Reversible cognitive disorders after sunitinib for advanced renal cell cancer in patients with preexisting arteriosclerotic leukoencephalopathy

In 2006, the Food and Drug Administration has approved sunitinib (sunitinib malate; SU011248; Sutent®) for the treatment of advanced renal cell cancer and imatinib-resistant gastrointestinal stromal tumors (GIST). Sunitinib is a novel oral tyrosine kinase inhibitor that targets multiple receptors, e.g. the vascular endothelial growth factor receptors (VEGFR-1 and VEGFR-2), platelet-derived growth factor receptors α and β (PDGFRs) and c-Kit and Flt-3 [1, 2]. Blocking VEGF and PDGF receptors will inhibit tumor angiogenesis.

In the past years, the standard treatment of metastatic renal cell cancer (mRCC) has been on the basis of cytokines, such as interferon-α (IFN-α), but only <20% of patients have a response. A summarized analysis of two phase II studies on second-line sunitinib in mRCC has revealed a partial response in 42% of patients and stable disease for >3 months in 24% of patients [3, 4].

A recently completed, large randomized phase III trial has shown a significant increase of the median progression-free survival time in patients treated with sunitinib when compared with that in patients on IFN-α (11 versus 5 months) [5].

In advanced GIST after failure on imatinib, sunitinib has also demonstrated significant clinical benefit with a progression-free survival time of 27 weeks as compared with 6 weeks in patients on placebo [6].

Sunitinib is tolerated reasonably well. In general, side-effects graded according to National Cancer Institute–Common Toxicity Criteria do not exceed grade 2 and are reversible upon dose reduction or discontinuation of the drug. The most important side-effects are fatigue, diarrhea, nausea, stomatitis, hypertension, hand–foot syndrome, leucocytopenia and thrombocytopenia [3–6]. In the previous trials, patients included had to fulfill prespecified criteria, but currently the drug can be prescribed widely to patients in the general oncology practice.

Here, we describe three elderly patients with mRCC who developed cognitive and behavioral changes during sunitinib treatment. In all three patients, brain metastases were excluded. The neurological symptoms disappeared after discontinuation of sunitinib.

An 84-year-old female patient was known since 2002 with a local recurrence and liver metastases of renal cell cancer after a nephrectomy in 1997. For aggravating trigeminal neuralgia, she received gabapentin 300 mg three times per day. For one episode of atrial fibrillation in 2006, she received metoprolol. Additional medication consisted of risedronate for osteoporosis, diclofenac/misoprostol for arthritis and pantoprazole to prevent gastritis. In 2004, she was on treatment of mRCC with IFN-α for 6 months
without clinical benefit. Because of progressive disease in 2006, the patient started sunitinib (50 mg daily oral dosing for 4 weeks, followed by a 2-week rest period in a cycle of 6 weeks). On a regular visit on day 12, her blood pressure had raised as compared with the baseline value (from 128/55 to 142/72 mmHg as measured by ambulatory 24-h blood pressure monitoring). On day 14, the patient visited the outpatient clinic because of periods of confusion and disorientation. She also had word-finding difficulties and a walking disorder. Furthermore, the pain of the trigeminal neuralgia had increased. At that time, sunitinib was temporarily interrupted. The next day the patient was admitted to the hospital because of increased confusion. The neurologist diagnosed cognitive disorders consisting of disorientation for time, expressive aphasia, perseveration and a gait disorder. A computed tomography (CT) scan of the brain demonstrated preexisting leukoencephalopathy consistent with subcortical arteriosclerotic encephalopathy (SAE), but excluded brain metastases (Figure 1A). Of interest, a magnetic resonance imaging (MRI) scan carried out in 2004 for trigeminal neuralgia had already demonstrated SAE of sufficient severity to fulfill criteria for vascular dementia according to the radiological criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) (Figure 1B) [7]. Vascular dementia, however, had never been a clinical diagnosis in this patient. Three days after discontinuation of sunitinib, she completely recovered. Recovery from excessive pain of the trigeminal neuralgia did not occur until stereotactic radiotherapy. Sunitinib was not restarted. Thus far, 7 months later, the neurological symptoms did not recur.

A 74-year-old male patient was diagnosed in 2006 with locoregional metastases, lung metastases and bone metastases of renal cell cancer after a nephrectomy in 2000. The patient was also known with coronary artery disease with pectoral angina for which he received isosorbide mononitrate, calcium carbosate and nitroglycerine. Furthermore, he received metoprolol for hypertension, pravastatin for hypercholesterolemia, esomeprazole for heartburn and salmeterol with fluticasone for emphysema. He likely had beginning dementia because of episodes of amnesia and hallucinations, but brain imaging had never been carried out. For progressive mRCC, the patient started in 2006 with sunitinib (50 mg daily 4 weeks on, 2 weeks off). On a regular visit on day 13, the blood pressure had raised as compared with the baseline value (from 110/60 to 122/71 mmHg as measured by ambulatory 24-h blood pressure monitoring). On day 18, the patient was admitted to the hospital because of a change in behavior suspected for brain metastases. Neurological examination showed a mask face, severe apathy, moderate bradyphrenia, moderate hypokinesia and moderate rigidity with cog wheeling. Retrospectively, the patient’s family had noticed these changes since the start of sunitinib treatment. CT and MRI scans excluded brain metastases, but demonstrated SAE with ischemic defects fulfilling the radiological criteria of NINDS-AIREN (Figure 2) [7]. Sunitinib was discontinued and 3 days thereafter the neurological symptoms disappeared. After a rest period of 2 weeks, sunitinib was restarted at a dose of 37.5 mg. Nine days later the patient was admitted to the hospital again because of recurrent bradyphrenia, hypokinesia and rigidity. At this second admission, the symptoms were less severe and the blood pressure had not changed. It was decided to permanently discontinue sunitinib, after which the patient recovered promptly within 4 days. Seven months later the neurological symptoms have not recurred.

Since 2004, an 82-year-old male patient was known with lung metastases of renal cell cancer. In 1992, the patient had a durable complete remission of the lung metastases after nephrectomy and one dose of interleukin-2. In 2002, he received an endoprosthesis for an abdominal aortic
aneurysm. The patient did not have a history of cognitive problems. His medication consisted of diclofenac and paracetamol/codeine for pain in the chest and right hip, lactulose for constipation, esomeprazole for heartburn and temazepam to treat insomnia. In 2006, the patient started with sunitinib (50 mg daily 4 weeks on, 2 weeks off) for progressive mRCC. CT scan evaluation after two cycles demonstrated stable disease. At the end of the fourth cycle, the patient visited the outpatient clinic because he experienced visual hallucinations and word-finding difficulties. Other neurological symptoms were absent. The blood pressure had raised as compared with the baseline value (110/59 versus 160/75 mmHg). A CT scan excluded brain metastases, but visualized age-related SAE (Figure 3). The severity was not sufficient to fulfill the NINDS-AIREN criteria [7]. During the rest period, the cognitive symptoms recovered promptly. Because the neurological symptoms were possibly related to sunitinib, the fifth cycle was started at a reduced dose of 37.5 mg. The complaints did not recur during the following cycles.

We describe three elderly patients with mRCC and preexisting cerebral vascular changes, who developed cognitive disorders on treatment with sunitinib. Since all patients recovered within 1 week, which is in line with the elimination half-life of sunitinib of 41–86 h [8], a causal relationship with the drug seems evident. Rechallenge with a reduced dose was successful in the third patient. The recurrent symptoms upon dose reduction in the second patient are also indicative for a causal relation.

In our patients, we did not detect brain metastases, and cerebrovascular accident or delirium caused by a metabolic disorder or co-medication could be excluded. Since sunitinib is metabolized in the liver by cytochrome P450 isoenzyme 3A (CYP3A), attention should be paid to a drug interaction caused by co-medication. Inhibitors (e.g. clarithromycin or verapamil) and inducers (e.g. fenobarbital or fenytoine) of CYP3A can affect the plasma concentration of sunitinib and should be avoided. Our patients did not use co-medication that requires CYP3A for metabolism. Recovery from neurological symptoms also occurred in the patient on continuous gabapentin for trigeminal neuralgia.

Cognitive disorders during sunitinib treatment have not been described before. There is a case report, however, on a transient ischemic attack upon bevacizumab treatment [9]. Further, reversible neurological symptoms during treatment with bevacizumab and sorafenib (BAY 43-9006) have been reported [10–13]. In these cases, a reversible posterior leukoencephalopathy syndrome (RPLS) was the underlying
C15O is a valuable imaging modality to quantify regional blood flow and cerebral blood flow before and during sunitinib treatment. Ideally, future studies should investigate the vasoconstriction which might become symptomatic in elderly patients. Conceivable that sunitinib decreases the cerebral blood flow by a variable degree. VEGF(R) inhibitors on the cerebral vasculature are warranted.

Vascular dementia is known to be associated with a reduced cerebral blood flow, especially in the frontal lobes. It is conceivable that sunitinib decreases the cerebral blood flow by vasoconstriction which might become symptomatic in elderly patients with preexisting cerebral vascular disease, such as microangiopathy. Ideally, future studies should investigate the cerebral blood flow before and during sunitinib treatment. Positron emission tomography utilizing 15O-labeled H215O and C15O is a valuable imaging modality to quantify regional blood flow and volume.

These three case reports strongly indicate a relationship between cognitive disorders and sunitinib. All three patients appeared to have preexisting arteriosclerotic leukoencephalopathy which most likely has contributed to the development of these side-effects. Treating physicians should be aware of the occurrence of cognitive disorders in elderly patients using this new multitargeted inhibitor. Fortunately, the neurological symptoms seem to be reversible upon discontinuation or a dose reduction of sunitinib. Additional investigations of the effects of VEGF(R) inhibitors on the cerebral vasculature are warranted.

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