Complete cerebral response with sunitinib for metastatic renal cell carcinoma

Renal cell carcinoma (RCC) is a relatively rare cancer, representing 2–3% of the neoplasms in the adult population. Metastasis is in 30% of cases synchronous to the diagnosis of RCC. The most frequent common sites of metastasis include lung, liver, bone, brain and adrenal gland [1]. Brain metastasis from RCC is responsible for significant mortality [2].

RCC is characterized by the inactivation of the von Hippel–Lindau tumour-suppressor gene, which results in the deregulation of hypoxia response genes, including an overproduction of vascular endothelial growth factor (VEGF), which promotes tumour angiogenesis, growth and metastasis. Small-molecule inhibitors of VEGF and platelet-derived growth factor receptor (PDGFR) tyrosine kinases, such as sunitinib (Sutent®, Pfizer Laboratory) and sorafenib (Nexavar®, Bayer Pharmaceuticals) showed a 70% stabilization of disease. Sunitinib has been approved for the treatment of patients with advanced or metastatic RCC and/or metastatic malignant gastrointestinal stromal tumours after disease progression or intolerance to imatinib mesylate [3, 4]. An extended access program to sunitinib before market approval was proposed to patients with metastatic RCC and bad-performance status or clinical status, including brain metastasis.

We present the case of a patient with RCC showing a complete response of brain metastasis and a long-lasting partial response of other metastasis after 21 months of sunitinib treatment.

A 77-year-old male had excision of a cutaneous tumour located in the skull. Pathology was in favour of a metastasis of renal clear cell carcinoma. Whole-body computed tomography (CT) scan showed a left renal tumour. Brain CT and bone scintigraphy were normal. Nephrectomy with adrenalectomy was performed and pathology showed a RCC of pT3 stage, with venous thrombosis. No further treatment was proposed and the patient was regularly followed up.

Seven months later, the patient was referred to the Department of Medical Oncology in Georges Pompidou European Hospital, Paris, France, because a nodular lesion in the nephrectomy area and pulmonary metastasis appeared on whole-body CT scan. The brain CT scan revealed a right frontal lesion, 10 mm in diameter, with perilesional oedema. This single lesion was confirmed by brain magnetic resonance imaging (MRI). The patient was treated with sunitinib delivered consecutively for 4 weeks, followed by 2 weeks off per treatment cycle, at 50 mg/day given orally.

Whole-body and brain CT scan were performed after 6 weeks and they showed no progression of the disease. After 12 weeks of treatment, the brain CT scan showed complete regression of brain metastasis. A partial response (PR) of 79% (RECIST criteria) on the pulmonary and nephrectomy area lesions was noted at this time. After 21 months of sunitinib treatment, brain MRI confirmed the maintenance of complete response of brain metastasis.

Figure 1 presents the results of brain MRI performed at diagnosis and after 21 months of sunitinib.

We present a case of a patient with pathology-proven RCC and probable metachronous metastasis in the lung, nephrectomy area and brain. The expanded access program allowed the enrolment of patients with well-controlled brain metastasis. The patient showed no neurological symptoms and his brain metastasis was small and single. A close follow-up with clinical exam and brain CT scan every 6 weeks were performed and no other anti-cancer treatment except sunitinib was administered, considering that treatment such as radiosurgery or conventional radiotherapy could be performed later in case of progression of brain metastasis. Furthermore, mild-to-moderate haemorrhages have been described with bevacizumab in advanced colon cancer and non-small cell lung cancer. Such side effects are rare (<5%) with sunitinib [3, 4]. The risk of bleeding of brain metastasis is not well documented because only a few patients receive sunitinib in that situation. For example, a phase II clinical trial of bevacizumab and irinotecan in recurrent gliomas was conducted in 32 patients. No central nervous system haemorrhage occurred [5].
Development of brain metastasis seems to be closely related to VEGF expression and angiogenesis, as it was noted in animal models using breast cancer cells [6]. Small-molecule inhibitors of VEGF and PDGF receptor tyrosine kinases, such as sunitinib and sorafenib, are probably able to penetrate the blood–brain barrier. Sorafenib has been shown to significantly reduce the occurrence of brain metastasis and to prolong progression-free survival compared with placebo [7]. Among sorafenib-treated patients the incidence of brain metastasis was 3%, versus 12% for patients receiving best supportive care. The 1- and 2-year incidences of developing brain metastasis for patients treated with sorafenib versus best supportive care were 3 and 4 versus 10 and 20%, respectively. The distribution of sunitinib and its active metabolite in brain and spinal cord tissue following oral or intravenous administration in rodents and monkeys was studied by Patyna S et al. [8]. Sunitinib or its metabolite penetrate the CNS of monkey with rapid clearance, but does not appear to accumulate. This result might suggest potential anti-tumour activity of sunitinib in the brain.

Our observation suggests that inhibitors of tyrosine kinase receptors can be used safely for asymptomatic brain metastasis in advanced RCC and that this treatment is efficient. To our knowledge, this is the first described complete response of brain metastasis of RCC treated with sunitinib.

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references
8. Patyna S, Peng J. Distribution of sunitinib and its active metabolite in brain and spinal cord tissue following oral or intravenous administration in rodents and monkeys. Eur J Cancer 2006; 4; 21.

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