Case: Secondary polycythemia due to pazopanib in patients with metastatic renal cell carcinoma

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Introduction

Clear-cell renal cell carcinoma (RCC) is the most common primary malignant renal neoplasm. Up to 30% of patients have metastatic disease at the time of initial diagnosis.[1] Small molecule inhibitors of vascular endothelial growth factor receptor tyrosine kinase (VEGFR TKIs) are used as first-line treatment for most patients with incurable RCC. Pazopanib is a TKI inhibiting VEGFR,[1-3] as well as platelet-derived growth factor receptors (PDGFRs) α and β and stem cell receptor c-kit. The most common side effects of pazopanib are diarrhea, hypertension, changes in hair colour, anorexia, nausea, and vomiting. Severe hepatic toxicity is the adverse effect of greatest concern,but is uncommon. Myelosuppressive effects are also noted, such as anemia, thrombocytopenia, and leukopenia, and are presumably mediated through c-kit inhibition. Erythrocytosis is a well-recognized paraneoplastic syndrome associated with RCC; however, erythrocytosis due to pazopanib therapy has only recently been described. We report two cases and review of the literature related to this phenomenon.

Case 1

A 55-year-old man presented eight years after partial nephrectomy for clear-cell carcinoma of the left kidney with multiple bilateral pulmonary nodules, low left renal nodules, and a soft tissue lesion in the right orbit. He had right nephrectomy for clear-cell cancer 16 years previously, and had required three cryoablation procedures for recurrent lesions in the left kidney since his partial nephrectomy. Resection of orbital lesion showed clear-cell RCC. He met International Metastatic Renal Cell Carcinoma Database (IMDC) favourable-risk criteria, with a Karnofsky performance score of 90% and corrected calcium and blood counts within the normal range, including hemoglobin (Hb) of 152 g/L (normal range 135–170) and hematocrit (Hct) of 48% (normal range 40–51). Serum creatinine was 150 µmol/L (estimated creatinine clearance 101 mL/min).[2] He started pazopanib 400 mg daily titrated up to 600 mg daily two weeks later.

He was noted to be hypertensive and treated with amlodipine. Four weeks after initiation of pazopanib, the patient's Hb was 182 g/L (Fig. 1) and Hct 56%. The serum erythropoiten level (EPO) was 15.4 IU/L (normal range 2.6–18.5) despite the erythrocytosis. Pazopanib was held and after three weeks Hb was 155 g/L and pazopanib was restarted at 400 mg daily. The patient returned for followup two weeks later and Hb was 175 g/L. Phlebotomy of 500 ml of blood was performed and the patient continued on pazopanib 400 mg daily with monitoring every two weeks. After four weeks a second phlebotomy was performed when the Hb was 171g/L. The patient has remained on pazopanib for 13 months with evidence of objective tumour response, and has received eight phlebotomies to date.

EPO level has been elevated while on pazopanib treatment, ranging from 32.8–40.2 IU/L.

Case 2

A 74-year-old woman presented eight years after right partial nephrectomy for a 6.0 cm Fuhrman grade III, clear-cell RCC with pulmonary metastases. Fourteen months previously, she had metastatectomy of RCC metastases in pancreas by distal pancreatectomy, and 19 years previously, she had left radical nephrectomy for localized clear-cell carcinoma. She met IMDC intermediate-risk criteria, with a Karnofsky performance score of 70% at presentation, normal corrected serum calcium level, and normal blood counts, including baseline Hb of 156 g/L. Pazopanib 200 mg daily was started.

Three months after starting treatment, she was symptomatically hypertensive with Hb 181 g/L, Hct 0.53 L/L, and EPO increased at 43.3 IU/L. Phlebotomy was performed for 500 ml of blood. Pazopanib was discontinued and she has been observed since without evidence of disease progression.

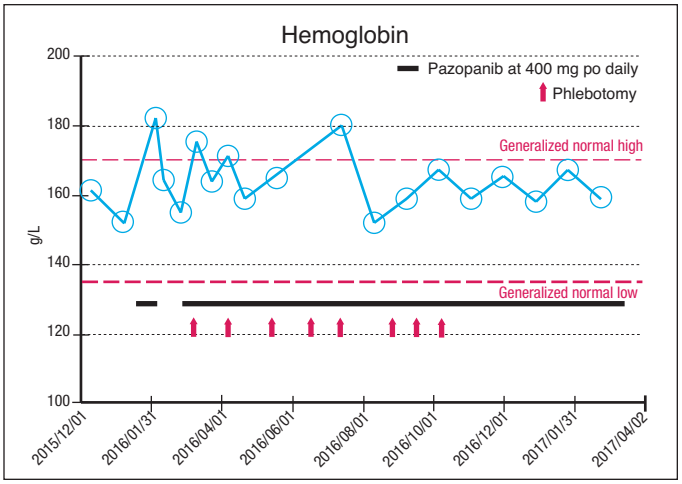

Fig. 1. Hemoglobin response to pazopanib and phlebotomy for case 1.

Discussion

Paraneoplastic erythrocytosis has been observed in 1% of RCC patients undergoing nephrectomy and is thought due to uncontrolled tumour EPO production.[3] EPO is produced by the kidney and mainly regulated transcriptionally by HIF-α, which is overexpressed in most RCCs due to dysfunction of VHL, which is a negative regulator of HIF-α.

We report two cases of secondary erythrocytosis due to treatment of metastatic clear-cell RCC with pazopanib. In those patients, Hb and Hct levels increased significantly from normal baseline levels and normalized when pazopanib was discontinued. Re-challenge in one patient resulted in re-emergence of erythorcytosis. This condition developed rapidly, within weeks of initiation of treatment, and required intervention with therapeutic phlebotomy.

Erythrocytosis due to VEGFR TKIs was first reported by Alexandrescu et al in 2008.[4] Five patients were reported and three had metastatic RCC treated with sunitinib. Alexandre et al reported the same phenomenon in a RCC patient treated with axitininb, and Wang et al recently reported six RCC patients treated with axitinib, pazopanib, or bevacizumab.[5,6] The reports are consistent with our observations of rapid onset within weeks of initiating therapy, frequent occurrence of symptoms related to elevated Hct, unsuppressed or elevated serum EPO levels, and benefit of phlebotomy.

Erythrocytosis induced by VEGFR TKI therapy appears to be due to overproduction of EPO.[7] It has been proposed that the source is the RCC metastases; however, occurrence in patients without RCC and with papillary RCC argue against this.[5,6] We speculate that the source of EPO is the remaining normal kidney tissue. Osumi et al reported secondary polycythemia due to increased EPO production in a patient with leukemic infiltration of the kidneys.[8] HIF-1α expression was present in the renal tubule compressed by the leukemia infiltrate, suggesting intrarenal ischemia. VEGF plays an important role in normal glomerular function, and secondary erythrocytosis may represent an extreme in the spectrum of renal toxicity due to VEGFR TKIs.[9] Both of our patients had prior partial nephrectomies and ablations of their remaining single kidney, and reduced nephron mass may have been a predisposing factor for this toxicity. Tripathi et al recently reported that increases in hemoglobin were associated with a worse prognosis with VEGFR TKI treatment in RCC.[10]

Conclusion

Treatment with pazopanib and other VEGFR TKIs can induce secondary polycythemia. Awareness of this and attention to blood counts and symptoms suggesting erythrocytosis are important in monitoring RCC patients receiving these therapies. Phlebotomy may allow continuation of treatment. Further research is required to understand the etiology of this phenomenon.

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This paper has been peer-reviewed.

References

1. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib vs. sunitinib in metastatic renal cell carcinoma. *N Engl J Med* 2013;369:722-31. https://doi.org/10.1056/NEJMoa1303989
2. Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicentre study. *J Clin Oncol* 2009;27:5794-9. https://doi.org/10.1200/JCO.2008.21.4809
3. Moreira DM, Gershman B, Lohse CM, et al. Paraneoplastic syndromes are associated with adverse prognosis among patients with renal cell carcinoma undergoing nephrectomy. *World J Urol* 2016;34:1465-72. https://doi.org/10.1007/s00345-016-1793-7
4. Alexandrescu DT, McClure R, Farzanmehr H, et al. Secondary erythrocytosis produced by the tyrosine kinase inhibitors sunitinib and sorafenib. *J Clin Oncol* 2008; 26:4047-8. https://doi.org/10.1200/JCO.2008.18.3525
5. Alexandre I, Billemont B, Meric JB, et al. Axitinib induces paradoxical erythropoietin synthesis in metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:472-3. https://doi.org/10.1200/JCO.2008.20.1087
6. Wang W, Cheng J, Mallon C, et al. Symptomatic secondary polycythemia induced by anti-VEGF therapy for the treatment of metastatic renal cell carcinoma: A case series and review. *Clin Genitourin Cancer* 2015;13:e391-5. https://doi.org/10.1016/j.clgc.2015.07.003
7. Ueda K, Suekane S, Chikui K, et al.Successful treatment of erythropoietin-producing advanced renal cell carcinoma after targeted therapy using sunitinib: Case report and review of the literature. *Mol Clin Oncol* 2013;1:112-6. https://doi.org/10.3892/mco.2012.5
8. Osumi T, Awazu M, Fujimura E, et al. Leukemia kidney infiltration can cause secondary polycythemia by activating hypoxia-inducible factor (HIF) pathway. *Eur J Pediatr* 2013;172:829-32. https://doi.org/10.1007/s00431-013-2030-7
9. Doi K1, Noiri E, Fujita T. Role of vascular endothelial growth factor in kidney disease. *Curr Vasc Pharmacol* 2010;8:122-8. https://doi.org/10.2174/157016110790226606
10. Tripathi A, Jacobus S, Feldman H, et al. Prognostic significance of increases in hemoglobin in renal cell carcinoma patients during treatment with VEGF-directed therapy. *Clin Genitourin Cancer* 2017;15:396-402 https://doi.org/10.1016/j.clgc.2016.12.009

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