Beyond the Maths of Biology: Long-term Spontaneous Tumoural Regression After Sunitinib-Withdrawal

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Running head: Long-term Spontaneous Tumoural Regression After Sunitinib-Withdrawal

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Abstract

A 65 year old man presented with asymptomatic relapse of renal cell carcinoma with distant metastasis following radical nephrectomy for pT3 pNx kidney cancer 7 years ago. Sunitinib was commenced with partial response as best response by the 9th month. Patient subsequently developed RECIST-defined radiographic progressive disease with associated clinical deterioration. Sunitinib was stopped and best supportive measures implemented. However, the patient’s metastatic lesions began to regress and is currently maintaining good functional status and has near complete radiographic response, approximately 40 months since cessation of sunitinib. Literature review revealed only two other cases of disease regression upon cessation of anti-angiogenic tyrosine kinase inhibitors. Potential mechanisms are discussed as well.

The Case

A 65 year old gentleman was referred to the medical oncology clinic following radiographic evidence of disseminated metastatic disease. His oncologic history was significant for a renal cell carcinoma treated with a right radical nephrectomy 7 years prior. Histopathologic examination at that time revealed a conventional clear cell tumour measuring 13cm in maximum dimension, extending through full thickness of renal capsule and into perirenal fat, invasion of renal vein, with negative margins. Fuhrmann grade 2 and final staging was pT3 pNx M0. His other medical history of note was hypertension and diabetes mellitus managed with oral hypoglycaemics.

The gentleman went on surveillance. Approximately six years after surgery, a routine CT scan revealed two large pulmonary nodules in the right lower lobe. Follow-up scan showed enlargement of these nodules, measured at 2.9cm and 0.8cm, respectively, and a new 3.7x3.1cm lesion in segment VII of the liver (figures A & B), which was also visible on hepatic MRI. Percutaneous fine needle aspirate of the liver lesion confirmed malignant cytology consistent with metastatic disease.
with recurrent metastatic renal cell carcinoma. The patient had an excellent performance status. Blood tests showed haemoglobin of 11.3g/dL (range: 13.5 – 18.0g/dL), corrected calcium 2.49mmol/l (range: 2.05 – 2.60mmol/l) and normal level serum lactate dehydrogenase. His metastatic renal cell carcinoma was stratified as intermediate risk according to both MSKCC and Heng criteria. The patient was commenced on sunitinib at the standard dose of 50mg/day, 4 weeks on 2 weeks off (see graph: blue arrowhead).

Treatment with sunitinib was uneventful other than a dose reduction to 37.5mg after cycle four for persistent fatigue and development of subclinical hypothyroidism (thyroid stimulating hormone [TSH] level 10mU/L; normal range: 0.5 – 5.0mU/L) for which replacement therapy was initiated. He did not experience any high grade adverse effects. Best radiographic response was partial response which was achieved 9 months after commencing therapy (see graph). 15 months into treatment, restaging CT scan showed enlargement of pulmonary nodules with on-going response in the hepatic lesion (see graph: green arrowhead; also Figures C & D). Assessment by RECIST criteria showed 18% enlargement from nadir. Sunitinib dose re-escalation was attempted in order to regain disease control, however, subsequent scan showed unequivocal disease progression, with RECIST progression of 45% from nadir (see graph: red arrowhead). Clinically at this point, the patient also began demonstrating a deterioration in functional status.

An attempt to commence on sorafenib was interrupted by hospital admission for acute pulmonary oedema which resolved with treatment. After consultation with the patient and his family, a decision was taken for best supportive care only and a routine follow up appointment was made in case he changed his mind. As the patient continued in clinic follow up, his clinical condition improved gradually and serial CT scans began to show regression of existing lesions, culminating with complete resolution of pulmonary nodules. With follow-up of 44 months since discontinuation of Sunitinib, the gentleman remains clinically well with good performance status and a stable solitary 1.2cm hepatic lesion on most recent imaging (Figures E & F).

Discussion
The clear cell variant of renal cell carcinoma constitutes 75 – 80% of all kidney cancers. They are frequently characterised molecularly by loss of von-Heppel-Lindau protein and subsequent over-expression of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors.

Sunitinib is a multi-targeted tyrosine kinase inhibitor which confers benefit in renal cell carcinoma\(^1\) predominantly by inhibition of VEGF receptors, leading to reduced tumoural angiogenesis and disease response\(^2\). However, resistance to sunitinib generally develops after 9 – 12 months on treatment.

Albeit rare, spontaneous regression of metastatic disease in renal cancer is a well-documented phenomenon, known historically as St. Peregrine’s tumour. A survey of medical literature between 1900 and 1966 identified over 170 cases of reported spontaneous regression which were significantly over-represented by renal cell carcinoma\(^3\). A more recent review of literature between 1951 and 2008 showed that 58% of published cases were attributed to renal cell carcinoma\(^4\). The incidence of metastatic regression in renal cell carcinoma, however, represents less than 1% of all cases\(^5\).

Our report describes a case of sustained spontaneous regression upon cessation of sunitinib following unequivocal evidence of sunitinib resistance and disease progression. To date, there are only two other reports on similar phenomenon in the medical literature\(^6,7\). In Yanagihara’s case, the patient received less than two cycles of sunitinib due to significant toxicities and radiographic evidence of disease progression. Persistent regression was observed approximately eleven months after cessation of treatment. In the case described by Rothermundt et al, the patient had a progression-free period of eleven months. Disease regression was first noted in the 12\(^{th}\) month and persisted at the time of reporting two months later.

The mechanisms underlying such regression remain unclear and speculative. Rothermundt et al drew comparison to anti-androgen withdrawal syndrome as seen in advanced prostate cancer. It was speculated that mutation in the androgen receptor could lead to antagonists acting as agonists\(^8\). Acquired mutation has also been observed in non-small cell lung cancers harbouring mutation in epithelial growth factor receptors (EGFR). In fact, the conversion
from "oncogene addiction" to "drug addiction" in lung cancer with EGFR mutation under intensive kinase inhibition has recently been demonstrated in an in vitro study. Specific single-nucleotide polymorphisms for VEGFR have been shown to correlate with poor treatment response to sunitinib but to date, evidence pointing to acquired mutation in VEGF receptors under selection pressure is lacking. With the recent recognition of intratumoural heterogeneity and therefore complexity of tumours’ genomic landscape, it is not inconceivable that a sunitinib-addicted population of cancer cells were favourably selected.

Other proposed mechanisms include the immunomodulatory effect of sunitinib. It has long been known that renal cell carcinoma is a highly immunologic tumour and manipulation of the immune system towards a Th1 population with interferon and interleukin-2 has been able to induce prolonged disease control and even remission in selected patients. The presence of intratumoural regulatory T-cells has been correlated with poor survival. The effect of sunitinib on the immune system has been actively studied. Sunitinib may inhibit proliferation of peripheral blood T-cells, arrest T-cell development and inhibits pro-inflammatory cytokines production from T-cells. On the other hand, studies have demonstrated sunitinib’s ability to reduce regulatory T-cell levels. How these differential effects combine to alter the natural history of disease remains to be elucidated.

In our case, our patient enjoyed a progression-free survival of almost 20 months, on-going regression of hepatic lesion over 60 months since initiation of sunitinib and complete resolution of pulmonary metastases. The sustained remission is highly suggestive of an immune-mediated phenomenon. This is even more remarkable as late-stage disease might be more effective at evading host immunity. Spontaneous remission in previously-treated renal cell carcinoma has rarely been observed as compared to treatment-naïve cases. In fact, therapeutic immunomodulation conferred only minimal response in second-line setting compared to up-front treatment. Also, potentially immunomodulated responses were frequently more pronounced in pulmonary lesions, as have been seen in our case as well.
Of note, the differential responses exhibited by the pulmonary and hepatic metastases suggested different biological characteristics, as only the pulmonary metastases progressed on sunitinib while the latter continued to decrease in size. In fact, this was recently confirmed by demonstration of significant intratumour heterogeneity and mutational burden.12

Although the hepatic lesion in our case was biopsy-confirmed recurrence, the diagnosis of pulmonary metastases was based on clinical and radiographic grounds. However, the concurrent progression prior to initiation of sunitinib, the typical “cannonball” appearance on thoracic imaging and initial response to sunitinib render an alternative diagnosis, such as benign inflammatory lesions, less plausible in this clinical setting.

It is difficult to estimate how common the above-described phenomenon is, with a high likelihood of under-observation as second line therapies are regularly initiated instantly upon evidence of progression. Interestingly, the phase 3 RECORD-1 trial which compared everolimus plus best supportive care to placebo plus best supportive care in renal cell carcinoma progressed on VEGF inhibition recorded up to 10% of minor tumoural response in the control arm17 despite not reaching RECIST criteria for partial response.

Conclusion

In summary, we have described the first case of sustained spontaneous regression following progression on anti-VEGF tyrosine kinase inhibitor in a disease where median overall survival for patients with intermediate risk group was 27 months18. We propose that a short washout period between therapies for asymptomatic patients with radiographic monitoring could potentially assist in identify cohort of patients with similar “anti-VEGF withdrawal” effect to further understand the biology and possible underlying mechanisms.

Clinical Practice Point
Spontaneous regression of metastatic clear cell renal cell carcinoma is a rare but well-documented phenomenon. It is thought to be immunogenic in origin. Immunologic response in second line setting, however, is uncommon. Modern tyrosine kinase inhibitors exert efficacy in renal cell carcinoma predominantly via inhibition of VEGF pathways but early pre-human studies have suggested that these agents exert effect on the immune system as well. Our case described a case of sustained spontaneous regression upon cessation of sunitinib for progressive disease. A survey of literature identified only two other identical cases but this phenomenon might be under-reported as in clinical practice, patients would routinely rotate through available agents as soon as evidence of progression was documented. Indeed, in the control arm of the RECORD-1 study, 10% minor tumoural response was observed following progression on anti-angiogenic agent. This phenomenon could potentially impact routine clinical practice as well as reporting of clinical trial results in second or third line setting.

Graph: Sizes of metastatic lesions during treatment and follow-up period. (Blue arrowhead: commencement of sunitinib; Green arrowhead: radiographic progression of pulmonary lesions with response in hepatic lesion; 18%)
enlargement from nadir; Red arrowhead: unequivocal radiographic progression with 45% increment from nadir)

Figures A – F: Axial cuts of contrast-enhanced CT scans of patients at various time points. (A-B: at diagnosis of metastatic disease, corresponding to blue arrowhead in Graph; C-D: time of radiographic and clinical progression, when sunitinib was stopped, corresponding to red arrowhead in Graph; latest restaging CT scan, and month 60 since commencement of sunitinib)


