Sunitinib Re-challenge in Metastatic Renal Cell Carcinoma Treated Sequentially with Tyrosine Kinase Inhibitors and Everolimus

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Abstract. *Therapy of patients with metastatic renal cell carcinoma (mRCC) requires sequential use of several agents with different mechanisms and minimal cross-resistance between the different agents. Tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors prolong progression-free survival (PFS) in patients with mRCC. Re-challenge with TKIs provides clinical benefit after everolimus in patients with mRCC. We report the case of an mRCC patient with lung and bone metastases, treated sequentially with sunitinib, sorafenib and everolimus. The patient had an objective response in reducing bone metastases, but adaptative and concomitant progression in lung metastases during sunitinib re-challenge. Previously, these lung metastases had responded to sunitinib. This intriguing paradox suggests that not only was sunitinib able to target a specific metastatic site during the re-challenge, as seen by the reduction of bone metastases, but it also elicited a more invasive adaptation and progression of lung tumor cells.*

Vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (VEGFR-TKI) and drugs that inhibit the mammalian target of rapamycin (mTOR) signaling pathway have become the mainstay for the treatment of metastatic renal cell carcinoma (mRCC) based on improved progression-free survival (PFS) or survival outcomes. According to the latest evidence-based treatment guidelines published by the European Association of Urology Guideline Group for renal cell carcinoma, the VEGFR-TKI sunitinib is the standard of care for first-line therapy for patients with low- or intermediate-risk mRCC (1). Treatment with sorafenib prolongs PFS in patients with advanced clear-cell RCC in whom previous therapy has failed; however, treatment is associated with increased toxic effects (2). Switching to the mTOR inhibitor everolimus has been shown to provide significant benefit in terms of increased PFS in patients with mRCC who progressed on sunitinib or sorafenib. In a double-blind, randomized, placebo-controlled phase III trial (RECORD-1: Renal Cell Cancer treatment with RAD001), Motzer *et al*. (3) showed that daily treatment with everolimus prolonged PFS relative to placebo in mRCC patients that progressed on VEGFR-TKI therapy (sunitinib or sorafenib). In a retrospective analysis of RECORD-1 data in patients who were subsequently switched to TKI after everolimus therapy, Blesius *et al*. (4) demonstrated that despite progression on TKI during the initial phase of sequential treatment, TKI provided further clinical benefit when given after everolimus, with a median duration of response of 6.6 months.

This case study reports the case of a patient with mRCC treated sequentially with sunitinib, sorafenib, and everolimus, with an objective response in reduction in bone metastases after re-challenge with sunitinib, but adaptative and concomitant progression in lung metastases.

Case Report

In September 2005, a 54-year-old woman was referred to the Henri Mondor-Albert Chenevier Hospital after a 7 cm tumor in the right kidney was discovered during a computed tomography (CT) scan of the abdomen. A laparoscopic left nephrectomy was performed on 19 September 2005. Histopathological analysis identified a renal clear cell adenocarcinoma pT2 Nx R0 (TNM 2000), Fuhrman grade IV, with a sarcomatoid component. The tumor over expressed genes known to be associated with the development of bones metastases: vascular endothelial growth factor receptors

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(VEGFR) 1, 2, hypoxia-inducible factor-1 alpha (HIF-1α), plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) (5).

Sunitinib as first-line therapy. On 5 October 2007, a lung CT scan showed mediastinal adenopathies and a right lung nodule. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status (6) of zero and was classified as 'good' using the Memorial Sloan Kettering Cancer Center Prognostic Nomogram (7).

In October 2007, she received sunitinib at 50 mg/day for 4 weeks out of every 6-week cycle. After two cycles, the dose was reduced to 37.5 mg/day because of emetic events (grade III), thrombocytopenia (grade II) and Grade 2 hypertension. After 3 months of treatment, on 6 February 2008, a lung CT scan showed a decrease in mediastinal nodes (22 mm), stability of the right upper lobe nodule (10 mm) and stability of the right hilar lymphadenopathy (8.9 mm). Sunitinib was continued at a dose of 37.5 mg/day. On 3 June 2008, a lung scan showed stable lesions. In November 2008, the lung scan showed a decrease of 10-20% in the mediastinal lymphadenopathy, and stability of the right upper lobe nodule. The patient was hospitalized for melena due to thrombocytopenia <50,000/ml requiring transfusion of platelet units (1 unit platelets/kg) and sunitinib was withdrawn.

Surgical resection of the pulmonary nodule of the right upper lobe with mediastinal and hilar lymph node dissection was performed on 18 March 2009. Histological analysis identified the nodule right upper lobe as a primary pulmonary adenocarcinoma (immunohistochemistry: cytokeratin 20 negative (–), cytokeratin 7 positive (+++) and thyroid transcription factor (TTF1) positive (+++). The mediastinal and hilar metastases corresponded to a clear cell adenocarcinoma of the kidney. The other pulmonary nodule was a metastasis of a clear cell adenocarcinoma.

After surgery, treatment with oral sunitinib was started at a dose of 37.5 mg/day for 15 days a month due to the iterative thrombocytopenia, for 3 months.

On the 27th of April 2009, a CT scan of the left femur performed before the onset of pain showed an osteolytic metastatic posterior cortex at upper metaphyseal/diaphyseal junction. On the 31st August 2009, complete resection of a metastasis of the scalp skin was carried out. On the 28th September 2009, a 18 fluoro-deoxy-D-glucose positron emission tomography (FDG PET) reassessment showed tumor recurrence in the mediastinal and hilar right bone, at the fifth and sixth cervical vertebra, sternum and left iliac wing. The patient had a painful mass of the sternum, and neck pain with right radicular C5-C6 topography.

Sorafenib as second-line therapy. Treatment with oral sorafenib 400 mg twice daily and zoledronic acid (4 mg by *i.v.* infusions every 3 weeks) was stopped after 3 months due to the appearance of disabling hand-foot syndrome grade IV. Everolimus as third-line therapy. Sorafenib was replaced by everolimus 10 mg/day on 9th January 2010. After 8 months of treatment, a FDG PET showed a tumor progression in the mediastinum, the cervical spine and the bones of the sternum. The patient had pain in the cervical spine and sternum and was treated with prednisone at 1 mg/kg/day and morphine 60 mg at morning and evening. Inflammatory syndrome was apparent with 632,000 platelets/μl, lactate dehydrogenase (LDH) >400 IU/l, anemia (hemoglobin 8 g/dl), and C-reactive protein (CRP) 80 mg/l.

Rechallenge with sunitinib. The patient received sunitinib at 50 mg/day for 4 weeks of every 6-week cycle. After 2 months' treatment, the neck pain with right radicular C5-C6 topography and swelling of the sternum resolved, the inflammation regressed, with normalization of platelet count, hemoglobin and CRP. A pelvic bone scan showed a disappearance of the lytic lesion of the left iliac wing, the osteolytic lesion of the left femur and a 25% reduction in the size of the sternal metastasis. However, the lung scan showed an increase in lung metastases.

Discussion

Patients with mRCC require the sequential use of several agents with different mechanisms and minimal cross-resistance between the different targeted agents. TKI and mTOR inhibitors prolong the PFS of patients with mRCC. The results from the RECORD-1 trial showed that switching to everolimus provided a significant benefit in terms of increased PFS in patients who had progressed on sunitinib and/or sorafenib (3). The risk of progression was reduced by 61% and the median PFS was 4.9 *vs.* 1.9 months for those treated with everolimus or placebo, respectively ($p<0.001$; hazard ratio [HR] 0.33, 95% confidence interval [CI]=0.25-0.43). Patients pre-treated with sunitinib achieved a median PFS of 3.9 *vs.* 1.8 months when treated with everolimus or placebo, respectively ($p<0.001$; HR=0.34, 95% CI=0.23-0.51). Everolimus-treated sorafenib-refractory patients achieved a median PFS of 5.9 *vs.* 2.8 months for those treated with placebo ($p<0.001$; HR=0.25, 95% CI=0.16-0.42). Patients refractory to both sunitinib and sorafenib achieved a median PFS of 4.0 months when treated with everolimus, compared with 1.8 months for those treated with placebo ($p<0.001$; HR=0.32, 95% CI=0.19-0.54). In a retrospective analysis of RECORD-1 data, Blesius *et al.* (4) showed that patients treated sequentially with TKI-everolimus-TKI obtained a median duration of response of 11 months, 8.4 months and 6.6 months. In our patient, the duration of response was similar: the PFS for the sequence sunitinib-sorafenib-everolimus-sunitinib was 13 months, 3 months, 8 months and 4 months.

Everolimus provided significant clinical benefit in patients treated previously with either one or two VEGFR-TKIs (8). However, with everolimus, the median PFS was greater in patients treated with one prior VEGFR-TKI (5.42 months, 95% CI=4.30-5.82) compared with two VEGFR-TKIs (3.78 months, 95% CI=3.25-5.13) (9). In the RECORD-1 trial, the presence of bone metastases and prior treatment with sunitinib were associated with a decrease in PFS and were predictive of everolimus response (3). In our patient, neither the presence of bone metastases nor prior treatment with sunitinib was associated with a decrease in PFS. The cumulative duration of PFS of 40 months is similar to that reported by Oudard *et al*. (10).

Two retrospective studies demonstrated a clinical benefit in patients receiving previous therapy with sunitinib (9,11). Our patient was intolerant to sorafenib; sorafenib was stopped and replaced by everolimus. Use of everolimus after VEGFR-TKI avoids the toxicity associated with sequential VEGFR-TKI therapy, as reported by Motzer *et al*. (3). For our patient, no toxicity was observed during the treatment with everolimus.

After 13 months of sunitinib, disease progression was observed in our patient with bone metastases. The primary renal tumor overexpressed four genes that have been specifically associated with the development of bone metastases (VEGFR-1, VEGFR-2, HIF-1α, uPA and PAI-1), as previously described (5). Treatment with sunitinib did not prevent the appearance of bone metastases, suggesting that adjuvant treatment with sunitinib after nephrectomy in patients whose primary tumor overexpresses these four genes is not likely to be effective. Adjuvant short-term VEGFR-TKI treatment after resection of the primary tumor has been shown to enhance micrometastatic tumor burden in bone (12, 13). After prolongation of PFS with everolimus, clinical response does not endure and patients experience relapse because tumor cells elicit evasive resistance (14). The phosphoinositide 3-kinase (PI3K)-mTOR pathways contain a negative feedback loop downstream from mTOR, activating the potent survival protein kinase B (AKT) through mTORC2-mediated phosphorylation (15). In addition, strong negative feedback exists with active mTORC1 and active S6K (p70 S6 kinase) suppressing PI3K activation (16). By inhibiting only mTORC1, current therapies allow reactivation of PI3K within the tumor cells (16). Novel dual kinase inhibitors that target both PI3K and mTOR kinase activity by binding to the ATP-binding cleft of those enzymes could be useful after patients become resistant to everolimus (16-18).

In patients previously treated with TKI-everolimus sequential therapy, TKIs have been shown to provide a benefit after everolimus resistance, with a median duration of response of 6.6 months (4). In a recent retrospective review of 23 patients, re-challenge with sunitinib in patients with disease progression on sunitinib and other therapies, resulted in 5 patients (22%) achieving a partial response and 17 patients (74%) achieving stable disease (19). Sunitinib re-challenge was associated with a median PFS of 7.2 months compared with 13.7 months on initial sunitinib treatment (p=0.04) (19). In addition, patients with more than 6 months between sunitinib treatments had significantly longer PFS than those receiving re-treatment with sunitinib within 6 months (16.5 and 6.0 months, respectively; p=0.03) (19).

In our patient, re-challenge with sunitinib achieved an objective response in terms of a reduction in bone metastases and the duration of response was 4 months. Palmieri *et al*. (20) suggest a new definition of targeted therapy, not only targeting a particular receptor but also having the capacity to target a specific metastatic site. Paule *et al*. (21) have reported on two patients with unresectable bone metastases treated with sunitinib. Both patients achieved long-term stabilization of surgically unresectable bone metastases, with one patient remaining stable up to 31 months (21). Furthermore, a retrospective analysis conducted by Zolnierek *et al*. (22), which investigated the emergence and progression of metastatic bone lesions in patients with mRCC, showed that treatment with sunitinib reduced the incidence of new metastatic bone lesions and significantly prolonged the mean time to occurrence of new lesions compared with sorafenib. The results reported in these cases, suggest that re-challenge with sunitinib has the capacity to target a specific metastatic site, such as bone metastases.

In our patient, progression of pulmonary metastases but not mediastinal lymph node metastases was observed on CT scan during the re-challenge with sunitinib. Previously, these lung metastases had responded to sunitinib. This intriguing paradox suggests that sunitinib elicited a more invasive adaptation and progression of lung tumoral cells, as previously reported by Paez-Ribes *et al*. (13) and Ebos *et al*. (12).

Conclusion

Evidence suggests that patients receiving sequential VEGFR-TKI therapy can have a favorable evolution. Furthermore, re-challenge with a VEGFR-TKI after initial TKI and everolimus therapy can provide additional clinical benefit. Our observations suggest that sunitinib has a dual effect: not only does it target a particular receptor and hence a specific metastatic site, but it can also elicit a more adaptative progression in another metastatic site after re-challenge.

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