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LETTER TO THE EDITOR

Progression of a caval vein thrombus in two patients with primary renal cell carcinoma on pretreatment with sunitinib

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To the Editor

Oral tyrosine kinase inhibitors (TKIs) and the monoclonal antibody bevacizumab have significantly changed the management and perspectives of patients with metastatic renal cell cancer (mRCC). Especially patients with a clear cell histological subtype gain benefit from therapies targeted against signalling of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor. Sunitinib has been registered as first- and second-line therapy for mRCC. This TKI can induce high partial response (PR) rates of up to 40% at metastatic sites and can prolong progression-free survival (PFS) and overall survival (OS) as compared to interferon-alpha (11 and 26 months *versus* 5 and 22 months, respectively) [1]. In primary tumours, sunitinib-induced responses as well as responses induced by the VEGF-directed monoclonal antibody bevacizumab have been described at a rate previously unknown for cytokine-based treatment [2–4]. Therefore, presurgical targeted therapy might facilitate nephrectomy by downsizing primary tumours. In addition, responses have been reported in bulky retroperitoneal lymph nodes and even in tumour thrombi with caval vein extension, which may improve the surgical management of these tumour sites [5–11]. In contrast to these promising reports, we describe two patients with mRCC of a clear cell subtype who developed a progressive caval vein thrombus during sunitinib, which resulted in a negative impact on surgical management.

Case reports

Two patients were treated in accordance with a phase II trial in which sunitinib-induced responses in primary tumours were investigated. The main inclusion criteria of this trial were histologically confirmed mRCC of the clear cell subtype with a resectable *asymptomatic* primary tumour *in situ*, extensive metastatic disease defined as non-resectable metastases in case of one metastatic site *or* $\geqslant$ two metastatic sites, a World Health Organization (WHO) performance status of 0 or 1, an intermediate risk profile according to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, and no prior systemic treatment with biological response modifiers, TKIs, monoclonal antibodies or chemotherapy. Patients were treated with sunitinib 50 mg/day four weeks on and two weeks off for two cycles. At completion of the second treatment cycle, a computed tomography (CT) scan was performed for response evaluation and patients were admitted for surgery within one week.

Case 1

A 49-year-old male patient presented with a primary RCC tumour in the right kidney with thrombus extension into the infrahepatic caval vein up to the liver. The patient had metastatic disease in lungs and para-aortic lymph nodes. Metastatic burden was limited and the sum of the longest diameter of all

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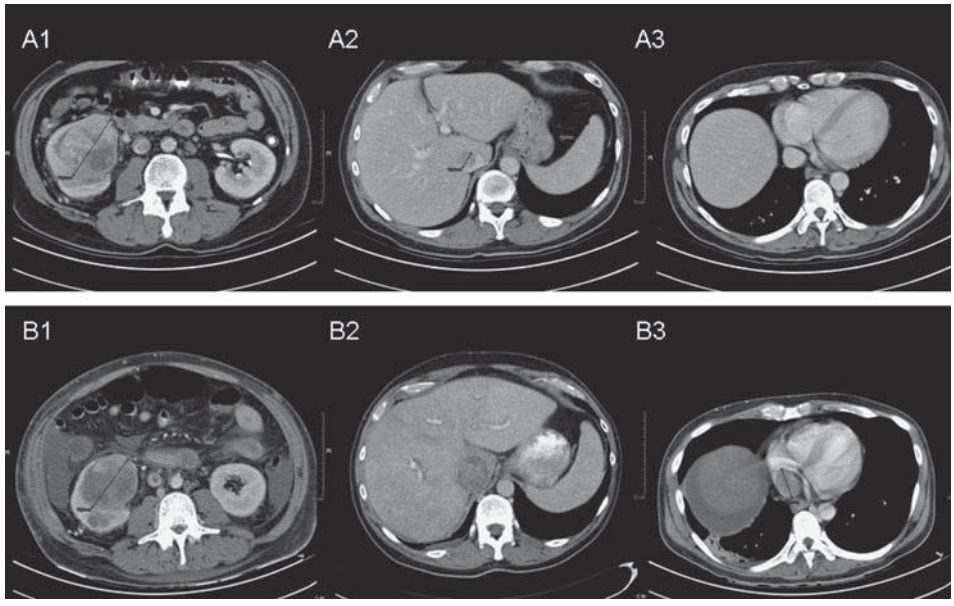

Figure 1. CT scans of the first patient at baseline (A) and after (B) one cycle of sunitinib. A1 and B1: The primary tumour has decreased in size. A 2-3 and B 2-3: The caval vein thrombosis has increased in size (A2 and B2) and extends from infrahepatic (A2) towards the right atrium (B3). Note the absence of the thrombus in the right atrium before treatment (A3).

metastatic lesions was only 2.8 cm. Resection of the primary and thrombus was feasible, but it was decided to include the patient in the protocol and take advantage of potential downsizing of the thrombus. The patient started sunitinib 50 mg/day (four weeks on and two weeks off) as first-line treatment. During the first week of the second cycle the patient was admitted with fatigue grade 3, dyspnoea and ascites. The CT scan revealed extension of the thrombus into the right atrium with liver congestion. The size of the primary tumour and metastases, however, had remained stable (Figure 1). The performance score deteriorated rapidly from WHO 0 to 3 and nephrectomy could not be performed anymore. The patient died two months after the start of sunitinib due to thrombus-induced backward and liver failure.

Case 2

A 35-year-old male patient was diagnosed with resectable primary RCC in the left kidney, one liver metastasis and bone metastases. After pain-alleviating radiotherapy for metastases in spine and hip, the patient initiated first-line sunitinib treatment at 50 mg/day (four weeks on and two weeks off). At response evaluation in the last week of the second cycle, the liver metastasis showed a minor reduction of 19% in size, while the primary tumour had not changed. In addition, the CT scan revealed a newly developed thrombus in the caval vein (Figure 2). Nephrectomy was performed in a trans-abdominal approach requiring extension of the surgical field to safely perform a cavotomy. The adjacent tissues to

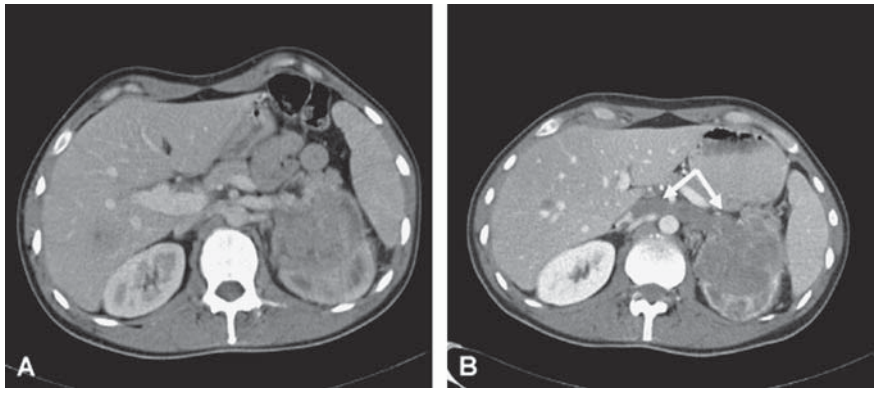

Figure 2. CT scan of the primary tumour of the second patient at baseline (A) and after two cycles of sunitinib demonstrating a newly formed thrombus in the caval vein (arrows) (B).

the renal vein were adhesive due to a reaction of the thrombotic material. Histopathological examination demonstrated a primary tumour of 10 cmin diameter with clear cell histology and a necrotic centre. The thrombus contained tumour cells as well (Figure 3). The patient recovered and continued on sunitinib until progressive disease (PD) in liver and bone lesions five months thereafter. He died from disease after a survival period of 12 months from the time of diagnosis.

Discussion

We here describe two mRCC patients on presurgical sunitinib to facilitate secondary nephrectomy who developed a progressive caval vein thrombus while on treatment. In the first patient, an initially resectable caval vein thrombus progressed into the right atrium and surgery could not be performed due to rapid clinical deterioration as a result from backward and liver failure. In the second patient, a tumour thrombus developed with extension into the caval vein which required extended surgery, while the liver metastasis demonstrated regression. It cannot be excluded that progression of the thrombus in the first patient may have been related to venous thrombotic events [12], but histology revealed a tumour thrombus in the second patient.

In the cytokine era, responses in primary tumours and caval vein thrombi were rare. mRCC patients with primary tumours *in situ* were more likely to die from distant metastases than from local progression [13]. Therefore, initial cytokine therapy was used to select patients for nephrectomy that showed a response in metastases. For two reasons, however, this strategy may be less logical in mRCC patients treated with targeted agents, such as sunitinib. First, mixed responses in the primary tumour and metastases may occur, indicating the risk of progression of initially resectable primaries to inoperable tumours despite a sunitinib-induced response in metastases. Second, after development of PD during sunitinib and subsequent discontinuation of this drug, a resectable primary tumour may rapidly progress or may cause severe symptoms requiring palliative treatment.

The effect of downsizing primary tumours is most prominent in the first three months, suggesting that a few cycles of sunitinib may be sufficient to facilitate the subsequent surgical procedure. In previous reports on sunitinib, however, the PD rate in primary tumours varied from 0 to 47% [4,14]. The study by Thomas et al. [14] and the present cases indicate that initially resectable primaries and tumour thrombi can progress to inoperable tumours within a few months. The wide range of the PD rate may reflect a high variability in sunitinib sensitivity of primary tumours and indicates that biomarkers are warranted to early identify mRCC patients with failure of downsizing primaries. Since a 24 hour discontinuation period of sunitinib appears to be safe to perform surgery [15], the management plan can be changed rapidly in case patients develop PD in resectable primaries or tumour thrombi in the presence of stable disease in metastases.

Combined therapy of presurgical sunitinib followed by nephrectomy in mRCC patients might improve the quality of life and even prolong PFS and OS. Several patients have been described in whom sunitinib could be discontinued during a disease-free period after this treatment procedure [16]. Since there is no evidence from randomized controlled trials, the role and sequence of cytoreductive surgery in combination with targeted therapy in mRCC are open for debate. Currently, a number of trials have been initiated to investigate the efficacy of presurgical sunitinib in mRCC patients with a primary tumour *in situ*. The present two cases illustrate, however, that not each patient benefits from this approach. Whether caused by thrombotic events or true tumour growth, caval vein thrombi can develop and progress under targeted therapy. Physicians should be aware of progressive primary tumours and tumour thrombi to avoid missing an opportunity for nephrectomy.

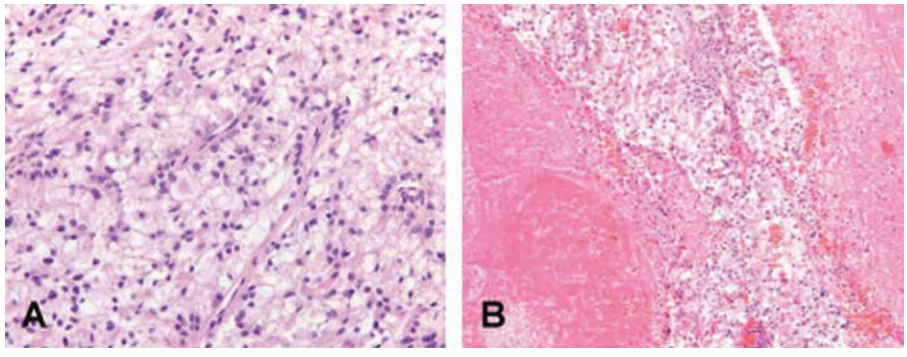

Figure 3. Histology of the primary tumour (A) (H&E, 200×) and the caval vein thrombus which contains vital tumour cells of clear cell histology (B) (H&E, 100×).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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