Brain Metastasis in Renal Cell Cancer Responding to Sunitinib

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Abstract. *Background: Sunitinib (SU011248; Sutent™) is a new small molecule that inhibits members of the split-kinase domain family of receptor tyrosine kinases (RTKs), with established antitumor activity in renal cancer. In the current report, we describe a patient with a solitary brain metastasis from renal cell carcinoma who achieved partial response of the cerebral lesion following treatment with sunitinib. To the best of our knowledge, this is the first report of sunitinib activity in brain metastases from kidney cancer. A limited number of publications support the hypothesis that small tyrosine kinase inhibitors may cross the blood-brain barrier. Although the role of sunitinib in advanced renal carcinoma has been evaluated through prospective trials, the efficacy of the drug in patients with brain metastases has not been explored, since patients with cerebral lesions were excluded in those studies. Thus, we believe that accumulating evidence from personal experience or limited reports could be useful. Moreover, in our case, sunitinib was found to be safe, leading to considerable shrinkage of the brain metastasis without any serious adverse events or central nervous system toxicities. We consider this observation to be important, given the absence of data regarding the activity of the drug in this particular clinical setting.*

Case Report

A 40-year-old woman underwent nephrectomy for a moderately differentiated, clear cell adenocarcinoma of the left kidney in August 2004. The pathological stage of the disease was II (T2N0M0). In February 2006, the patient complained of numbness of the left upper limb, focal seizures and headache. Computed tomography (CT) and magnetic resonance imaging revealed a solitary mass in the right parietal-occipital lobe. The patient underwent surgical excision of the lesion which was histopathologically confirmed to be a metastasis from clear cell renal cancer. Postoperatively, evaluation with CT scan did not reveal residual disease in the brain. Moreover, evidence of the disease elsewhere in the body was not apparent.

Immunotherapy consisting of interferon alpha (10 mU 3 x weekly) was started in March 2006. Five months later, repetition of imaging procedures (CT scan) demonstrated relapse of the disease in the brain, with a lesion located in the right parietal-occipital lobe (maximum diameter 4 cm), together with peritumoral edema (Figure 1). Again, CT scan of the abdomen and the lungs was negative for local relapse and other metastatic sites. The lesion was considered inoperable and the patient started (August 2006) sunitinib monotherapy at a dose of 50 mg orally once daily for 4 weeks, followed by 2 weeks off, in repeated 6-week cycles. The patient also received methylprednisolone at a dose of 16 mg daily, which was progressively decreased until discontinuation, during the following months. At that time, the patient was in a good clinical condition (Eastern Cooperative Oncology Group Performance Status=0, lactate dehydrogenase=145 U/L, haemoglobin=10.9 g/dL, corrected calcium=9 mg/dL and alkaline phosphatase=63 U/L). The treatment was tolerated fairly well without serious adverse events.

The patient developed grade 1 hypertension (according to National Cancer Institute Common Toxicity Criteria, version 3.0) after the first cycle of the treatment, which was successfully controlled with olmesartan. Other side-effects included anemia grade 1 and hand-foot syndrome grade 1 (according to the above mentioned criteria). Evaluation of the patient with CT scan after 2 cycles of treatment (November 2006), revealed a reduction of the metastatic lesion (maximum diameter 3.2 cm), together with significant resolution of the associated edema (Figure 2). Given the response of the disease and the lack of considerable toxicity, treatment was continued at the same dose. Re-evaluation of the patient after the completion of the fifth cycle (March 2007) demonstrated further reduction of the lesion (maximum diameter 2 cm), without any signs of disease elsewhere (Figure 3). The patient remains on treatment with sunitinib at the same dosage, without clinical or radiographic evidence of disease progression.

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Key Words: Sunitinib, renal cell cancer, brain metastases.

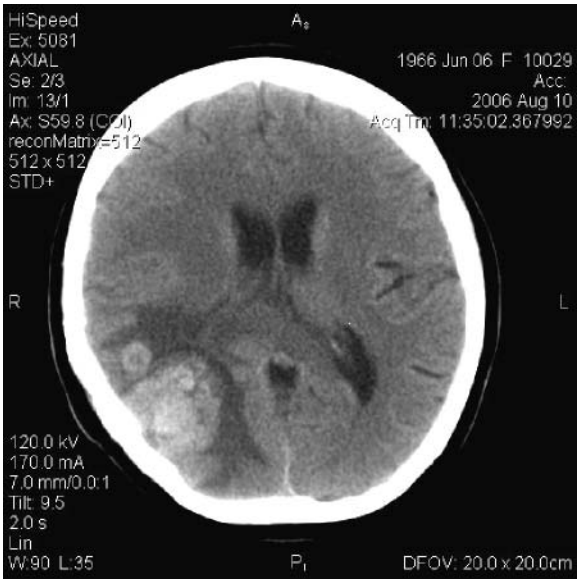

Figure 1. *CT scan of the brain before the administration of sunitinib.*

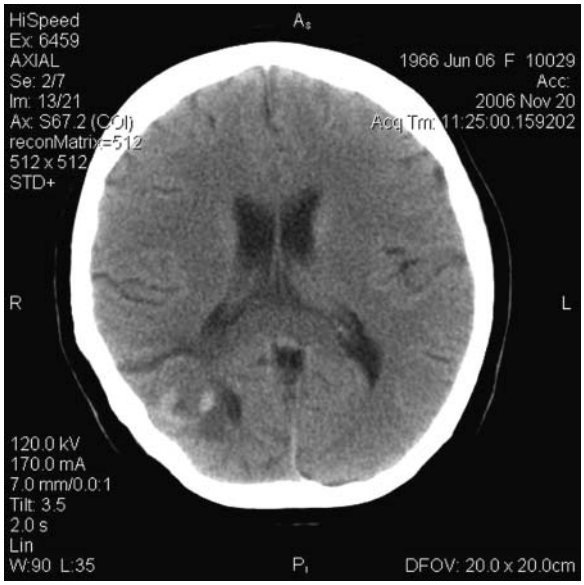

Figure 2. *CT scan of the brain after 2 cycles of treatment with sunitinib.*

Discussion

Sunitinib (SU011248; Sutent™) is a new, orally administered, small molecule that inhibits members of the split-kinase domain family of receptor tyrosine kinases (RTKs), including the vascular endothelial growth factor receptors (VEGFRs) types 1 and 2, platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), the stem cell factor receptor c-KIT, the FLT3 and RET kinases (1). Sunitinib exhibits potent antiangiogenic and antitumor activity. Considerable clinical activity has been demonstrated in patients with advanced renal cell carcinoma (2-4).

Brain metastases are not a rare occurrence in patients with kidney cancer (5). Whole-brain radiotherapy is the standard treatment, although generally, renal tumors are relatively radioresistant and more aggressive approaches such as surgery or radiosurgery are indicated only in a subset of patients. In the current report, we describe a patient with a solitary brain metastasis from renal cell carcinoma who achieved partial response of the cerebral lesion, following treatment with sunitinib. To the best of our knowledge, this is the first report of sunitinib activity in brain metastases from kidney cancer. It is noteworthy that our patient continued to respond further, seven months after the initiation of the treatment, as was demonstrated by CT scan in March 2007. It is also interesting that seizures or other central nervous system (CNS) toxicities were not observed during the treatment, although prophylactic anticonvulsant therapy was not administered.

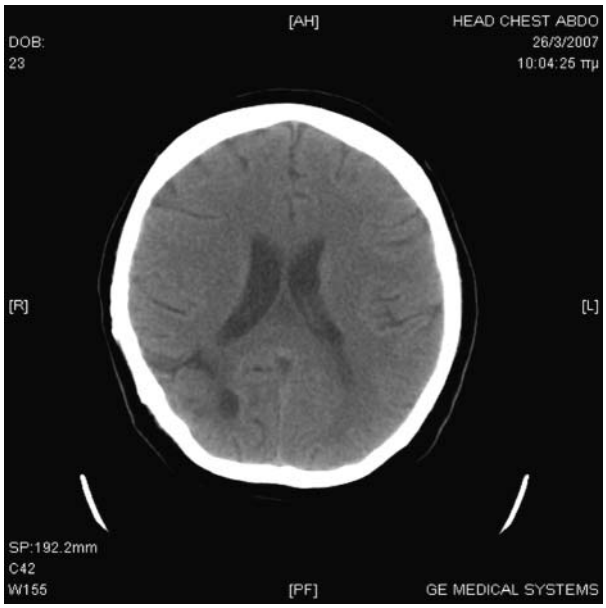

Figure 3. *CT scan of the brain after 5 cycles of treatment with sunitinib.*

A limited number of publications support the hypothesis that small tyrosine kinase inhibitors (TKIs) may cross the blood-brain barrier. Gefitinib, an oral selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has shown activity in brain metastases from non-small cell lung cancer (NSCLC) (6-8). Responses have also been reported with erlotinib, another EGFR tyrosine kinase

inhibitor, in patients with intracranial lesions from NSCLC (9, 10). Lapatinib, another small molecule, is a dual reversible inhibitor of the tyrosine kinase activity of EGFR and human epidermal growth factor receptor 2 (HER-2). In a randomized study comparing lapatinib plus capecitabine *versus* capecitabine in patients with HER-2 positive refractory advanced breast cancer, the authors reported an advantage of the combination in terms of less CNS progression (11). That observation suggests that the low molecular weight TKIs may penetrate the blood-brain barrier and may be useful in the management of patients with brain metastases.

Although the role of sunitinib in advanced renal carcinoma has been evaluated through prospective trials, the efficacy of the drug in patients with brain metastases has not been explored, since patients with cerebral lesions were excluded in those studies (2-4). We acknowledge that trials designed to address prospectively the feasibility of sunitinib in these patients are difficult to conduct and hence, accumulating evidence from personal experience or limited reports could be useful. It might also be useful to consider the randomized study comparing sunitinib to interferon alpha in metastatic renal cell carcinoma (4), and assess the proportion of patients per arm who developed progression of the disease in the brain to identify whether there is an advantage favoring sunitinib use.

Initial experience with sunitinib suggested a mild and manageable adverse event profile. However, it has become clear with additional experience that antiangiogenic agents are associated with a distinct array of toxicities, such as hemorrhage. Further investigation is warranted to determine risk factors for the development of hemorrhagic events with such agents. Hemorrhagic complications, some of them fatal, have rarely been observed in patients receiving sunitinib for gastrointestinal stromal tumors or squamous cell lung carcinomas. Undoubtedly, there is a concern related to the safety of antiangiogenic factors in patients with CNS lesions. On the other hand, prognosis of patients with brain metastases from renal cell carcinoma is usually dismal, since no effective treatments are currently available. Thus, sunitinib could be a potentially active therapeutic option in certain patients.

In conclusion, sunitinib was found to be effective and safe, leading to considerable shrinkage of brain metastasis without any serious adverse events. Our case highlights the potential of sunitinib in patients with CNS metastases from renal cell carcinoma. We consider this observation to be important, given the absence of data regarding the activity of the drug in this particular clinical setting.

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