ were found between the three groups. In the VEGFR TKI group 22 pts received treatment with sunitinib and 7 with sorafenib; 25 pts had a diagnosis of mRCC and 4 of GIST. Pts on treatment with VEGFR TKI showed a significant impairment in memory and learning, executive functioning and abstract reasoning (all $p < 0.05$) compared with the healthy controls. The differences were modest to large (effect sizes Cohen's *d* ranging from -.48 to -.81) indicating that they are clinical relevant. Also, not-systemically-treated mRCC pts showed impairments on neuropsychological tests concerning memory, executive functioning and abstract reasoning, but on fewer tests than the VEGFR TKI group. No differences were observed between the VEGFR TKI group and the not-systemically-treated mRCC pts. No differences in the tests on attention and concentration were found between the three groups.
Conclusions: Our data demonstrate that the VEGFR TKIs sunitinib and sorafenib have a negative impact on cognitive functioning, specifically on memory and learning, and executive functioning. Patients treated with VEGFR TKIs have to be informed on this newly described adverse event.

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Treatment (tx) Patterns and Toxicity of Angiogenesis Inhibitors in Patients (pts) With Advanced Renal Cell Carcinoma (RCC) in Spain

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Background: This study evaluated the frequency of and reasons for tx modifications and frequency of adverse events (AEs) among pts with advanced RCC treated with anti-angiogenic agents in Spanish clinical practice.
Materials and Methods: Medical records, not part of a disease-based registry, from adult pts with advanced RCC who received sunitinib [SU] (N = 60), sorafenib [SOR] (N = 23), bevacizumab (N = 6), or temsirolimus (N = 1) as 1st-line tx from 1/1/2005 to 9/15/2010 were retrospectively reviewed at 2 large oncology centers in Spain. Kaplan–Meier survival analysis was used to estimate tx duration. Proportions of pts with and reasons for tx modifications (discontinuation, interruption, dose reduction) were determined. Proportion of pts with all grade and grade 3/4 AEs were also determined.
Results: Only results for SU and SOR with sufficient sample sizes are presented. 26.7% (SU) and 13.0% (SOR) of pts had prior immunotherapy, 73.3% (SU) and 60.9% (SOR) of pts had history of nephrectomy, and 50.0% (SU) and 43.5% (SOR) of pts had metastasis at $\geqslant$2 sites. 83.3% of SU pts and 91.3% of SOR pts started tx at recommended dosing levels. Median 1st-line tx duration for all pts was 5.6 months for SU and 11.5 months for SOR. 1st-line tx discontinuation occurred in 91.7% (SU) and 69.6% (SOR) of pts. 40.0% of SU pts and 43.5% of SOR pts experienced grade 3/4 AEs and an average of 5.5 (SU) and 2.7 (SOR) all-grade AEs were experienced by each pt. Most common all grade AEs were mucositis or stomatitis (73.3% of SU pts; 43.5% of SOR pts), fatigue (70.0% of SU pts; 47.8% of SOR pts), diarrhea (43.3% of SU pts; 34.8% of SOR pts) and hand-foot syndrome (43.3% of SU pts; 39.1% SOR pts). AEs led to tx modification in 55.0% of SU pts and 73.9% of SOR pts (Table). 55.6% of SU pts who discontinued due to AEs did so within 12 weeks of tx initiation.

Tx Modifications, n (%)	SU (n = 60)	SOR (n = 23)
Pts with tx discontinuation	54 (90.0)	16 (69.6)
Due to progressive disease	40 (66.7)	14 (60.9)
Due to AEs	9 (15.0)	1 (4.3)
Pts with tx interruption	27 (45.0)	15 (65.2)
Due to AEs	26 (43.3)	13 (56.5)
Pts with dose reduction	24 (40.0)	11 (47.8)
Due to AEs	20 (33.3)	8 (34.8)
Pts with $\geqslant$1any of the above tx modifications	59 (98.3)	22 (95.7)
Due to AEs	33 (55.0)	17 (73.9)