



# Long-term use of sunitinib in metastatic renal cell carcinoma: no unpleasant surprises about tolerability

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Metastatic relapse occurs in approximately 30% of patients who have previously undergone nephrectomy for renal cell carcinoma (1). Anti-angiogenic agents, such as tyrosine kinase inhibitors (TKI), have played a leading role in the treatment of metastatic renal cell carcinoma (mRCC) because it is highly resistant to chemotherapy. Sunitinib is a first-line TKI targeting both the vascular endothelial growth factor receptor (VEGFR) and the platelet-derived growth factor receptor (PDGFR). Treatment of mRCC with sunitinib has been shown to increase progression-free survival (PFS) to 11 months (95% confidence interval 0.32–0.54) versus 5 months with baseline interferon alpha treatment ( $P < 0.001$ ) (1), and to improve overall survival (OS) and quality of life. However, patients receiving sunitinib experience specific treatment-related adverse events, including hypertension, epistaxis, hypothyroidism, hand-foot syndrome, hair color changes, fatigue, diarrhea and hematological toxicity. Although almost all patients will develop secondary resistance to sunitinib, 10% remain progression free during >24 months' therapy (2). This chronic use of sunitinib raises the question of long-term safety for patients treated for more than 2 years (3).

A recent study by Porta *et al.* provided long-term follow-up data on more than 5,000 patients from phase II and III clinical trials who received sunitinib for mRCC, 1% of whom were treated for at least 5 years (4). The results showed that grade 3 and 4 treatment-related adverse events reached a peak during the first year of treatment, while rates of most adverse events were stable over the duration of treatment. Specifically, hand-foot syndrome, which is an important cause of treatment discontinuation due to its negative impact on quality of life, occurred at a constant rate of about 30%. The rate of hypertension was also stable

around 30% for the 6 years of treatment. This finding contradicts the results of other studies that have reported large, treatment duration-related increases in systolic and diastolic blood pressure during sunitinib treatment (5).

The mechanism by which TKIs cause hypertension has been suggested to be a inhibition of VEGFR-2 signalling and reduced nitric oxide production, resulting in systemic vasoconstriction (6). It is possible that the finding of a stable long-term hypertension rate by Porta *et al.* (4) may be the result of antihypertensive treatment given to control blood pressure while on sunitinib. The study does not report data on concomitant medication or the type of antihypertensive agents used, some of which might have increased activity due to interaction with sunitinib (7). Hypothyroidism appeared to be the only cumulative toxicity of sunitinib, and is related to vascular regression of capillaries in the thyroid and induction of type 3 deiodinase activity, as well as a reduction in triiodothyronine (T3) and thyroxine (T4) levels (8,9).

The study by Porta *et al.* was the first to gather long-term safety data on sunitinib. The results are quite reassuring given that they don't show cumulative toxicity after more than 2 years' sunitinib treatment, except for hypothyroidism that can be managed with hormonal substitution. However, there is a lack of information regarding the sunitinib dose given, and the dose of sunitinib in current practice tends to reduce over time. It is also important to take into account the sunitinib administration schedule (2/1 versus 4/2), which was not reported but could reduce toxicity (10).

The success of TKIs for increasing survival in mRCC means that a number of additional agents have been developed and are in use as first-line or second-line treatment (Table 1). However, long-term safety remains an issue and there are fewer data on these newer agents. Over

**Table 1** Common treatment-related adverse events (all grades) after 1 year of treatment with different tyrosine kinase inhibitors in metastatic renal cell carcinoma

Adverse events	Sunitinib <sup>a</sup> (%)	Axitinib <sup>b</sup> (%)	Sorafenib <sup>c</sup> (%)	Pazopanib <sup>d</sup> (%)
Hypertension	29	42	–	45
Hand-foot syndrome	39	22	51	32
Diarrhoea	60	63	74	45
Fatigue	44	55	38	82
Rash/desquamation	15	22	51	–
Nausea	24	45	–	25
Hypothyroidism	29	–	–	–
Hair toxicity*	18	–	39	44
Anorexia	21	30	–	–

<sup>a</sup>, Porta *et al.*, *Eur Urol* 2016 (4); <sup>b</sup>, Cohen *et al.*, *Cancer Chemother Pharmacol* 2014 (11); <sup>c</sup>, Hutson *et al.*, *Eur J Cancer* 2010 (12); <sup>d</sup>, Sternberg *et al.*, *Oncology* 2014 (13); \*, alopecia, color changes.

a median treatment duration of nearly 3 years with axitinib, the most common grade 3/4 treatment-related adverse events (including hypertension, diarrhea, proteinuria and fatigue) occurred in the first 6 months (11). In another analysis of pooled data of long-term axitinib use, rates of proteinuria, peripheral edema and renal failure increased over time, whereas the rate of all other adverse events remained stable or decreased (14). In the TARGET study, Hutson *et al.* (12) reported moderate toxicities after 1-year of treatment with sorafenib, such as diarrhea, cutaneous adverse events (rash or desquamation), hand-foot syndrome, alopecia, and fatigue, most of which appeared early during treatment. Similar findings have been reported for pazopanib (15). In one study, over a median 9.7 months' treatment, recurrent adverse events were hypertension, diarrhea, hair color changes, anorexia and nausea (13); in this study toxicity was lower than that reported in the COMPARZ trial (16). Overall, current data suggest that all available TKIs share the same safety profile.

The next question is whether new targeted therapies for mRCC will challenge existing TKIs in term of efficacy and safety. Cabozantinib is a new TKI targeting MET, VEGFR, and AXL. In the METEOR trial, second-line treatment of mRCC with cabozantinib was associated with better PFS and OS than mTOR inhibitors (17). With a median follow-up of 18.8 months, the most frequent treatment-related adverse events were similar to those with currently-available TKIs, and the main grade 3/4 events were hypertension, diarrhea, fatigue, hand-foot syndrome, anemia, hyperglycemia and hypomagnesemia (17); there

were no data regarding toxicities over time. Immunotherapy has shown promise in the treatment of mRCC resistant to anti-angiogenic therapies. The recent CheckMate 025 study brought hope for second-line treatment of mRCC with nivolumab, an anti-PD1 agent, which was shown to be more effective than everolimus (18). After treatment for a median of more than 8 months, OS was of 28.1 months, although the rate of any grade treatment-related adverse events and immune-mediated toxicities was 70% (18).

Available data suggest that the long-term safety of TKIs has been well assessed, and it is now widely accepted that the most severe treatment-related adverse events occur in the first year of therapy. However, some toxicities remain difficult to manage on a long-term basis (e.g., hypertension, hypothyroidism and hand-foot syndrome). Education of both patients and clinicians is important to decrease the intensity of side effects and a lot of work has been done in this regard. New therapies are challenging TKIs for first- and second-line treatment of mRCC. However, there are few data on long-term safety compared with well-known TKIs.

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