Direct Visualization of the Antiangiogenic Effects of Sunitinib During the Treatment of Metastatic Clear Cell Renal Cell Carcinoma

Ciska-Anne Van Keerberghen,[1] Johnny Jean-Baptiste,[2] Pascal Wolter,[1] Jessica Zucman-Rossi,[2] Patrick Schöffski,[1] Benoit Beuselinck[1,2]

Clinical Practice Points

- Anti–vascular endothelial growth factor receptor tyrosine kinase inhibitors are thought to exert their antitumoral activity through the normalization of tumoral blood vessels.
- This case report illustrates this concept through sequential endoscopies in a patient with gastric metastases of a clear cell renal cell carcinoma responding to the anti-VEGFR-TKI sunitinib.

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Introduction

Although sunitinib inhibits several other targets, it is thought to exert its antitumor activity mainly through the inhibition of the vascular endothelial growth factor (VEGF) receptors 1, 2, and 3.[1] The VEGF pathway is believed to be the dominant regulator of tumoral angiogenesis and anti–VEGF receptor tyrosine kinase inhibitors (anti-VEGFR-TKIs) are capable of reducing and normalizing tumor angiogenesis.[2,3] Clear cell renal cell carcinomas (ccRCC) are hypervascular tumors. Treatment with anti-VEGFR-TKIs is the current standard of care for advanced inoperable ccRCC. The anti-VEGFR-TKI sunitinib is approved for the first-line treatment of ccRCC and is provided for 4 weeks on and 2 weeks off every 6 weeks. During the 2-weeks-off treatment, or in individuals who have to interrupt treatment with anti-VEGFR-TKI, a flare-up of tumor proliferation may be observed, with clinical or radiologic signs of disease progression.[4] Moreover, in several animal models, rapid vascular regrowth in tumors has been described after withdrawal of VEGF inhibitors.[3,5]

Case Report

We report a case of direct macroscopic visualization of the antiangiogenic effects of anti-VEGFR-TKIs in a patient with disseminated ccRCC.

[1]Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium
[2]INSERM U1162, Université Paris-Descartes, Paris, France

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Address for correspondence: Benoit Beuselinck, MD, PhD, University Hospitals Leuven, Leuven Cancer Institute, KU Leuven, Herestraat 49, 3000 Leuven, Belgium
E-mail contact: benoit.beuselinck@uzleuven.be

This 67-year-old man was diagnosed in 2000 with a right-sided Fuhrman grade 4 ccRCC, for which he underwent radical nephrectomy. The primary tumor was classified ccRCC2 in the

Figure 1 Lesions Before Initiation of Systemic Therapy. In the Proximal Stomach are Found Several Polypoid Lesions With a Diameter of Several Centimeters. In the Distal Stomach are Found Several Lesions With a Diameter Between 5 and 15 mm. All the Lesions Appear Hypervascular. The Lesions in the Proximal Stomach Appear Hemorrhagic

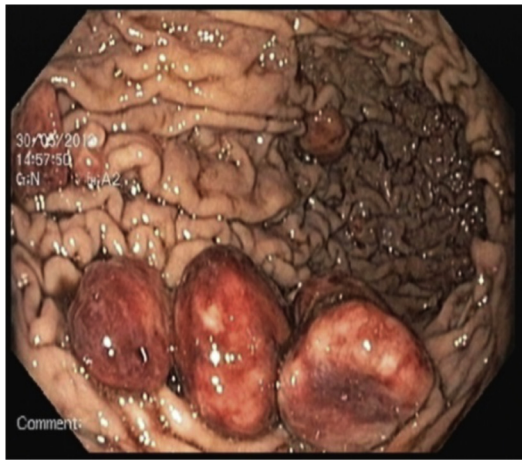

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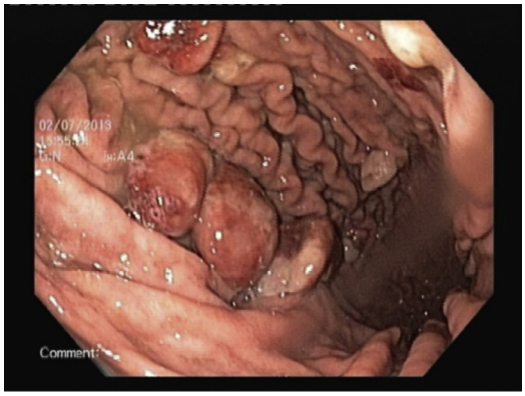
Figure 2 Lesions on Day 21 After First Cycle of Sunitinib. On Day 21 of the First Cycle of Sunitinib, the Lesions Appear Less Hypervascular



expression-based classification described by Beuselinck et al,[6] a subgroup with a high probability of response to sunitinib. The tumor was mutated for *VHL* in exon 1. Between 2009 and 2011, he underwent consecutively 4 resections of metastases at different anatomic sites (distal ureter, left adrenal gland, left lower lung, and pleural lesions). Frozen tumor tissue was available from the left adrenalectomy, which was performed in 2009. This metastasis could also be classified as ccRCC2.

In May 2013, persistent iron deficiency anemia (hemoglobin 8.5-9 g/dL) triggered an endoscopic evaluation of the upper gastrointestinal tract. On esophagogastroduodenoscopy (EGD), multiple polypoid, partially hemorrhagic masses, ranging from 5 cm to several centimeters in size, were found throughout the stomach, especially in the proximal gastric area (Figure 1). Biopsy of these lesions was performed and confirmed the presence of multiple gastric metastases of ccRCC. Staging computed tomography scan of the thorax and abdomen revealed the gastric metastases as well as a peritoneal metastasis. Systemic therapy with sunitinib was initiated in June 2013 at the labeled dose and at a schedule of 50 mg/day, 4 weeks on 2 weeks off. Baseline Memorial Sloan Kettering Cancer Center[7] and International Metastatic Renal Cell Carcinoma Database Consortium[8] prognostic risk score was intermediate as a result of low hemoglobin levels. Nevertheless, other prognostic factors in metastatic ccRCC treated with anti-VEGFR-TKI were favorable in this patient: there were no bone metastases, baseline C-reactive protein level was low, and the primary tumor did not display sarcomatoid dedifferentiation.[9-11]

On day 21 of the first cycle of sunitinib, the lesions appeared less hypervascular and less hemorrhagic on EGD compared to baseline endoscopic findings. There was a small reduction in the size of the lesions (Figure 2). Clinically, after treatment initiation, melena resolved and a significant rise in hemoglobin levels (up to 13 g/dL) was observed (Graph 1), which indicates that there was no more leakage of blood by the hypervascular gastric metastases. VEGF is very potent in inducing vascular permeability.

On day 28 of the fourth cycle of sunitinib, EGD revealed 8 tumoral lesions in the stomach, ranging from 7 to 15 mm. The lesions did not only decrease in diameter but also appeared less hypervascular and less hemorrhagic compared to the baseline EGD (Figure 3). On computed tomographic scan, the gastric metastases were smaller and the peritoneal implant could no longer be visualized.

On day 1 of the sixth cycle of sunitinib—and thus at the end of the scheduled treatment break—EGD revealed an increased hypervascular appearance of the metastatic nodules (Figure 4).

On day 28 of the eighth cycle of sunitinib, EGD revealed only 5 remaining gastric metastases, with a maximal diameter of 15 mm and a hypovascular aspect (Figure 5).

In January 2015, after 20 months of sunitinib, the patient had a confirmed partial response according to Response Evaluation

Graph 1 Evolution of Blood Hemoglobin Levels by Time Showing Clear Rise After Treatment Initiation (Normal Hemoglobin Range 14.0-18.0 g/dL)