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# Anti-Angiogenic Treatment (Sunitinib) for Disseminated Malignant Haemangiopericytoma: A Case Study and Review of the Literature

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## Key Words

Haemangiopericytoma · Platelet-derived growth factor receptor · Sunitinib · Vascular endothelial growth factor receptor

## Abstract

**Introduction:** A meningeal haemangiopericytoma (HP) is a mesenchymal tumour that makes up less than 1% of all CNS tumours. HPs arise from pericytes and present high rates of recurrence and distant metastasis. The primary treatment option is surgery. When the disease is disseminated, chemotherapy produces a weak and short-lived response; therefore, new drugs are needed.

**Case Presentation:** We describe the case of a 65-year-old woman with a 13-year history of recurrent HP. After local treatment with radiotherapy, she developed metastases that required systemic treatment, and treatment with sunitinib, an oral inhibitor of the vascular endothelial growth factor receptor and the platelet-derived growth factor receptor, was initiated. As a result, radiological stabilisation of the systemic disease was maintained for over 12 months.

**Conclusions:** Anti-angiogenic agents can be useful for treating disseminated HP, but further studies are needed to confirm their possible role in controlling metastatic disease.

## Introduction

A meningeal haemangiopericytoma (HP) is a rare mesenchymal tumour that arises from the cells surrounding the capillary wall. Its aetiology is unknown, and 25% of cases occur in the head or neck. Meningeal HP makes up less than 1% of all CNS tumours; it is very aggressive and presents high rates of local recurrence and distant metastasis, most

frequently in the lungs and the bones. Surgery is the normal treatment, and no clear role has been established for either radiotherapy or chemotherapy.

The hypothesis that this type of tumour could be sensitive to angiogenesis inhibitors is based on the fact that these tumours are highly vascularised and express platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR). However, few cases of patients treated with anti-angiogenic drugs have been reported. The low prevalence of this tumour prevents the implementation of clinical trials that could confirm our hypothesis.

### Case Presentation

A 65-year-old woman with a personal history of arterial hypertension who had been treated for parotid adenoma came to our clinic in November 1997. She was diagnosed with a 30-mm meningeal tumour in the sellar cavity. A biopsy was performed, and the anatomopathological results were compatible with meningeal HP. Resectioning of the tumour was decided against in view of the likely outcome, and so the patient was given 17 Gy of stereotactic radiotherapy in one fraction. Complete radiological remission was achieved. At 39 and at 65 months, local relapses occurred, and stereotactic radiotherapy was administered.

In January 2009, the patient complained of pain, which had developed over months, in the right upper arm. Radiography was performed and revealed a 70-mm permeative lesion in the middle third of the right humerus. MRI of this area showed the lesion to be of a lytic nature, with an intermediate signal in T1 and T2 and perilesional oedema. An extension study was performed, involving a helical computerised axial tomography (CAT) scan, which revealed a nodular image measuring 22 mm in the paraspinal muscles between the 11th and 12th ribs and two hepatic lesions in segments 3 and 7, measuring 24 and 22 mm, respectively. A humeral biopsy was then performed, and the anatomopathological results revealed the existence of HP.

With clinical evidence of HP metastatic relapse in the bone, soft tissues and liver, we decided to apply radiotherapy to the lesions in the humerus and the lower left dorsal paraspinal muscles due to the pain experienced in those regions and to obtain evolutive control of the hepatic lesions.

After 4 months of monitoring, a CAT re-evaluation was performed, and the diameter of the irradiated paravertebral lesion had decreased by 50%, while the hepatic lesions had enlarged to 38 and 25 mm, respectively ([fig. 1](#)). The cranial CAT revealed a hyperechoic mass measuring 20 mm with a meningeal base at the apex of the petrous bone; it could not be discerned whether this corresponded to residual remains or to a tumoural relapse.

In June 2009, progression to the liver suggested the need to begin treatment with 37.5 mg sunitinib daily. Initially, the patient suffered increased abdominal pain and jaundice. After 1 month of treatment with anti-VEGFR, analysis revealed a two-fold increase in the values of GOT, GPT and GGT to 80, 83 and 81 U/l, respectively, while AP levels rose to 169 U/l and LDH to 567 U/l. Abdominal echography was performed, and the two hepatic lesions in segments 3 and 7 were observed to measure 30 and 70 mm, respectively. One of the lesions, thus, was smaller while the other was larger than at the time of the previous CAT scan. We assumed that ischemia of the lesions might have been induced by the administration of sunitinib, and so the treatment was continued.

In the control echography carried out after 1 month, the same lesions were observed, measuring 30 and 55 mm, respectively. They were more hypoechoic than they had been previously. The patient showed an acceptable degree of tolerance, although with grade II thrombocytopenia and grade III neutropenia, with episodes of epistaxis and petechiae on the lower eyelids, it was necessary to reduce the dose of sunitinib to 25 mg daily for 4 weeks, followed by 2 weeks of rest.

The image tests carried out from the start of anti-VEGFR treatment in June 2009 until September 2010 revealed disease stabilisation ([fig. 2](#)) in the liver and head. The patient therefore continued the same treatment, and no significant level of toxicity was observed.

## Discussion

Meningeal HP is a very rare tumour, but it is aggressive, with a tendency to recur and to metastasise. In studies by Mena et al. [1] of 94 patients and Guthrie et al. [2] of 44 patients with HP, recurrences were reported in 60.6 and 65% of the cases, and metastases were reported in 23.4 and 33% of the patients, respectively.

The normal treatment for meningeal HP is surgical resection. In some clinics, adjuvant radiotherapy is applied, although the retrospective study by Dufour et al. [3] did not find any reduction in the rate of metastasis with adjuvant radiotherapy.

The utility of chemotherapy is unclear; various chemotherapeutic agents have been used in the treatment of metastatic HP, but no consensus has been reached as to the most appropriate drug, dose, form of administration, scheme or response criteria, and so the results obtained should be interpreted with caution. Adriamycin, alone or in combination, appears to be the most effective agent, with 6/12 (50%) complete or partial responses and 4/12 (33%) minor responses. Other drugs, such as cyclophosphamide, vincristine, methotrexate, actinomycin and DTIC, may exert some anti-tumoural activity, but due to the small number of patients under such treatment and because these drugs are often used in combinations, it is not possible to establish a protocol for application based on the results of previous studies [4, 5].

The immunohistochemical expression of VEGFR has been described in the tumoural cells of HP and in the endothelium, with overexpression of VEGFR1 and VEGFR2 only in the endothelium, suggesting that the autocrine and paracrine activation of the VEGF–VEGFR pathway may participate in the biology of HP [6]. A study by Dietzmann et al. [7] showed that angiomatous meningiomas and HPs frequently overexpress PDGFR and that this overexpression is detectable by immunohistochemistry.

Sunitinib is a tyrosine kinase inhibitor of VEGFR, PDGFR and fibroblast growth factor, with antiproliferative and anti-angiogenic properties. Among the anti-angiogenic treatments used for HP, interferon- $\alpha$  and/or thalidomide [8] have been shown to induce partial responses and disease stability. Other patients have been treated with tyrosine kinase inhibitors such as sunitinib [9, 10], sorafenib [10] or dasatinib [11] as first-line or successive treatments. In some of these patients, disease stabilisation lasting over 6 months has been achieved; others have enjoyed clinical benefits or even durable partial response ([table 1](#)).

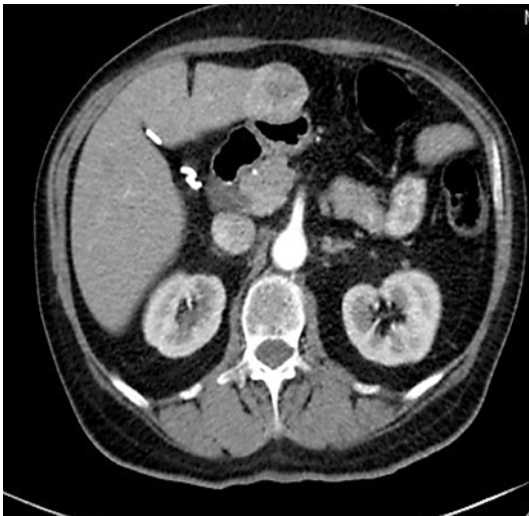
## Conclusions

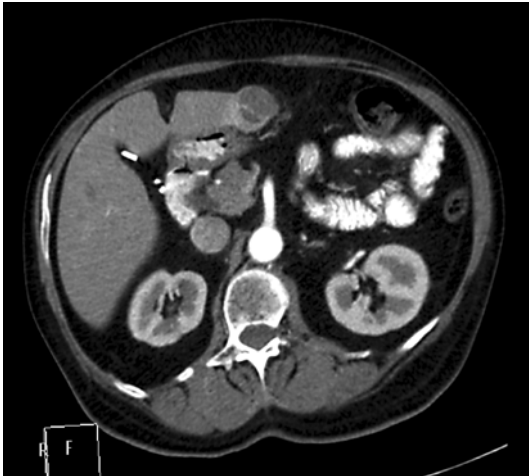
Because HP is a tumour with a high probability of distant metastasis that shows little and short-lived response to chemotherapy, new drugs are needed to tackle disseminated disease. Anti-angiogenic treatment, for example, utilising anti-VEGFR drugs, could play a role in these new treatment regimens, but trials are needed to test this hypothesis because, to date, only individual cases have been reported.

**Table 1.** Overview of previous studies of anti-angiogenic treatment

Study	Anti-angiogenic treatment	Previous systemic treatments	Response to anti-angiogenic treatment
Delgado et al.	sunitinib (1 case)	no	DS after >15 months
Kirn and Kramer [8]	IFN- $\alpha$ (2 cases)	no no	PR after 16 months DS after 24 months
Mulamalla et al. [9]	sunitinib (1 case)	no	DS after >10 months
Domont et al. [10]	sorafenib (1 case) sunitinib (1 case)	cisplatin, epirubicin, I-phosphamide, trabectedin, paclitaxel, dacarbazine anthracyclines	DS after 15 months DS after 6 months (suspended due to toxicity)
Peters et al. [11]	dasatinib (1 case)	octreotide and (90)Y-dodecane- tetraacetic acid Phel-Tyr3-octreotide	DS after >24 months

DS = Disease stabilisation; IFN = interferon; PR = partial response.

**Fig. 1.** Metastatic hepatic lesion in segment 3 measuring 38 mm before treatment with sunitinib. April 2009.



**Fig. 2.** Metastatic hepatic lesion in segment 3 measuring 30 mm after treatment with sunitinib. May 2010.

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