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Case Report 3. Sunitinib malate in patients with cerebellar metastases

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1. Introduction

Successful inhibition of angiogenesis with the multi-targeted tyrosine kinase inhibitor sunitinib has provided superior response rates and prolonged survival compared with immunotherapy in RCC.[1] Several studies have explored the use of sunitinib in patients with central nervous system (CNS) metastases. The results of subgroup analysis of a large expanded-access program ($N = 182$),[2] and a single-centre study in patients with pre-treated CNS metastases ($N = 23$)[3] suggest treatment is effective in this setting. In addition, a recent case report described complete response of brain metastases and long-lasting partial response of other metastases of RCC after 21 months of sunitinib treatment.[4] However, prospective trials in patients with previously untreated brain metastases are yet to be undertaken. We report two cases of clear-cell RCC with cerebellar metastases treated with sunitinib.

2. Case Report

Patient 1, a 55-year-old man, presented with clear-cell RCC pT_3 N0M0 grade 2 and underwent a right nephrectomy in 2003. In 2004 cerebellar metastases were identified and the patient underwent surgery and radiation therapy. Later that year, radiography revealed a 2.5 cm residual renal tumour. In early 2005, the patient's renal lesion progressed, and partial nephrectomy considered but ultimately rejected.

In June 2005, the patient presented with frontal brain metastasis. Two months later, a CT scan showed a bulky central renal tumour, with metastases to the pancreas and liver (Fig. 1). Gamma knife radiosurgery of the brain metastases was carried out and treatment with sunitinib initiated at a dose of 50 mg/day for 4 weeks followed by 2 weeks off (4/2 schedule). During sunitinib therapy, the patient experienced hypertension (defined as blood pressure >160/100 mmHg), which was controlled, and cutaneous toxicity, grade 3 asthenia and oesophagitis, which were also controlled.

At the third cycle, treatment was interrupted after three weeks. Further cycles were given at a dose of 37.5 mg/day (4/2 schedule). After approximately 10 months of sunitinib treatment, major partial response of the renal mass, and liver and pancreatic metastases was observed (Fig. 2).

Patient 2, a 49-year-old woman, presented with clear-cell RCC pT_2 N0M0 and underwent surgery in 2001. In September 2005, she re-presented with back pain and large metastases on dorsal vertebras (T_{11} and T_{12}),

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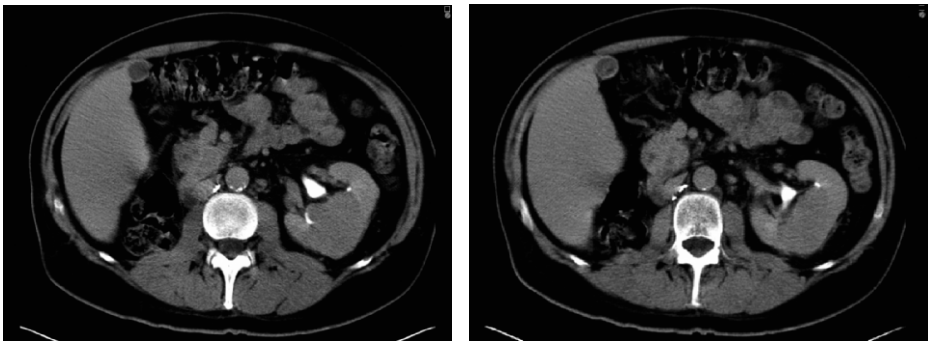

Fig. 1 – Bulky central renal tumour in a patient with metastases to the pancreas and liver.

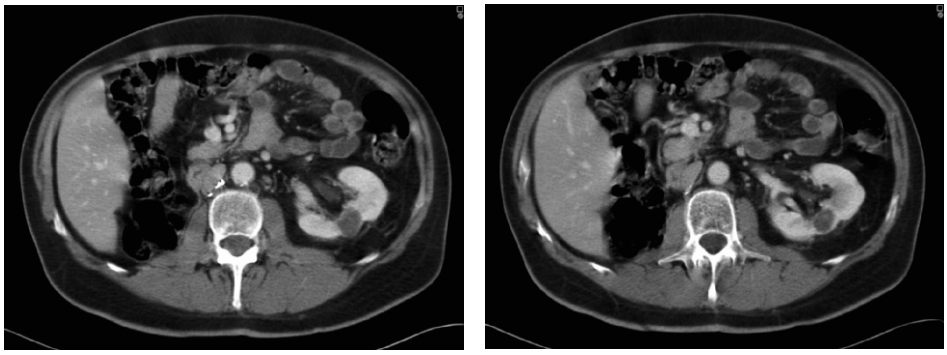

Fig. 2 – Following sunitinib treatment, partial response of the renal mass and metastases of the pancreas and liver.

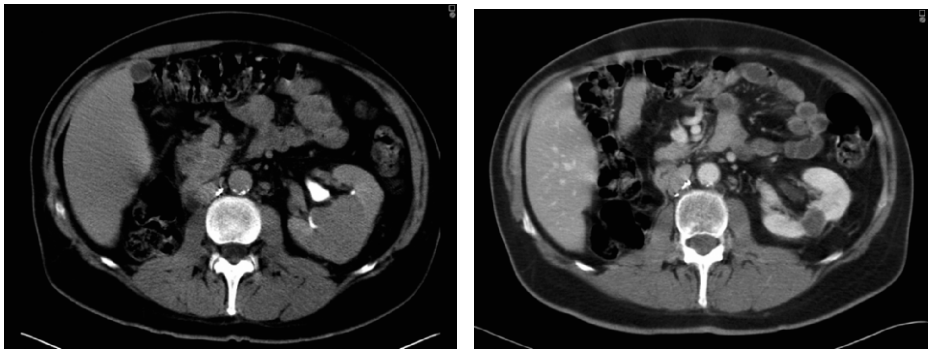

Fig. 3 – Tumour regression in pleura, hilar lymph nodes and cerebellar lesion following sunitinib treatment.

and right cerebellar, pleural and hilar metastases were diagnosed. Surgery was carried out on the vertebra, followed by radiation therapy. The patient was then treated with interferon for 3 months. After treatment, a CT scan showed stable pleural and hilar metastases and slight regression of the vertebral metastases. Interferon treatment was stopped and the patient received radiation therapy for her cerebellar metastases.

Two months later, CT scan showed progression of the thoracic metastases and stable cerebellar tumour. Sunitinib was initiated at a dose of 50 mg/day for 4 weeks followed by 2 weeks off (4/2 schedule) as part of the treatment use programme. No major toxicity was observed during treatment. At follow-up in February and March 2006, CT scan and brain MRI showed some tumour regression in pleura, hilar lymph nodes and cerebellar lesion (Fig. 3). At 14 months, the dose of sunitinib was reduced to 37.5 mg/day (4/2 schedule) following diagnosis of neutropenia and evaluation revealed stable disease.

3. Discussion

Preclinical studies have been undertaken to assess the ability of sunitinib to cross the blood-brain barrier and penetrate the brain and spinal cord following oral or intravenous administration.[5] The results of these studies suggest that sunitinib and its major metabolite penetrates the CNS of mice, rats and monkeys. Interestingly, in monkeys, total drug concentrations in the CNS attained steady state after 4 weeks of treatment and decreased to negligible levels after a 2-week washout

period, providing support for the regimen of 4 weeks on treatment followed by 2 weeks off (4/2 schedule). While these observations suggest the potential application of sunitinib for the treatment of CNS tumours, further study is required to clarify the target drug concentrations in this setting and determine the safety and efficacy of this approach.

4. Conclusion

Our observations suggest that sunitinib can be used in patients with pre-treated brain metastases and that treatment is effective.

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Conflict of interest

S. Négrier: scientific consultant for Pfizer Europe and Pfizer France, member of scientific advisory boards for Wyeth and Sanofi Aventis.

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