could be the first description of a relation between the activation of psoriasis and spontaneous regression of metastases. Similar observation has recently been reported in a patient with rheumatoid arthritis and marginal zone B cell lymphoma treated with infliximab and methotrexate [8]. In that case spontaneous remission was noted after the withdrawal of infliximab and methotrexate. Allogeneic hematopoietic stem cell transplantation may be viewed as adoptive immunotherapy, and is frequently accompanied by graft-versus-host disease. A case of graft-versus-host disease manifesting as with psoriatic skin lesions has been described [9]. We can only speculate about the mechanism(s) of association between the course of psoriasis and metastatic RCC in the present patient. T lymphocytes isolated from psoriatic lesions exhibit cross reactivity to microbial and self antigens [7]. It is possible that similar cross reactivity exists between the putative tumor antigens responsible for tumor rejection and autoantigens in the skin, but this hypothesis remains speculative. The risk of cancer may be increased in patients with psoriasis, possibly as the result of therapy [10], but increased incidence of RCC has not been observed and RCC is a rare event in patients with psoriasis.

In conclusion, this case report presents further indication that immune response may play a role in spontaneous regression of RCC metastases after nephrectomy.

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The reverse side of the victory: Flare up of symptoms after discontinuation of sunitinib or sorafenib in renal cell cancer patients. A report of three cases

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To the Editor,

The development of angiogenesis inhibitors introduced a new era in the treatment of metastatic renal cell carcinoma (mRCC). By now, sunitinib and sorafenib both multiple tyrosine kinase inhibitors (TKI) of the vascular endothelial growth factor (VEGF) pathway, are registered for the treatment of mRCC, as is bevacizumab, a monoclonal antibody against VEGF, in combination with interferon-α (IFN-α). With the introduction and, nowadays, the widespread use of these anti angiogenic drugs, many questions arise, such as the optimal timing of the start of these drugs, the duration of treatment, and the optimal policy beyond objective progression.

We describe three patients with mRCC who experienced unexpectedly rapid progression and tumour-related complaints after discontinuation of oral angiogenesis inhibitors and subsequent fast improvement with reintroduction of the same therapy. This flare up syndrome is clinically well known, although not frequently appearing and only once reported in literature [1]. We discuss the possible explanations and clinical consequences of this flare up phenomenon.

Case reports

Case 1

A 66-year-old male, underwent a tumour nephrectomy because of a clear cell RCC (ccRCC). Two years later, he presented with pulmonary metastases and a solitary costal metastatic lesion. After failure of bevacizumab with interferon alpha (IFN-α), sorafenib 400 mg bid was started. During sorafenib treatment his fatigue and dyspnoea decreased and he experienced hardly any toxicity. After an initial partial response (PR), eight months later he had progressive disease (PD) with pleural and bone metastases (Figure 1A). Sorafenib was stopped. Within one week he developed progressive pain and another two weeks later he presented at the emergency room with dyspnoea and thoracic pain. An angiographic CT excluded a pulmonary embolus (Figure 1B, exactly 1 month after CT Figure 1A), but showed progression of pleural effusion and of the number and size of the pulmonary metastases. Sorafenib was reintroduced and within a few days the dyspnoea and pain decreased. Because of

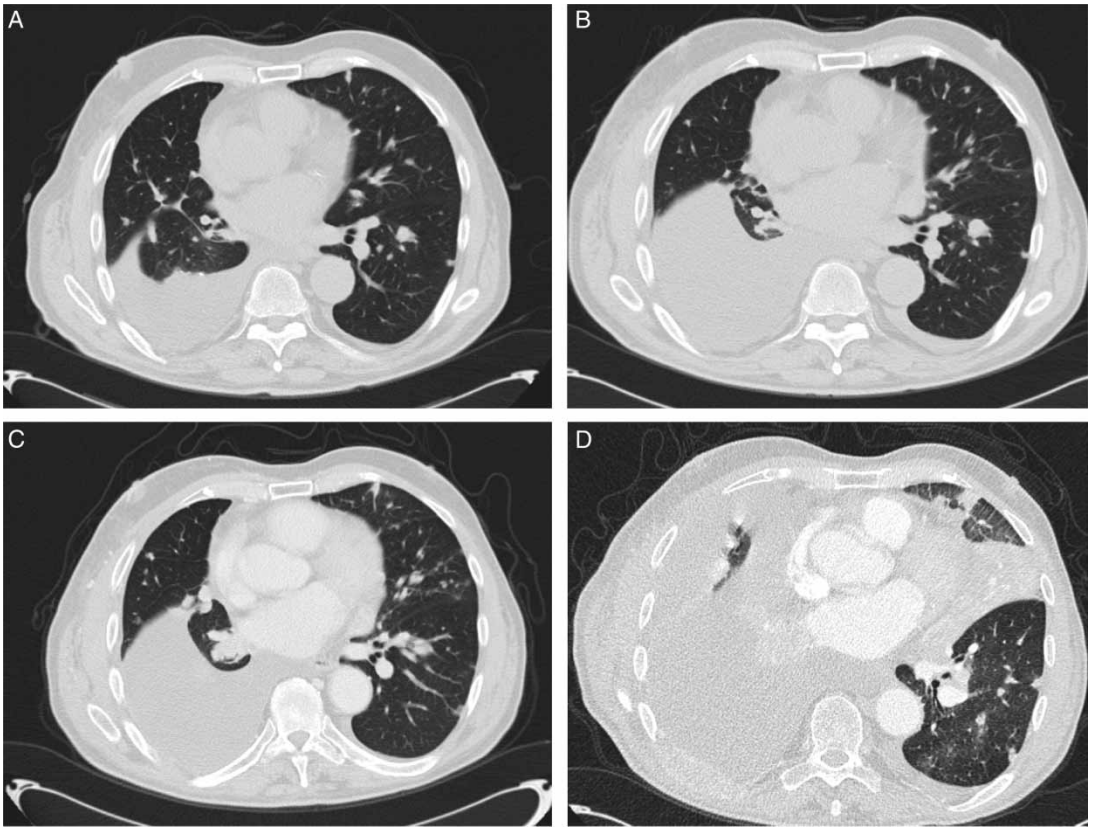

Figure 1. Patient 1. A. Pleural and intrapulmonary metastases with pleural effusion, short before discontinuation of sorafenib. B. Progression of number and size of pulmonary metastases with increased pleural effusion, one week after discontinuation of sorafenib. C. Latest CT before the second stop of sorafenib. D. Progressive disease after discontinuation of sorafenib with pulmonary, pleural and lymph node metastases, pleural and pericardial effusion.

serious progression four months later, the patient decided to participate in a radio immunotherapy study, for which reason the sorafenib was stopped (Figure 1C, latest CT before cessation). Within five days and without having had the radio immunotherapy, he was hospitalised because of dyspnoea due to lymphadenopathy, pleural and pericardial effusion (Figure 1D, 7 weeks after CT Figure 1C). This time his condition deteriorated rapidly and it was decided to choose for best supportive care. The patient died one month later.

Case 2

A 47-year-old male patient presented with dyspnoea, a productive cough, sweating and severe weight loss due to a renal tumour with lung- and lymph node metastases and pleural effusion (Figure 2A). He was included in a study protocol where he received neo-adjuvant four weeks sorafenib 400 mg twice daily prior to tumour nephrectomy. During treatment, the dyspnoea, and cough disappeared and his appetite returned. Two days after discontinuation of sorafenib he underwent an uncomplicated tumour nephrectomy as per protocol. A ccRCC was diagnosed. A few days after the nephrectomy, the dyspnoea returned. This time, his left thorax was almost completely shadowed (Figure 2B). Cytology obtained during bronchoscopy revealed a lymphangitis carcinomatosis of the left lung. Pleural effusion drainage was performed and sorafenib treatment 400 mg twice daily was restarted. The dyspnoea rapidly decreased and the appetite restored.

Case 3

A 63-year-old female underwent a tumour nephrectomy because of a ccRCC. One year later she developed pulmonary metastases. After failure of IFN-α, she participated in a phase I study with a radioactive labelled monoclonal antibody cG250. After progression she participated in a second phase I trial with a combination of a VEGFR and EGFR inhibitor, which resulted in a rapid PR. Ten months later therapy was stopped because of radiological PD of the lymph node, soft tissue and pleural metastases, without any tumour-related complaints. Six weeks later a new chest CT was made because of dyspnoea complaints, which showed severe PD. Sunitinib in a continuous schedule of 37.5 mg daily was started. Within days her dyspnoea disappeared. After three months she had a PR. One year later, radiological PD was found and the sunitinib was stopped (Figure 3A). Within one week she presented with dyspnoea and coughing. A PET-CT performed only one month after discontinuation of sunitinib showed progression in number and size of metastases, not only pulmonary and pleural but also in the lymph nodes, soft tissue and in the bones. (Figure 3B) We switched to sorafenib 400 mg bid and again a reduction of dyspnoea and cough was observed within days.

Discussion

We described three patients with a more than expected rapid clinical deterioration, after stopping of oral angiogenesis inhibitors for slowly PD. This flare up phenomenon is well recognized in daily clinical practice although not understood, and for mRCC only once reported in one patient [1].

How to explain this flare up phenomenon? It can be questioned if the effect of the angiogenesis inhibitors is fully exhausted at the moment that the RECIST criteria for progressive disease are reached. By cessation of therapy at this point, the residual inhibitory effect of the anti-angiogenic drug is removed. In this respect, the usefulness of the RECIST criteria in anti-angiogenic treatment

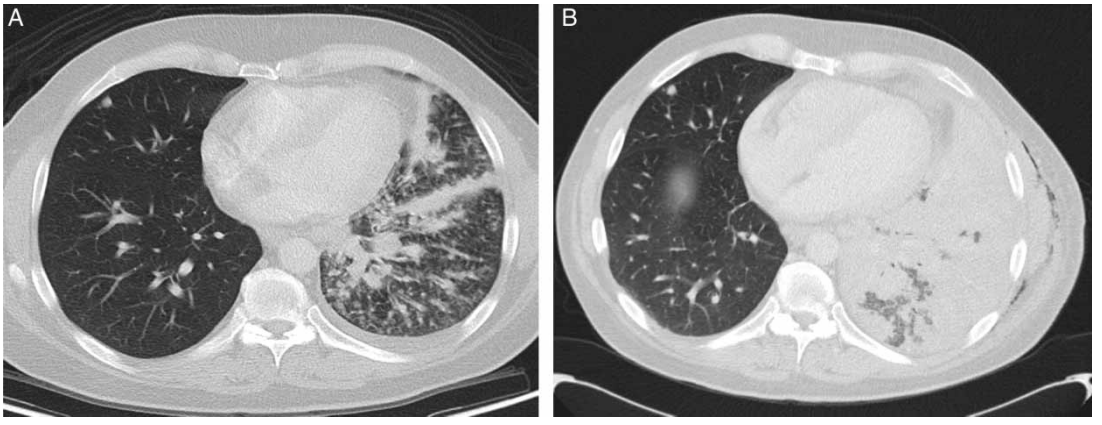

Figure 2. Patient 2. A. Pulmonary and lymph node metastases with pleural effusion. B. Increase lymphangitis carcinomatosis after discontinuation of sorafenib.

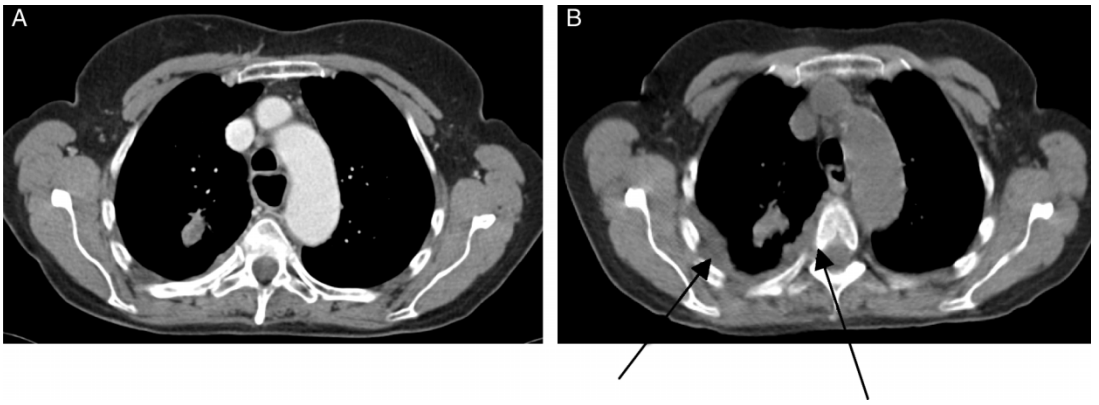

Figure 3. Patient 3. A. Pulmonary metastasis in left lung and limited thickness of the pleura of the left lung. B. Increased pleural metastases in left lung.

evaluation have been doubted since their rather cytostatic than cytotoxic effect.

An alternative explanation for the rapid increase in complaints is a rebound phenomenon regarding the blood vessels after withdrawal of the angiogenesis inhibitors. Blocking VEGF or VEGFR leads to apoptosis of endothelial cells and decrease in vascular diameters, density and permeability, which decreases interstitial fluid pressure and, in some tumours, increases oxygen tension [2–6].

Hypothetically cessation of anti angiogenic therapy leads to an increase of vascular density, tumour blood flow rate and permeability, with subsequent, extravasation of fluids leading to reactive edema, ascites and pleural effusions. The reported elevated serum VEGF levels during antiangiogenic treatment can be hypothesized to play a pivotal role in this [7]. Illustrative for the effect of angiogenesis inhibitors on edema is the rapid and significant reduction of edema in patients with glioblastoma multiforme treated with bevacizumab [8].

The complaints started shortly after cessation of therapy. The half-life of both sunitinib (including its active metabolite) and sorafenib is long (40–60 hours and 25–48 hours). However, in mice, after cessation of sunitinib an increase of mean tumour volume was observed within ten days [9], and the plasma VEGF, placental growth factor (PlGF) and serum levels of soluble VEGFR-2 returned to baseline levels even faster [10]. A mice study with two VEGFR inhibitors observed that seven days after cessation the tumours were completely revascularised, starting already one day after withdrawal [11]. In a study with sunitinib in a four week on and two week off treatment schedule in patients with acute myeloid leukaemia, an increase in peripheral blasts was found during the rest period [12]. These data all suggest that the anti tumour effects of angiogenesis inhibitors already alter within days after cessation, although the half-life of these drugs is relatively long. This also suggests an individual dose-effect response, which has not been subject of studies until now.

In case of patient 3, after progression at sunitinib with subsequent severe tumour related complaints, sorafenib was administered and reintroduction also led to rapid clinical improvement. When another anti angiogenic agent is available, this might be preferable. However, when this is not the case, reintroduction of the same angiogenesis inhibitor as a palliative treatment strategy should also be considered, especially when the experienced side effects were limited during treatment. Also, time schedules, for example the four weeks up- two weeks off sunitinib schedule or the time between switch of anti angiogenic drugs, should be adjusted for these subgroup of patients.

The described patients show a clinical relevant flare up phenomenon. In order to understand the underlying mechanisms, to identify the patients at risk for this phenomenon and to decide what will be the best practice after PD for the individual patient, more knowledge is necessary. Especially studies focusing on the endpoints of response to anti angiogenesis inhibitors, surrogate biomarkers, dynamic and functional imaging techniques, pharmacokinetics during prolonged exposure, the optimal timing of angiogenesis inhibitors focussing on the optimal interval between first and second line angiogenesis, rest periods within treatment schedules, and the best practice after PD should be initiated. Solving these questions is a major challenge in the new fascinating era of anti angiogenic treatment in mRCC.

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Salvage therapy with sorafenib plus vinblastine and fluorouracil for metastatic renal cell carcinoma

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To the Editor,

Sorafenib is a multi-kinase inhibitor and is effective in the treatment of metastatic renal cell carcinoma (RCC) [1,2]. However, the median treatment duration for RCC in published articles is around 24 weeks [2]. But for responsive patients, no published reports have discussed when sorafenib should be discontinued. We report a patient with metastatic RCC who responded to treatment with sorafenib plus chemotherapy, and the treatment was discontinued at his own insistence. Thirty months after the first dose of sorafenib plus chemotherapy and 15 months after discontinuing treatment, he was still alive without disease progression.

An 81-year-old man presented with severe pain in his right hip joint and underwent hip joint replacement in October 2006. A specimen from the resected hip joint was sent for pathologic studies and was diagnosed as metastatic renal cell carcinoma with bony metastasis. A computed tomographic (CT) scan (Figure 1) revealed a right kidney tumor and enlarged calyx, so he was referred to our medical oncology department for treatment. Because of the patient's age, sorafenib was administered at a reduced dosage of 400 mg/day to avoid toxicity. One month later, vinblastine (8 mg/m^2) plus fluorouracil (500 mg/cycle) were given as conjunct medication and repeated every two weeks. Bisphosphonate (pamidronate) was also given with 90 mg/month. The patient tolerated the treatment well and the disease remained stable without further metastasis for 15 months, when he

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