

Vascular-endothelial-growth-factor (VEGF) expression and possible response to angiogenesis inhibitor bevacizumab in metastatic alveolar soft part sarcoma

Amedeo A Azizi,* Christine Haberler,* Thomas Czech, Astrid Gupper, Daniela Prayer, Helene Breitschopf, Till Acker, Irene Slavic

Alveolar soft part sarcoma is a rare tumour of unknown histogenesis. Although tumour growth is slow and often asymptomatic, vascular invasion and metastatic dissemination (especially to the brain and lung) take place early in the course of disease. Resection is the treatment of choice and could lead to complete remission. If complete resection is not possible, the prognosis of alveolar soft part sarcoma is poor, since conventional cytotoxic chemotherapy regimens have little efficacy in most patients.¹ Therefore, alternative treatment approaches are needed. We report tumour regression in a patient with disseminated alveolar soft part sarcoma during antiangiogenic treatment with the antibody against vascular endothelial growth factor (VEGF), bevacizumab.

An 8-year-old boy presented with a 2-week history of headaches in July, 2003. The boy was in good general condition, but physical examination revealed minor gait

ataxia, dysdiadochokinesis, bilateral pyramidal signs, papilloedema, and homonymous hemianopsia. MRI of the brain detected three solid contrast-enhancing lesions in the left cerebellum (3.2×3.7 cm), left occipital lobe (4.8×3.7×5.2 cm), and left parietal lobe (1.3×1 cm). Digital subtraction angiography showed all lesions to be highly vascularised. No notable findings were seen in MRI of the spinal cord. A multislice CT of the thorax and abdomen revealed 15 intrapulmonary lesions (the largest measuring 2.7×2.8 cm). Whole-body MRI detected a lesion (2.4×1.2 cm) in the left psoas muscle, which was regarded as the primary site.

Resection of the infratentorial tumour was undertaken to prevent brain-stem compression. Histopathological examination of the tissue revealed tumour cells arranged in solid nests and separated by thin sinusoidal vessels, characteristic of alveolar soft part sarcoma (figure 1A). The

Lancet Oncol 2006; 7: 521-23

*These researchers contributed equally to the report

Department of Paediatrics (A A Azizi MD, A Gupper MD, I Slavic MD), Institute of Neurology (C Haberler MD), Department of Neurosurgery (T Czech MD), Department of Radiology (D Prayer MD), Institute of Brain Research (H Breitschopf), Medical University of Vienna, Währinger Gürtel 18-20, A-1097 Vienna, Austria; and Neurological Institute University of Frankfurt, Frankfurt, Germany (T Acker MD)

Correspondence to: Dr Irene Slavic

irene.slavic@meduniwien.ac.at

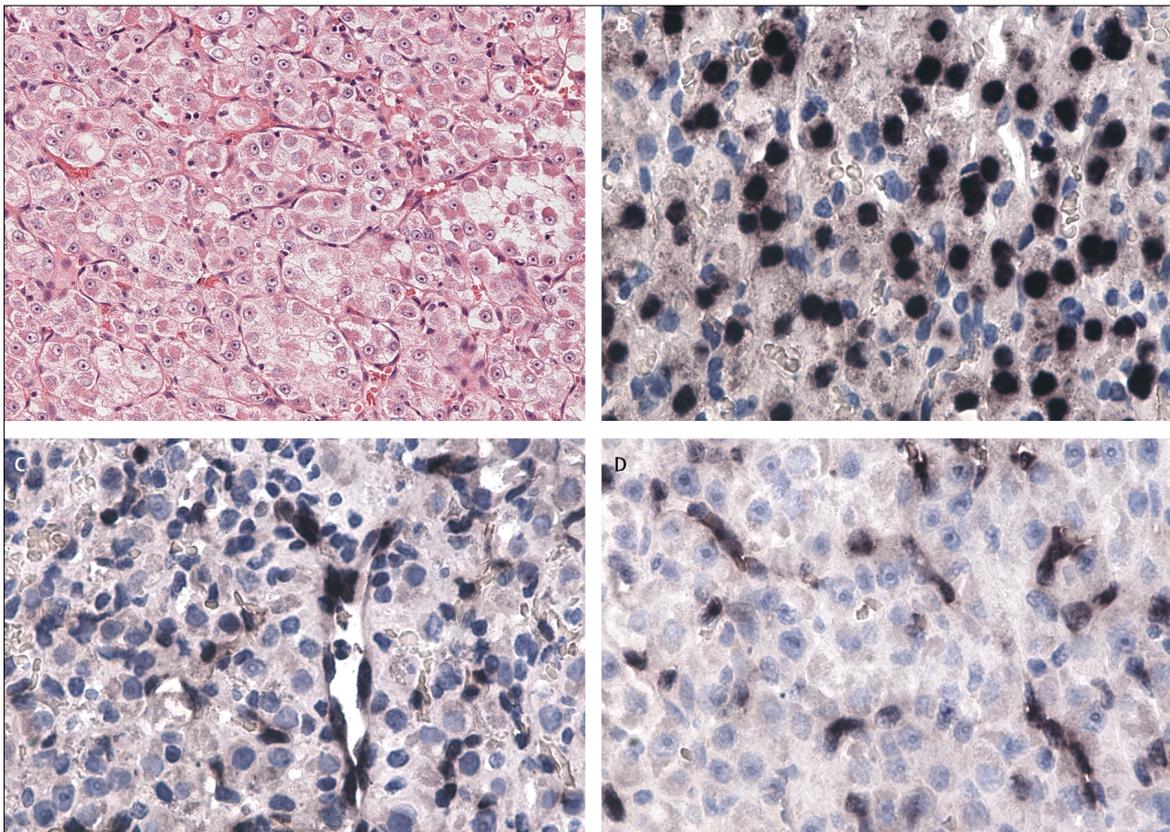


Figure 1: Histopathological slides of tumour cells at diagnosis

(A) Nest-like arrangement of tumour cells separated by thin vessels, representing characteristic features of alveolar soft part sarcoma. Expression of (B) VEGF in tumour cells, and (C) VEGF receptors 1 and (D) 2 in intratumoural endothelial cells from in-situ hybridisation (dark brown staining).

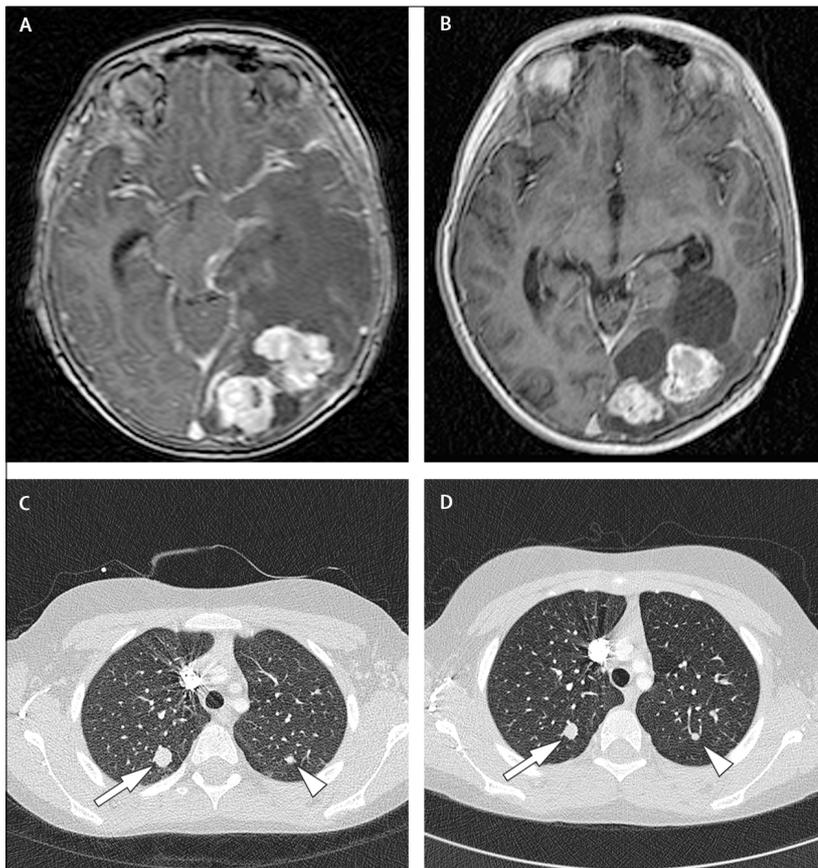


Figure 2: Radiological images before and after bevacizumab treatment

Axial, T1-weighted, contrast-enhanced MRI of the brain before treatment show (A) two intensely enhancing, space-occupying lesions in the left occipital lobe (20×25 mm, 32×35 mm; October, 2004), extensive perifocal oedema with obliteration of the left lateral ventricle, and midline shift. In the basal ganglia, a cystic component of the tumour can be seen. After treatment (B), nodular lesions are reduced in size (18×23 mm, 22×25 mm; June, 2005), with a different appearance of cystic areas. The space-occupying effects are reduced (left ventricle visible) and no oedema is seen. Axial, contrast-enhanced, CT images of the lungs show (C) two of the multiple lesions in the right (12 mm) and left (3 mm) posterior lower lobes (October, 2004), (D) which have shrunk after treatment (right 9 mm, left 1 mm; March, 2005).

patient received treatment with interferon alfa-2b, starting at 1.5 million U/day and increasing to 3 million U/day after 11 weeks. After an initial tumour progression and a cerebral midline shift, the disease was stable for 8 months.

In April, 2004, the boy had a first focal convulsion, after which treatment with carbamazepine was initiated. Radiological examination detected an increase in the size and number of all lesions (including new lesions in both axillae and the mediastinum). Interferon alfa-2b treatment was discontinued 1 month later because of further tumour progression. Treatment including ifosfamide, doxorubicin, dactinomycin, and vincristine was started according to the protocol of the German Society of Pediatric Hematology and Oncology (GPOH) Cooperative Soft Part Sarcoma study 2002 (CWS-2002P). After three courses of chemotherapy, progression and cystic enlargement of the cerebral lesions caused headache and obtundation. The cyst was drained via a Rickham reservoir, after which we began treatment with thalidomide (two doses of

100 mg/day). The cyst fluid had to be aspirated about every 10 days, because of recurrent episodes of increased intracranial pressure.

Restaging in October, 2004, showed a reduction in tumour load at all sites and revealed progression of the 15 known lesions as well as 12 new pulmonary lesions (figure 2A,C). After November, 2004, thalidomide was no longer available at our institution, and we reintroduced interferon alfa-2b (three doses of 1.5 million U/week) concurrently with chemotherapy. The patient's general condition and cognitive functions deteriorated; he had a secondary generalised seizure, and supplement treatment with valproate was started. After we obtained informed consent from the patient's parents, cytotoxic chemotherapy was discontinued after eight courses and we began treatment with bevacizumab in combination with interferon alfa-2b. Bevacizumab was given intravenously for 1 h at 5 mg/kg in a biweekly schedule, and the dose was increased to 10 mg/kg after four cycles. No substantial side-effects were noted.

Restaging showed a reduction in tumour load at all sites. The best response at the primary site in the psoas muscle was seen after 14 weeks of treatment with bevacizumab, with a reduction from 3.3×2.4×5.9 cm to 2.8×2×4.9 cm. The greatest regression of metastases in the lung was seen after 20 weeks, with the disappearance of three lesions (including two subpleural lesions) and decrease in size of almost all other nodules (diameters of three largest lesions: 3.4 cm reduced to 2.7 cm; 2.7 cm to 1.9 cm; 1.2 cm to 0.9 cm; figure 2). The cerebral metastases regressed until 6 months after the initiation of bevacizumab treatment, with the larger of the two occipital nodules reduced from 3.2×3.5 cm to 2.2×2.5 cm (figure 2). The sum of the longest diameters of these target lesions showed a reduction of 22.7%, according to response evaluation criteria in solid tumours (RECIST).² MRI of the brain also showed a regression of the cerebral oedema and midline shift (figure 2B). No further episode of increased intracranial pressure was recorded, and the patient's cognitive functions improved.

We did in-situ hybridisation for VEGF and VEGF receptors 1 and 2 on the brain metastasis. VEGF mRNA was expressed in most of the tumour cells (figure 1B). We detected mRNA of VEGF receptors 1 (figure 1C) and 2 (figure 1D) in intratumoural endothelial cells. After a progression-free survival period of 6 months, the last radiological scanning in November, 2005, showed a small increase in the size of the tumour cyst, solid cerebral tumour nodules, cerebral oedema, and lung metastases. At the last contact, the patient was still in a good general condition after 26 cycles of bevacizumab treatment. The bi-weekly schedule on an outpatient basis has allowed him to have an almost normal life and to attend school regularly.

The decision to use antiangiogenic treatment for our patient was based on three factors: (1) the high vascularisation of the tumour, (2) the ineffectiveness of cytotoxic chemotherapy regimens in our patient, and

(3) the known benefit of antiangiogenic treatment in tumours that are highly vascularised (eg, angioblastoma)³ and slow-growing (eg, renal-cell carcinomas).⁴ Antiangiogenic drugs can be classified according to their mechanism of action—eg, those inhibiting the breakdown of basement membrane, endothelial-cell migration and proliferation, cell-adhesion molecules, or angiogenic growth factors or their receptors.^{5,6} Additional compounds with established antineoplastic or antiproliferative functions, such as thalidomide or interferon alfa-2b, have been reported to have antiangiogenic activities.^{7,8}

In our patient, interferon alfa-2b treatment was used on the basis of reports describing the drug's effects of tumour stabilisation and regression in metastatic alveolar soft part sarcoma.^{9,10} Since treatment with interferon alfa-2b and thalidomide could not stop progression of disease in our patient, we attempted the use of bevacizumab. Failure of interferon alfa-2b treatment has been reported previously in a 7-year-old girl with metastatic, alveolar soft part sarcoma.¹¹

Bevacizumab is a human monoclonal antibody directed specifically against VEGF α .¹² VEGF is a key regulator of angiogenesis, which binds to the tyrosine-kinase VEGF receptors 1 (FLT1), 2 (FLK1/KDR), and 3 (FLT4); and to the neuropilin receptors 1 and 2.¹² Bevacizumab inhibits VEGF, reduces the number of intratumoural blood vessels, decreases vascular permeability, and induces the formation of a non-altered capillary-growth pattern.⁵ In combination with cytotoxic chemotherapy, bevacizumab is first-line treatment in metastasised colorectal carcinoma.⁸ VEGF expression has been shown in many human tumours¹³ but has not been reported in alveolar soft part sarcoma previously. Tumour regression after the inhibition of VEGF suggests a role of VEGF in the tumour progression of our patient. Furthermore, the reduction in size of the intracerebral tumour cyst and the cerebral oedema during bevacizumab treatment is probably due to a decrease in vascular permeability induced by this drug, as similarly reported elsewhere.¹⁴ An association between the clinical improvement and the cessation of cytotoxic chemotherapy seems unlikely, since the midline shift first appeared well before chemotherapy had been started.

Although spontaneous stabilisation could occur in alveolar soft part sarcoma, this event is unlikely, because of the close temporal correlation between the onset of bevacizumab treatment and tumour regression. Synergistic therapy effects with the cotreatment of interferon alfa-2b could also have further enhanced the effects of bevacizumab. Therefore, we cannot rule out the notion that only the combination of these two drugs led to a response in our patient, nor can we exclude the theory that antibodies against VEGF could have inhibited an autocrine mechanism mediated by other VEGF receptors, such as neuropilin receptors 1 or 2 (or both).

Although regression of the lesions could be achieved, the last radiological controls revealed a small tumour progression in our patient. Loss of efficacy of bevacizumab

could be due to a change in the genetic status of the tumour cells and expression of other proangiogenic factors, processes which are not inhibited by the drug. The emergence of phenotypic resistance to continued antiangiogenic treatment targeting the VEGF pathway has been reported in a study,¹⁵ and has been associated with the induction of other proangiogenic factors. In this study, drugs targeting different angiogenic proteins or mechanisms were thought to still be effective if a compound targeting only one angiogenic factor loses efficacy. Therefore, we plan to treat our patient with antiangiogenic drugs targeting factors other than VEGF.

We conclude that inhibition of the VEGF signalling pathway alone or in combination with drugs targeting other proangiogenic factors could be an important new treatment option in alveolar soft part sarcoma. To further analyse the potential efficacy of antiangiogenic treatment, expression of proangiogenic factors should be studied systematically in alveolar soft part sarcoma.

Conflicts of interest

We declare no conflicts of interest.

Acknowledgments

We thank G Amann for securing pathological diagnosis and for helpful comments, and C Kulinna-Cosentini for radiological assistance in remeasuring the tumour lesions in the lung. A Azizi is supported by a grant from the *Forschungsgesellschaft für cerebrale Tumore*.

References

- Reichardt P, Lindner T, Pink D, et al. Chemotherapy in alveolar soft part sarcomas. What do we know? *Eur J Cancer* 2003; **39**: 1511–16.
- Therasse P, Arbuuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
- Marler JJ, Rubin JB, Trede NS, et al. Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of 2 cases. *Pediatrics* 2002; **109**: E37.
- Beecken WD, Fernandez A, Jousse AM, et al. Effect of antiangiogenic therapy on slowly growing, poorly vascularized tumors in mice. *J Natl Cancer Inst* 2001; **93**: 382–87.
- Jain RK. Antiangiogenic therapy for cancer: current and emerging concepts. *Oncology (Williston Park)* 2005; **19** (suppl 3): 7–16.
- Liekens S, De Clercq E, Neyts J. Angiogenesis: regulators and clinical applications. *Biochem Pharmacol* 2001; **61**: 253–70.
- Folkman J. Angiogenesis inhibitors: a new class of drugs. *Cancer Biol Ther* 2003; **2**: S127–33.
- Lenz HJ. Antiangiogenic agents in cancer therapy. *Oncology (Williston Park)* 2005; **19** (suppl 3): 17–25.
- Kuriyama K, Todo S, Hibi S, et al. Alveolar soft part sarcoma with lung metastases. Response to interferon alpha-2a? *Med Pediatr Oncol* 2001; **37**: 482–83.
- Roosendaal KJ, de Valk B, ten Velden JJ, et al. Alveolar soft-part sarcoma responding to interferon alpha-2b. *Br J Cancer* 2003; **89**: 243–45.
- Bisogno G, Rosolen A, Carli M. Interferon alpha for alveolar soft part sarcoma. *Pediatr Blood Cancer* 2005; **44**: 687–88.
- Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005; **23**: 1011–27.
- Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004; **25**: 581–611.
- Pichelmayer O, Zielinski C, Raderer M. Response of a nonmalignant pleural effusion to bevacizumab. *N Engl J Med* 2005; **353**: 740–41.
- Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005; **8**: 299–309.