

## Tyrosine kinase inhibitors for the treatment of metastatic renal cell carcinoma: what urologists should know?

Metastatik renal hücreli karsinom tedavisinde tirozin kinaz inhibitörleri: Ürologlar ne bilmelidir?

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### Abstract

Tyrosine kinase inhibitors (TKIs) are currently the preferred treatment for metastatic renal cell carcinoma (mRCC). However, many urologists are not fully aware of the serious complications of TKI treatment, which require close monitoring. Some clinical and pathological findings associated with TKI treatment may also require further evidence-based characterization, including non-clear cell histology, sarcomatoid differentiation, the role of cytoreductive nephrectomy, and the interactions of other drugs with TKIs. The aim of this review was to provide information the urologists should know before beginning treatment of mRCC with TKIs. A review of all Medline and DOAJ articles related to TKI treatment was undertaken. In this review, 49 publications that were sufficiently relevant and informative were analyzed. As a conclusion, TKIs represent an effective treatment option for patients with metastatic clear cell RCC. TKIs may exhibit favorable effects on metastatic chromophobic RCC; however, no significant effect on metastatic papillary RCC was reported. The currently available data cannot ignore the role of cytoreductive nephrectomy as a prerequisite to the favorable effect obtained through TKI treatment. Neoadjuvant TKIs represent a challenge to anaesthetists and urologists, and special precautions should be taken. Sarcomatoid differentiation of RCCs of clear cell histology may exhibit a favorable response to TKI treatment, provided that prevalence of sarcomatoid cells in the primary tumor is less than 30%.

**Key words:** Cytoreductive nephrectomy; metastatic renal cell carcinoma; tyrosine kinase inhibitors.

### Özet

Tirozin kinaz inhibitörleri (TKİ), metastatik renal hücreli karsinom (mRCC) için günümüzde tercih edilen tedavidir. Ancak, çoğu ürolog TKİ tedavisinin yakın izlem gerektiren ciddi komplikasyonlarından tam olarak haberdar değildir. Ayrıca TKİ tedavisinin eşlik ettiği bazı klinik ve patolojik bulgular, “non-clear” hücre histolojisi, sarkomatoid farklılaşma, sitoredüktif nefrektominin rolü ve diğer ilaçlar ile TKİ’lerin etkileşimi gibi ileri kanıta-dayalı tanımlama gerektirebilir. Bu derlemenin amacı, mRCC’nin TKİ’ler ile tedavisine başlanmadan önce ürologların bilmesi gereken bilgilerin sunulmasıdır. TKİ tedavisi ile ilişkili tüm Medline ve DOAJ makaleleri gözden geçirilmiştir. Bu derlemede, konu ile yeterli düzeyde ilişkili ve bilgilendirici 49 yayın analiz edilmiştir. Sonuç olarak, “clear” hücreli mRCC hastalarının tedavisinde TKİ’ler etkili bir tedavi seçeneğidir. TKİ’ler kromofobik mRCC üzerinde olumlu etki gösterebilirler; ancak papiller mRCC üzerinde anlamlı etkileri yoktur. Mevcut veriler TKİ’nin olumlu etkilerinin elde edilmesi için ön koşul olarak sitoredüktif nefrektominin rolünün gözardı edilemeyeceğini göstermektedir. Neoadjuvan TKİ’ler anesteziistler ve ürologlar için zorluk oluşturmaktadır ve özel önlemler alınmalıdır. Primer tümörde sarkomatoid hücre prevalansının %30’dan az olması koşuluyla, “clear” hücre histolojisine sahip RCC’nin sarkomatoid farklılaşması, TKİ tedavisine olumlu yanıtı neden olabilir.

**Anahtar sözcükler:** Metastatik renal hücreli karsinom; sitoredüktif nefrektomi; tirozin kinaz inhibitörleri.

Sunitinib and sorafenib are tyrosine kinase inhibitors (TKIs) targeting growth factor receptors; the most important of these receptors are the vascular endothelial growth factor (VEGF), the platelet derived growth factor (PDGF) and the stem cell factor KIT receptors. Both TKIs target the von Hippel Lindau/hypoxia-inducible factor (HIF) gene pathway.<sup>[1]</sup> These receptors possess an extracellular domain that binds specific ligands, a transmembrane domain and an intracellular domain that contains a tyrosine kinase domain. TKIs act by competing for ATP on the ATP pocket of the kinase domain, thus blocking the phosphorylation process of the downstream substrates.<sup>[2,3]</sup>

Currently, sunitinib is the main treatment for most patients with metastatic RCC (mRCC) with clear cell histology, achieving objective remission in 47% of patients and obtaining a progression-free survival (PFS) of 11 months.<sup>[4]</sup>

Sunitinib is recommended to be given orally as a 50 mg single daily dose for four weeks, followed by two weeks of no treatment in repeated six-week cycles. The half-life of sunitinib is 40 hours.

#### **Possible serious complications of TKI treatment**

A pivotal trial of sunitinib as a first-line therapy for mRCC reported hypertension in 24% of patients, with resistant or life-threatening hypertension in 8% of cases.<sup>[5]</sup>

Wu et al.<sup>[6]</sup> conducted a systematic review and a meta-analysis of the occurrence of hypertension with sorafenib treatment. They indicated that sorafenib was associated with all grades of hypertension and high-grade hypertension in 23.4% and 5.7% of cases, respectively.

Aparicio-Gallego et al.<sup>[7]</sup> confirmed that treatment with sunitinib was associated with a significant and sustained increase in blood pressure (BP). They concluded that sunitinib exerts its hypertensive effect through vascular rarefaction, endothelial dysfunction and/or altered nitric acid metabolism. DePrimo et al.<sup>[8]</sup> indicated that sunitinib was associated with an increase in VEGF and a decrease in VEGF2 (soluble VEGF) and VEGF3. Because VEGF2 is the form responsible for nitric oxide release and vascular wall relaxation, the effect of sunitinib on the relative proportions of VEGF forms may explain the resulting hypertension.

The degree of TKI-associated hypertension was reported to be dose-dependent, beginning within one week of the start of treatment and resolving two weeks after the discontinuation of TKI, and no pretreatment characteristics of patients can predict its occurrence. Maitland et al.<sup>[9]</sup> conducted a prospective study for patients treated with sorafenib and detected a dynamic increase in BP from pretreatment measurements (as high as 29 mmHg in systolic BP and 27 mmHg in diastolic BP) within the first several days of treatment.

As a treatment for the hypertension resulting from TKI treatment, Maitland et al.<sup>[10]</sup> proposed the use of angiotensin-converting enzyme (ACE) inhibitors to produce rapid lowering of BP with or without calcium channel blockers such as amlodipine to modulate patients' BP. These proposed drugs, in our opinion, present a safe choice in treating TKI-induced hypertension, as both ACE inhibitors and dihydropyridine calcium channel blockers (e.g., amlodipine) do not prolong the Q-T interval.

Di Lorenzo et al.<sup>[11]</sup> studied cardiac toxicity associated with sunitinib and reported grade 3 left ventricular ejection fraction (LVEF) dysfunction in 6.9% of their patients, necessitating the discontinuation of treatment. Telli et al.<sup>[12]</sup> conducted a retrospective analysis on cardiotoxicity for patients treated with metastatic renal or gastrointestinal stromal tumors and reported symptomatic grade 3/4 heart failure in 15% of patients.

Schmidinger et al.<sup>[13]</sup> demonstrated that 33.8% of patients receiving either sorafenib or sunitinib experienced a cardiac event, suggesting that the cardiac damage induced by TKI is underestimated.

Kerkela et al.<sup>[14]</sup> obtained an endomyocardial biopsy in a patient who developed acute decompensated heart failure following 11 months of therapy for mRCC. The patient exhibited widespread and severe structural alterations in mitochondria, including markedly swollen mitochondria with disrupted or absent cristae.

Zhu et al.<sup>[15]</sup> indicated that sunitinib is associated with an elevated incidence of renal dysfunction, as 65.5% of patients with mRCC developed increased serum creatinine during sunitinib treatment. They explained these findings as being the result of both glomerulopathy caused by the direct effect of TKIs

on VEGF in renal glomeruli and the indirect effect of sunitinib on BP, resulting in renal trauma. Patel et al.<sup>[16]</sup> described a case series of seven patients who presented with preeclampsia-like syndrome; they presented with edema, hypertension, proteinuria and hypo-albuminemia at a median of 24 weeks after the start of TKI treatment, confirming the occurrence of TKI-induced glomerulopathy.

Choueiri et al.<sup>[17]</sup> conducted a meta-analysis of the arterial thromboembolic events associated with sunitinib and sorafenib treatment. Their study included 10,255 patients and reached the conclusion that TKI treatment was associated with a significantly increased risk of thromboembolic events, exhibiting a relative risk (RR) of 3.03. Je et al.<sup>[18]</sup> conducted a meta-analysis of the occurrence of bleeding in association with sorafenib and sunitinib treatment. Their study indicated that the incidence of all grades of bleeding was 16.7%, with no difference observed between the use of either sorafenib or sunitinib. Kamba et al.<sup>[19]</sup> explained the increased risk of bleeding risk associated with TKIs, noting that VEGF is important for the survival of endothelial cells, maintaining the architecture and integrity of the microvessels. Therefore, VEGF inhibition may cause the repair and renewal capacity of endothelial cells in response to trauma to be altered, increasing the risk of both hemorrhage and thromboembolic events.

Vaklavas et al.<sup>[20]</sup> reviewed all prospective phase I to phase III trials related to TKIs and found grades 3/4 hypertension for bevacizumab, sunitinib and sorafenib of 9.2%, 6.9%, and 7.2%, respectively, grades 3/4 LVEF dysfunction of 0.3%, 1.4%, and 0.05%, respectively, and grades 3/4 thromboembolism of 9.6%, 1.2%, and 3.8%, respectively, confirming the importance of screening for cardiovascular toxicity during the course of treatment with TKIs.

Martin et al.<sup>[21]</sup> reported a case of a 70-year-old woman who was treated with sunitinib following nephrectomy for mRCC. She developed hypertension, visual loss and convulsions two weeks after sunitinib treatment. Computed tomography (CT) and magnetic resonance imaging (MRI) both confirmed the diagnosis of reversible posterior leukoencephalopathy (RPLE) that was believed to be directly related to sunitinib treatment. The drug regimen was ended immediately, and the patient recovered within

several days, presenting completely normal CT and MRI findings one month later. In another report, van der Veldt et al.<sup>[22]</sup> reported another case of RPLE following treatment of a 54-year-old woman with sunitinib who was diagnosed using MRI. Their study explained the occurrence of RPLE by the effect of TKIs on the disruption of cerebral vascular endothelial cells and impaired cerebrovascular autoregulation, which resulted in edema. The presence of renal dysfunction, which can also be induced by TKIs, represents a risk factor for the development of RPLE.

In a phase III randomized trial using sunitinib in patients with mRCC, cutaneous side effects were common, including rash, xerosis, hair and skin pigmentations as well as hand-foot skin reaction (HFSR). HFSR was the most common finding, being characteristic to the drug and marked by erythema and parasthesia on the palms and soles, which may be also associated with edema and desquamation. Histologically, HFSR is characterized by thick, well-defined hyperkeratotic lesions.<sup>[23]</sup> Chu et al.<sup>[24]</sup> conducted a meta-analysis on the risk of HFSR and indicated that the overall incidence of all grades of HFSR and high-grade HFSR were 18.9% and 5.5%, respectively, for cases treated with sunitinib for mRCC, GIST and other solid tumors. The location of the cutaneous lesion within the palms and soles may be explained by the excretion of the drug in the sweat and because sunitinib is mainly secreted by eccrine sweat glands that are located in excess in the palms and soles. The National Cancer Institute (NCI) graded HFSR as grade 1 (minimal skin changes, such as erythema, with no pain), grade 2 (skin changes, e.g., peeling, blisters, bleeding or erythema, with pain, but not interfering with function) and grade 3 (ulcerative dermatitis with pain, interfering with function). Preventive measures include the avoidance of constrictive footwear, friction and trauma and the use of thick cotton gloves and socks.<sup>[25]</sup>

Other possible skin complications include spotty skin depigmentations, which may appear three to five weeks after the beginning of the treatment and can be explained by the effect of sunitinib on c-kit, which has a role in melatonin production.<sup>[26]</sup>

Dubauskas et al.<sup>[27]</sup> reported more serious skin complications in their review of 131 patients with mRCC who were treated with sorafenib. Their study

identified seven cases of cutaneous SCC and two cases of SCC keratoacanthoma, including two cases of focal squamous atypia and three cases of actinic keratosis, with a mean time to development of 9.3 months.

Hutson et al.<sup>[28]</sup> reviewed the sorafenib arm in the phase III TARGET study and could detect rash/desquamation in 51%, of patients, HFSR in 49% of patients and alopecia in 39% of cases.

Sahai et al.<sup>[29]</sup> demonstrated a positive prognostic association between TKI-induced cutaneous toxicity and disease course, which suggests a therapeutic response. Strumberg et al.<sup>[30]</sup> in a review of multiple phase I trials on patients with advanced solid tumors receiving sorafenib, observed a prolonged time to disease progression among patients who developed HFSR.

Desai et al.<sup>[31]</sup> reported an incidence of primary hypothyroidism in 36% of their cases treated with sunitinib, and they suggested that the incidence of hypothyroidism increases with the duration of treatment. They also indicated that an initial thyroiditis-inducing thyrotoxicosis may precede the development of hypothyroidism. Schmidinger et al.<sup>[32]</sup> confirmed the above finding, as they detected hypothyroidism in 36.1% of their cases treated with sunitinib; moreover; they reported that the occurrence of hypothyroidism was significantly associated with enhanced objective remission (28.3% and 3.3% remission rate in patients with hypothyroidism and euthyroid patients, respectively). In a multivariate analysis, the development of hypothyroidism was an independent significant factor that predicted improved survival (with a hazard ratio (HR) of 0.31). Their study indicated the development of hypothyroidism to be a marker of improved response to treatment and enhanced survival.

### **Role of cytoreductive nephrectomy**

Barbastefano et al.<sup>[33]</sup> identified 46 patients at the Cleveland Clinic who were treated by cytoreductive nephrectomy and TKIs and studied the association between the patients' fractional percentages of tumor volume (FPTV) removed and their progression-free survival (PFS). Their study indicated that removal of an FPTV of >90% is an independent factor predicting improved PFS following TKI treatment. Locatelli et al.<sup>[34]</sup> reported a case of an elderly patient with RCC and skin, lung, bone and brain metastases who was treated with cytoreductive nephrectomy followed by sunitinib treatment, which resulted in a prolonged response.

Although no publications are available to date comparing the PFS of patients on TKI therapy with or without CN, 67-100% of patients from two phase III trials administering TKI already exhibited CN before treatment with these agents.<sup>[23,35]</sup> Therefore, the beneficial role of TKI as a single treatment agent for mRCC without CN on the patients' outcome has not been reported.

In our institution, we do not advocate the use of TKI as a neoadjuvant treatment (NAT) prior to CN, as we believe that such treatment may delay the time to surgery. Hellenthal et al.<sup>[36]</sup> conducted a prospective trial evaluating preoperative sunitinib administered to patients with localized and metastatic RCC. Their study included 20 patients and demonstrated a mean decrease in tumor size of 11.8% with a high level of surgical safety and no major adverse events perioperatively related to the drug at a reduced daily dose of 37.5 mg. Thomas et al.<sup>[37]</sup> conducted a similar study on 19 patients with RCC who did not appear to be suited for resection. Their study suggested a partial response, stable disease and disease progression in 16%, 37% and 47% of cases, respectively. Kroeger et al.<sup>[38]</sup> reported a case of a patient with advanced RCC and atrial thrombus who underwent NAT with sunitinib followed by surgery that became amenable to abdominal access, with no need for sternotomy. Bex et al.<sup>[39]</sup> reported two cases with mRCC and IVC thrombus who received NAT with sunitinib. The two cases indicated progression of IVC thrombus with marked deterioration in general clinical status, suggesting that, although NAT with sunitinib may be feasible, it carries the risk of tumor progression.

Libert et al.<sup>[40]</sup> recently published a report indicating that, although NAT with TKIs represents a new hope for oncologists, it represents a strong challenge for anesthesiologists in two aspects: first, the treatment increases the risk of surgical complications, including hypertension, arrhythmia and blood loss; second, the treatment raises the possibility of interactions between TKIs and anesthetic drugs, such as isoflurane and halothane.

Wound healing did not appear to be a notable problem following surgery and NAT with TKIs, provided that the TKI treatment was discontinued for a sufficient length of time before surgery. Thomas et al.<sup>[41]</sup> reported minor wound complications in



two out of 19 patients included in their study. Other complications that the authors encountered included significant intraoperative hemorrhage in one patient and anastomotic bowel leak and abscess in another patient. Until that time, no study had been conducted regarding the appropriate length of time between discontinuing TKI treatment and performing surgery, or when safely to begin TKI treatment following surgery. We believe, based on the half-life of TKIs, that one week off TKI treatment before surgery and one month before commencing TKI treatment following surgery may be the safest plan of treatment. In our institution, the timing of TKI treatment relative to surgery has not been intensively studied, partly because we prefer to employ TKI treatment as an adjuvant treatment and not a neoadjuvant treatment and because we rarely perform renal biopsy, selecting instead to perform a nephrectomy, wait for the pathology result confirming clear cell histology and refer to the medical oncologist to begin TKI treatment. Therefore, an average of one month is required to begin the drug treatment. Bose et al.<sup>[42]</sup> also based on the half life of the drugs, recommended one week without TKI treatment before doing surgery, although, similar to our group, they did not intensively study the safety of shorter duration.

### **When to discontinue TKI treatment?**

Based on the currently available evidence, unless a patient develops grade 3/4 complications attributed to TKI treatment and as long as an objective response is detected, the treatment should not be stopped. Johannsen et al.<sup>[43]</sup> conducted a retrospective analysis on 12 patients who developed complete remission of mRCC under treatment with CN and TKIs followed by discontinuation of TKI. The median time without TKI treatment was 7.5 months. Disease recurrence was observed in five patients (41.6%), including three cases (25%) with new metastatic sites. The median time to recurrence was six months. During sunitinib retreatment, all metastatic sites exhibited complete or partial responses, indicating that TKI treatment may be safely continued on a long-term basis for patients with mRCC and evident response to treatment.

### **Drug interactions with TKIs**

TKIs are metabolized primarily with CYP3A4, implying that any drug that can be a potent inhibitor or inducer of that enzyme could possibly increase the toxicity of the drugs or decrease their efficacy.

The only scientific evidence available in the literature is that the administration of TKIs in combination with ketoconazole (a CYP3A4 inhibitor) results in drug toxicity, and the employment of sunitinib in combination with rifampin (a CYP3A4 inducer) decreases drug efficacy, necessitating dose adjustment.<sup>[44]</sup>

### **TKI treatment for non-clear cell RCC**

A phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma demonstrated a partial response in only one patient with unclassified histology and indicated no objective response for patients with papillary histology. The PFS for whole cases was 5.5 months.<sup>[45]</sup>

Choueiri et al.<sup>[46]</sup> recruited 53 patients with metastatic papillary and chromophobic renal cell carcinoma. Their overall PFS was 8.6 months, which was the average of PFSs of 11.9 and 5.1 months for patients treated with sunitinib and sorafenib, respectively. Dividing the response by the histological type, 3 patients (25%) of chromophobic RCC achieved a response (two with sunitinib and one with sorafenib), with a PFS of 10.6 months, and 2 patients (4.8%) out of 41 patients with papillary RCC achieved a response (both with sunitinib), with a PFS of 7.6 months.

### **TKI treatment for clear cell RCC with sarcomatoid differentiation**

Sarcomatoid differentiation in patients with clear cell RCC was considered by some urologists to be a relative contraindication for the use of TKI therapy; however, some recent reports could indicate a beneficial effect of TKI treatment for such a diagnosis.

Lekili et al.<sup>[47]</sup> recently published a case report of a 38-year-old man with mRCC that was managed with CN and who exhibited sarcomatoid differentiation with clear cell histology. On treatment with sorafenib, the patient exhibited a PFS of 22 months. Golshayan et al.<sup>[48]</sup> studied 43 patients with sarcomatoid mRCC. The patients indicated a partial response and stable disease in 19% and 49% of cases, respectively. In their study, the tumor response was limited to cases with a sarcomatoid component of less than 20%.

Although we believe that the sarcomatoid component does not respond to TKI treatment, the response obtained may be explained by the fact that

the metastatic component of RCC may not harbor the sarcomatoid component that is present in the primary tumor. Shuch et al.<sup>[49]</sup> conducted a histological evaluation of metastases of RCCs with sarcomatoid differentiation. Their study indicated that primary tumors with a high percentage of sarcomatous features were more likely to form metastases with sarcomatoid changes. Their study could define a cut-off value of 30% sarcomatoid differentiation in the primary tumor to predict its presence at metastatic sites.

## Conclusion

TKI treatment represents an effective treatment option for patients with metastatic clear cell renal cell carcinoma, allowing an average progression-free survival of 11 months. TKIs may indicate some favorable effects on metastatic chromophobic RCCs (specifically achieved with sunitinib); however, no significant effect was observed on metastatic papillary RCCs. The currently available data cannot ignore the role of cytoreductive nephrectomy as a prerequisite for the favorable effect obtained with TKI treatment. Neoadjuvant TKI treatment represents a challenge to anesthetists and urologists, and special precautions should be observed in addition to discontinuing the drug treatment one week before surgery and readministering it one month after surgery. The percentages of sarcomatoid differentiation of RCCs should be identified by pathologists, and sarcomatous RCCs in the primary tumor may not coincide with its presence in the metastases. A cut-off value of 30% sarcomatoid differentiation may be employed to predict the pathology of metastases and, therefore, the response to TKI treatment. TKIs may produce a robust response within the first several cycles of treatment; however, the treatment should still be continued for life, as discontinuation of the drug may result in tumor progression. TKI treatment does not represent a safe treatment option, as serious complications may occur during treatment.

## Conflict of interest

No conflict of interest was declared by the authors.

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