Metastatic Renal Cell Carcinoma Treated Sequentially with Multiple VEGF Receptor-targeted Inhibitors – A Case Report

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Abstract. *Six targeted agents [sorafenib, sunitinib, temsirolimus, bevacizumab (plus interferon), everolimus and pazopanib] have been approved for the treatment of patients with metastatic renal cell carcinoma. As disease progression is inevitable, most patients will receive several lines of treatment. However, the choice regarding which sequence of drugs to use remains unclear, particularly concerning the drug class, i.e. those targeting the vascular endothelial growth factor (receptor) [VEGF(R)] pathway versus those acting on the mammalian target of rapamycin pathway. There appears to be no absolute crossresistance between tyrosine kinase inhibitors (TKIs) acting on the VEGF(R) pathway, and there have been numerous reports of two TKIs being successfully used in sequence. We report the case of a 63-year-old woman who responded for 24 months to three successive lines of treatment with different TKIs (sunitinib, axitinib and sorafenib). This suggests that TKIs targeting VEGFR should be considered as individual drugs and not as a single class.*

Over the past five years, targeted therapies directed against vascular endothelial growth factor (VEGF) and its receptor (VEGFR), and mammalian target of rapamycin (mTOR) pathways have largely replaced immunotherapy in the treatment of metastatic renal cell carcinoma (mRCC). To date, six targeted therapies have been approved – sorafenib, sunitinib and pazopanib [VEGFR tyrosine kinase inhibitors (TKIs)]; bevacizumab (a monoclonal antibody against VEGF; approved in combination with interferon); and temsirolimus and everolimus (mTOR inhibitors). Several other molecules are also under development.

Randomized controlled trials have demonstrated the clinical benefits of targeted agents in mRCC, for both previously treated and treatment-naïve patients. Sorafenib was shown to be superior to placebo as second-line treatment after failure of immunotherapy in terms of progression-free survival (PFS) (median PFS 5.5 *versus* 2.8 months; $p<0.01$) (1). Sunitinib was shown to give significantly longer median PFS than interferon-alpha (11 *versus* 5 months; $p<0.001$) and was approved as first-line treatment for patients with mRCC (2). In the pazopanib phase III study, median PFS of patients who had received cytokines or who were treatment-naïve was 9.2 months for pazopanib *versus* 4.2 months for placebo ($p<0.0001$) (3). Recently, a randomized trial (the AXIS trial) showed that axitinib had superior efficacy to sorafenib as second-line treatment after one previous first-line systemic therapy with a sunitinib-, bevacizumab-, temsirolimus-, or cytokine-based regimen [objective response rates (ORRs), 19.4% *versus* 9.4%, $p=0.0001$; median PFS, 6.7 *versus* 4.7 months, $p<0.0001$] (4). Regarding the mTOR inhibitors, temsirolimus alone gave better overall survival than interferon alone or temsirolimus plus interferon in combination in first-line treatment of patients at high risk of progression (10.9 *versus* 7.3 *versus* 8.4 months, respectively) (5). Everolimus was shown to provide better median PFS than placebo (median PFS 4.0 *versus* 1.9 months, $p<0.0001$) in patients whose disease had progressed on sunitinib, sorafenib, or both (6).

Once treatment resistance occurs, a common practice is to switch to a drug with a different mode of action. Notably, TKIs have varying target profiles and different affinities for shared targets, and several cases have been reported showing the absence of crossresistance between them (7). Thus, the sequence in which the different drugs should be administered remains unclear. For the first time, we report the case of a patient who responded for 24 months to three successive lines of TKIs.

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Case Report

A 63-year-old woman with good performance status complained of back pain. She underwent a computed tomographic (CT) scan that showed a left renal tumour measuring 4×11×19 cm and multiple metastases in both lungs (Figure 1A). Left radical nephrectomy was performed. A renal clear-cell carcinoma, Fuhrman grade 2, invading the renal vein was diagnosed. The tumour was classified as pT3pN0M1. The patient's haemoglobin, lactate dehydrogenase and calcium levels were within normal ranges.

First-line treatment was started with sunitinib at a dose of 50 mg/day, on a four weeks on, two weeks off schedule. During treatment, the patient developed hypothyroidism requiring hormone replacement therapy; she also had grade 2 skin rashes and grade 3 neutropenia. After a dose reduction to 37.5 mg/day on the same schedule, her tolerance of the drug was better, with only moderate skin rash.

After 12 months of sunitinib, disease recurred at the site of nephrectomy, and the lung and liver metastases progressed (Figure 1B). The patient still had good performance status of 1. She was enrolled in a randomized clinical trial comparing the efficacy of axitinib and sorafenib. She received axitinib at 5 mg twice daily, which was well tolerated, except for controlled grade 1 hypertension. The dosage was increased to 7 mg twice daily after one month. Headache led to the diagnosis of non-documented non-neoplastic sterile meningitis, which resolved with corticosteroid treatment. Axitinib was stopped for two weeks and restarted at the dosage of 5 mg twice daily. No relationship between this episode and treatment with axitinib was established. The disease progressed after six months of treatment (Figure 1C).

Axitinib was discontinued and substituted by sorafenib at a dose of 400 mg twice daily, given as third-line treatment. Clinical tolerance was marked by the onset of grade 1 fatigue, anorexia and diarrhoea, and grade 2 hand–foot syndrome. The disease remained stable for six months. Pleural effusion and bone lesions in T4 and T5 vertebrae occurred, but the liver and lung metastases remained stable (Figure 1D). Spinal irradiation of 8 Gy in one fraction was performed. Sorafenib was discontinued and replaced with everolimus at 10 mg/day (fourth-line therapy). New tumour progression occurred after three months under everolimus treatment, which did not respond to fifth-line-treatment with bevacizumab and interferon. The patient died two months after from tumour progression.

Discussion

Sunitinib, sorafenib and axitinib are TKIs that share similar antiangiogenic properties, targeting VEGFR-2 and -3 and platelet-derived growth factor receptor β (PDGFR-β). However, they differ from each other in their affinities for their molecular targets, and they have distinct inhibitory profiles against many other kinases, including PDGFR-α, macrophage colony-stimulating factor receptor (CSF-1R), the proto-oncogene tyrosine kinases c-KIT, FLT-3, and *RET*, and the proto-oncogene serine/threonine-protein kinases c-Raf and b-Raf (7). Compared with the specific VEGF inhibitor bevacizumab, the multiplicity of their targets confers a variety of antitumour activities and different tolerability profiles. In particular, in addition to acting on mRCC, sunitinib has activity against gastrointestinal stromal tumours through inhibition of c-KIT and PDGFR-α, and sorafenib has a therapeutic activity against hepatocellular carcinoma in part via inhibition of RAF-1 (8, 9).

Sorafenib, sunitinib and axitinib exert their antiangiogenic activity by targeting normal endothelial cells and pericytes of the tumour microenvironment. Because of the genetic stability of normal cells, primary resistance to these agents is rare in clear-cell RCC and the development of acquired resistance is unlikely to be linked to mutations in the genes for VEGF or its receptors. Various mechanisms of transient resistance to TKIs have been reported, such as the expression of alternative proangiogenic pathways, recruitment of bone marrow-derived cells, increased pericyte coverage, or angiogenesis-independent tumour growth (7). Although the mechanisms of resistance to targeted therapies remain unclear, several reports estimate that there is no absolute crossresistance between TKIs (7).

Combination of targeted therapies has generally resulted in increased toxicity without improving survival (10). Sequential therapy appears to be better tolerated and has improved the duration of PFS. However, the sequence of the different agents that will provide the greatest benefit is still under discussion. Four prospective phase II studies all evaluated sorafenib as second-line therapy after sunitinib and reported PFS benefit in this setting ranging from 3.7 to ≥8 months (11-14). In addition, retrospective data suggest that switching from sorafenib to sunitinib is generally associated with a longer overall PFS than switching from sunitinib to sorafenib (7). The ongoing phase III open-label SWITCH study (NCT00732914) is trying to determine which sequence should be recommended. Finally, data from a phase II study of axitinib in patients refractory to sorafenib also suggested that there is no absolute crossresistance between these two agents; median PFS for axitinib after sorafenib was 7.4 months (15). Further studies are warranted to investigate the sequence of these two agents that would yield the greatest overall PFS benefit.

In conclusion, this case report suggests that the use of three TKIs in sequence (sunitinib, axitinib, and sorafenib) may be an effective treatment option. This suggests that there is no absolute crossresistance between TKIs that target VEGFR, and so they should be considered as individual drugs and not as a single class. However, the optimum sequence of TKIs remains to be determined.

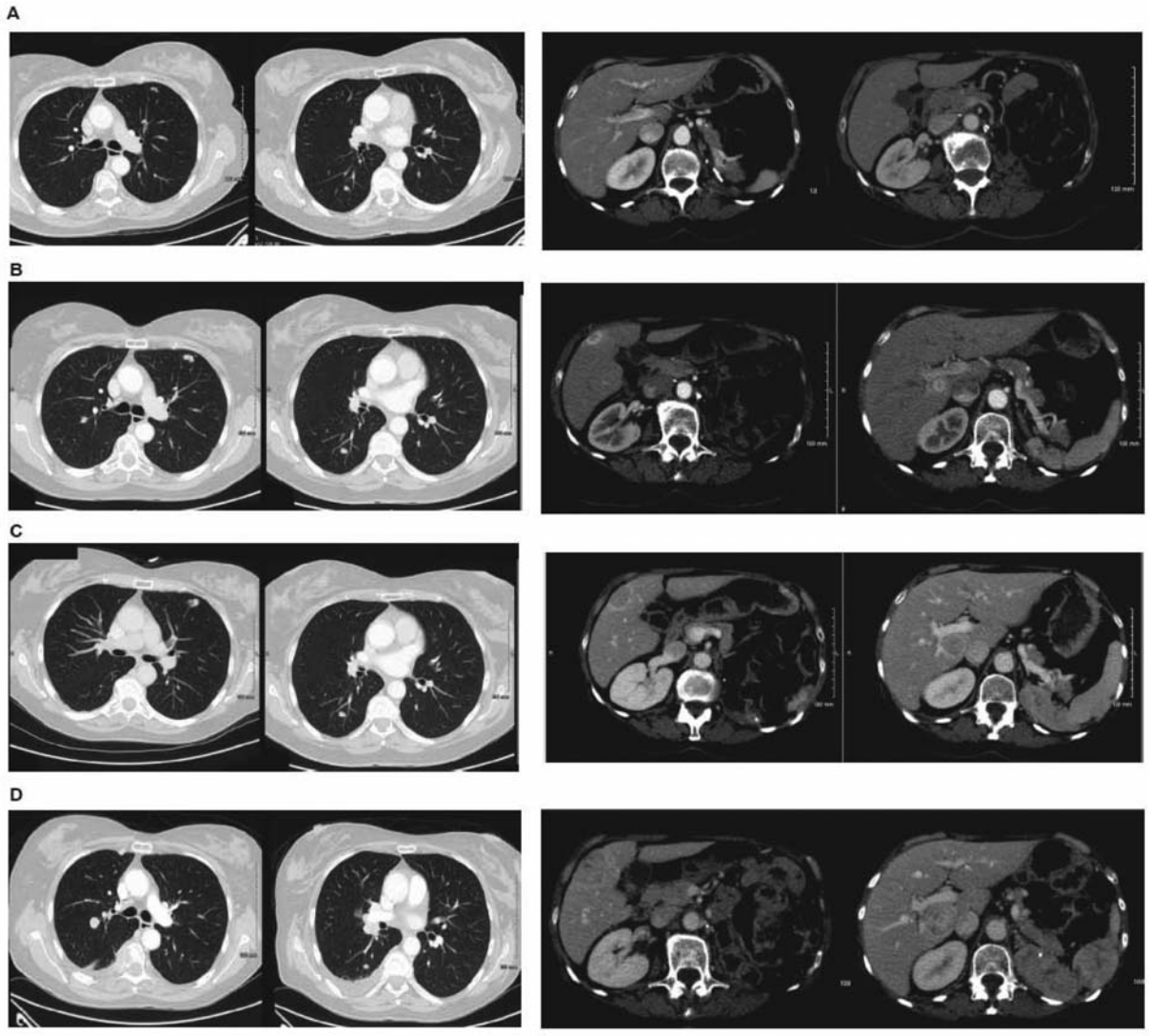

Figure 1. *Chest and liver computed tomographic scans at the time of initiation of sunitinib (A); after 12 months, at the time of progression under sunitinib (B); after 18 months, at the time of progression under axitinib (C); after 24 months, at the time of progression under sorafenib (D).*

Conflicts of Interest

CL has received research grants from Hoffmann-LaRoche and Schering-Plough and has acted as a paid speaker for Bayer HealthCare, Amgen and Vifor. DC, PC, BFD, FB and BN declare no conflicts of interest.

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