

# Secondary polycythemia in a sarcoma patient: a commentary about cediranib

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## INTRODUCTION

Cediranib, a potent inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor subunit B, and the c-Kit receptor tyrosine kinase, has shown antitumour activity as an antiangiogenic agent in preclinical models. Initial clinical trials with cediranib in a variety of tumour types, including glioblastoma multiforme, non-small-cell lung cancer, renal cell cancer, colorectal cancer, and prostate cancer, showed activity comparable to that for other vascular endothelial growth factor (VEGF) inhibitors, but with significant toxicities, resulting in abandonment of the drug's development in 2011. However, recent dramatic results in the ICON6 trial of cediranib in relapsed platinum-sensitive ovarian cancer (which demonstrated a 7.4-month improvement in overall survival) and significant activity in phase II studies in a rare soft-tissue sarcoma, alveolar soft part sarcoma (ASPS), could result in the drug's revival<sup>1,2</sup>. As of October 2017, eleven clinical trials were accruing, and fifty-six clinical trials using cediranib as single agent or in combination with other small molecules or chemotherapy had been completed. Here, we report a case of secondary polycythemia in a patient treated with cediranib for ASPS. Informed consent for publication was provided by the patient.

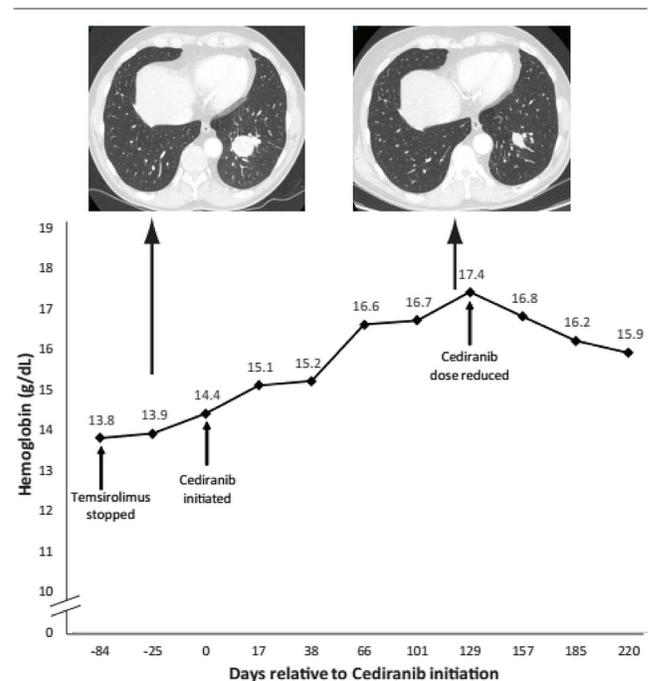
## CASE DESCRIPTION

Our patient is a 57-year-old man who in 2010 underwent resection of a left gluteal ASPS, followed by radiation therapy. Unresectable ASPS lung metastases developed 4 years later, confirmed on biopsy. The patient was treated with sunitinib, but developed disease progression after 6 months. He next received temsirolimus in a clinical trial setting, with disease progression after 18 months of treatment. As part of a compassionate access program, after permission from Health Canada and patient consent had been obtained, our patient was started on oral cediranib 30 mg once daily.

During treatment with cediranib, the patient developed mild hypertension and diarrhea. However, over 18 weeks, his hemoglobin increased to 174 g/L from a baseline of 144 g/L (increase of 30 g/L, Figure 1). His white blood cell count (with differential) and platelet count were both normal. He reported mild headaches without symptoms of thrombus or cerebrovascular accident. He is a never-smoker without a history of respiratory, cardiac, or liver disease, or

a suspicious renal mass. His medications did not include androgens or synthetic erythropoietin. He did not have the *JAK2* V617F mutation characteristic of polycythemia vera. However, his erythropoietin level, at 17.3 U/L (95% reference range: 3.3–15.9 U/L), was higher than the reference for his age and was particularly elevated in the context of his relatively high hemoglobin (167 g/L)<sup>3</sup>. We changed his daily dose of oral cediranib from 30 mg to an alternating schedule (30 mg one day, 15 mg the next) resulting in a decrease of his hemoglobin to 159 g/L and normalization of his erythropoietin at 8.9 U/L.

The patient experienced a partial response of the dominant lung metastasis, with stability of other lung metastases (Figure 1). He has been in partial remission for more than 2 years, with hemoglobin levels ranging stably between 150 g/L and 160 g/L on the daily alternating-dose cediranib regimen.



**FIGURE 1** Increased hemoglobin with cediranib and partial tumour response with reduction in hemoglobin after cediranib dose reduction for alveolar soft part sarcoma.

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## DISCUSSION

At core of this commentary is the issue of attributing a clinical complication, secondary polycythemia, to one of three possibilities: rare manifestation of a rare disease (ASPS), rare adverse effect of a rarely used medication (cediranib), or occurrence of another disease. The rare soft-tissue sarcoma subtype of ASPS, representing 1% of all sarcomas, presents clinically as a deep-seated painless soft-tissue mass that is often metastatic upfront. Although typically indolent, it is often lethal, with a reported 5-year survival rate of 61% at the metastatic stage. We have not been able to find any report of polycythemia as a manifestation of ASPS, or of paraneoplastic secretion of erythropoietin in that disease.

Alveolar soft part sarcoma is refractory to cytotoxic chemotherapy, but VEGF inhibitors have been used with some success. More specifically, an encouraging response rate of 35% has been seen with cediranib<sup>2</sup>, and that drug is now being studied in randomized phase II trials compared with sunitinib or a placebo.

Inhibitors of VEGF such as sunitinib, sorafenib, axitinib, and bevacizumab have been associated with subtle increases in hemoglobin<sup>4</sup>. It has been demonstrated in preclinical models that VEGF inhibition results in erythropoiesis through synthesis of hepatic erythropoietin<sup>5</sup>. Cediranib has high potency for VEGF receptor inhibition, and the dramatic rise in our patient's hemoglobin is, to our knowledge, the highest hemoglobin rise reported in the literature for any VEGF inhibitor. Our extensive work-up did not point to the occurrence of a separate disease process, although such an occurrence cannot be definitively excluded. Our patient developed a long-lasting partial response that has been maintained even with a cediranib dose reduction.

We suggest formal prospective assessment of hemoglobin as a potential biomarker for cediranib in clinical trials.

## SUMMARY

The present case illustrates the difficulty of dealing with an unusual complication in a patient taking a nonregistered drug for an uncommon disease and in the absence of available guidelines. A literature review and clinical judgment helped to achieve successful management.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

## AUTHOR AFFILIATIONS

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