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Safety and treatment (trx) patterns of multikinase inhibitors (MKI) in patients (pts) with metastatic renal cell carcinoma (mRCC) in Italy

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Background: The MKIs sunitinib (SU) and sorafenib (SOR) have become standard of care in mRCC. This study assessed safety and trx patterns for these agents in clinical practice.
Methods: A retrospective medical record review was performed at a tertiary oncology center in Italy. The study included non-trial patients who were ⩾18 yrs, MKI-naïve at study initiation, had a histological diagnosis of mRCC, and received ⩾1 trx with SU or SOR as 1st MKI from 9/05 to 7/08. Data were collected on adverse events (AEs) and trx modifications including discontinuations (d/c), interruptions, and dose changes, and reasons for these modifications.
Results: 145 pts were included; all 85 SU pts received the recommended starting dose of 50 mg QD 4/2; 59 SOR pts received the recommended starting dose of 400 mg BID, and 1 SOR pt received 400 mg QD. Median trx duration was 6.6 months for SU and 5.8 months for SOR. 97.6% of SU and 70.0% of SOR pts experienced ⩾1 AE; 27.1% and 31.7% had ⩾1 grade 3/4 AE. The most common all-grade and grade 3/4 AE for both MKIs was fatigue/asthenia, followed by mucositis/stomatitis and decreased taste sensation for SU, and hand-foot syndrome and diarrhea for SOR (Table). 40.0% of SU and 45.0% of SOR pts had ⩾1 trx modification due to AEs. The rates of trx d/c, interruption, and dose reduction due to AEs were 11.8% (10 pts), 23.5% (20 pts, 33 interruptions), and 30.6% (26 pts, 34 reductions) respectively for SU, and 5.0% (3 pts), 20.0% (12 pts, 15 interruptions), and 36.7% (22 pts, 26 reductions) respectively for SOR.
Conclusion: The most common all-grade and grade 3/4 AE was fatigue/asthenia. Other AEs relevant for tolerability were also frequent and resulted in trx modifications in 40% of SU and 45% of SOR pts. Results suggest a need for additional effective treatments in mRCC that may also provide improved tolerability.

	Sunitinib (N = 85)		Sorafenib (N = 60)	
Adverse events, n (%) with event	All grades	Grades 3/4	All grades	Grades 3/4
Any AE	83 (97.6)	23 (27.1)	42 (70.0)	19 (31.7)
Fatigue/Asthenia	69 (81.2)	8 (9.4)	26 (43.3)	6 (10.0)
Mucositis/Stomatitis	50 (58.8)	2 (2.4)	16 (26.7)	0 (0)
Hand-foot syndrome	29 (34.1)	2 (2.4)	23 (38.3)	2 (3.3)
Diarrhea	26 (30.6)	0 (0)	19 (31.7)	2 (3.3)
Hypertension	35 (41.2)	3 (3.5)	6 (10.0)	3 (5.0)
Decreased taste sensation	36 (42.4)	0 (0)	1 (1.7)	0 (0)
Nausea	25 (29.4)	3 (3.5)	2 (3.3)	0 (0)
Abdominal pain	16 (18.8)	3 (3.5)	9 (15.0)	1 (1.7)
Pain	15 (17.6)	0 (0)	5 (8.3)	4 (6.7)
Lack of appetite	12 (14.1)	0 (0)	5 (8.3)	1 (1.7)

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Efficacy of Olmesartan Medoxomil for hypertension control in advanced RCC patients under treatment with single agent Sunitinib

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Background: Sunitinib has been approved for the treatment of mRCC and GIST tumors. Sunitinib is a multi-tyrosine-kinase inhibitor, and its antitumour effect is mainly mediated by inhibition of angiogenesis. VEGF receptor is a principall target. Hypertension is one of the major side-effects of anti-VEGF drugs. Management of hypertension in patients under drugs with anti-VEGF activity in not clearly established.
Methods: In a prospective study, pts under Sunitinib Malate therapy (50 mg/d 4/2wks) presenting with increased systolic (⩾160 mmHg) and/or diastolic (BP) (⩾100 mmHg) were included. In pts with previous diagnosis of hypertension, a secondary cause was excluded. Pts treated with antihypertensive drugs carried out a washout period of 7 days. Pts initiated Olmesartan Medoxomil 40 mg once daily in the morning. BP goals were values below 140/90 mmHg at week 4. Pts not achieving the goal levels received 12.5 mg to 25 mg of hydrochlorothiazide/day. Clinical and analytic evaluation was performed on weeks 2, 4, 8, and 12. Clinical variables analysed were age, blood pressure, heart rate, weight, body mass index (BMI), and waist circumference. Biochemical parameters were analysed.
Results: Over 84 pts included only 19 pts reached grade 2−3 hypertension CTC 3.0 (mean age 57.3±,52.6% females). Four patients (21.1 %) were previously hypertensives on treatment with one antihypertensive drug. Mean dose of Sunitinib was 47.4±5.2 mg and no dose reduction was made because of side-effects. Systolic BP was significantly reduced from 189±13 mmHg to 142±5 mmHg after 12 weeks of therapy. Diastolic BP was significantly reduced from 98±6 mmHg to 88±3 mmHg. Those pts with previous diagnosis of hypertension (n = 4) showed a similar evolution of BP values albeit their systolic and diastolic BP levels at baseline were higher than in those without this diagnosis (systolic BP 200±8 mmHg vs 186±12 mmHg, p = 0.038, and diastolic BP 102±6 mmHg vs 98±6 mmHg, p = 0.261). Twelve pts (63.1%) needed addition of hydrochlorothiazide once daily to achieve BP objectives. None patient needed dose reduction or withdrawal Sunitinib because of uncontrolled hypertension. There were no significant changes in biochemical parameters.
Conclusions: Olmesartan Medoxomil represent a new challenge for control hypertension and cardiovascular risk factors in pts with advanced RCC under treatment with Sunitinib. Any hypertensive strategy to treat this specific group of hypertensive patients should include an RAAS inhibitor. In the future, recommendations to manage this secondary cause of hypertension are necessary

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Temsirolimus in second or subsequent line in patients with metastatic renal cell carcinoma (mRCC): better activity in good-intermediate prognosis patients

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Background: to evaluate the activity and safety of the inhibitor of mammalian target of rapamycin (mTOR) temsirolimus in unselected, pretreated patients with mRCC.
Methods: eligible cases had mRCC of clear or non-clear renal cell histology and accessibility for treatment. Any previous treatment was allowed. Patients received 25 mg of intravenous temsirolimus on a weekly basis and were evaluated every 8 weeks for tumor response.
Results: from March 2007 to date 33 patients have been evaluated and 28 treated (median age 54, range 24−76; male/female ratio: 23/6; clear vs non-clear histology: 24/4, one case not evaluable for histology; 18 cases were treated with sorafenib, 23 with sunitinib and 13 with both drugs). Median number of previous treatments was 2 (range 0−5). According to the Motzer prognostic criteria (more than one metastatic site, high corrected serum calcium, lactate dehydrogenase ⩾ 1.5×ULN, anemia, ECOG performance status ⩾ 2, metastatic lesions within 12 months from diagnosis), 17 were classified as poor-risk, 9 as good-intermediate risk, and 3 had an unknown status. Of 28 patients with an available actual tumour reevaluation none achieved an objective response, 16 a stable disease (57%) and 12 progressed (43%). Considering the prognostic criteria, 9/17 (35%) poor-risk and 8/9 (89%) good-intermediate risk patients achieved a stable disease. All the 4 patients with non-clear-cell histology achieved a progressive disease within the first 8 weeks. With a median follow-up of 7 months (range 1−17) the mean Progression-Free Survival was 4.8 months. Most common treatment related adverse events, mainly of grade 1−2, were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, neutropenia, lymphocytopenia, stomatitis, skin rash. Dose reduction have been provided in only 25% of the cases.
Conclusions: temsirolimus confirm its activity and good safety profile also in a strongly pretreated population of MRCC poor-risk patients. Further investigations of this drug are warranted.