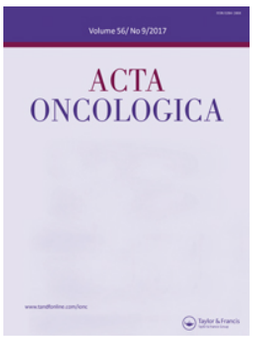

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

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To cite this article: Vicky L. M. N. Soomers, Ingrid M. E. Desar, Nielka P. van Erp, Jeroen Verwiel, Suzanne E. J. Kaal & Winette T. A. van der Graaf (2017) Fatal heart failure in a young adult female sarcoma patient treated with pazopanib, Acta Oncologica, 56:9, 1233-1234, DOI: 10.1080/0284186X.2017.1296582

To link to this article: https://doi.org/10.1080/0284186X.2017.1296582

Published online: 02 Mar 2017.

ACTA ONCOLOGICA, 2017
VOL. 56, NO. 9, 1233–1247
http://dx.doi.org/10.1080/0284186X.2017.1296582

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LETTER TO THE EDITOR

Fatal heart failure in a young adult female sarcoma patient treated with pazopanib

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Soft tissue sarcomas are rare malignancies of mesenchymal origin. Pazopanib is an oral tyrosine kinase inhibitor, targeting vascular endothelial growth factor receptors (VEGF1-2-3), platelet-derived growth factor receptors (PDGFR-α and -β) and stem cell factor receptor (c-KIT) and is approved for patients with metastatic non-adipocytic soft tissue sarcoma after anthracycline-based chemotherapy [1].

Pazopanib is usually well tolerated, with fatigue, diarrhea, nausea, weight loss and hypertension as the most frequently described side effects [1]. Symptomatic left ventricular systolic dysfunction is a rare side effect, occurring in 1% of patients with soft tissue sarcoma, and fatal outcome has been described once [2].

In this case report, we describe fatal congestive heart failure and hepatotoxicity in a young patient, occurring four weeks after commencing pazopanib, with high serum drug levels of pazopanib.

Case presentation

A 27-year-old woman presented elsewhere with potentially resectable liver metastases of a leiomyosarcoma of the colon. Unfortunately, after one cycle of induction chemotherapy with doxorubicin and ifosfamide, bone metastases became overt and were histologically proven, which made a curative treatment intent no longer a realistic option. Therefore, she continued with monotherapy doxorubicin with a palliative intention. After five further courses of doxorubicin, radiological evaluation showed stable disease. Treatment was discontinued after a cumulative doxorubicin dosage of 450 mg/m^2. Six months later, pazopanib 800 mg OD was initiated because of progressive disease. The patient was referred for a second opinion. On presentation, she had been using pazopanib for four weeks, she was complaining of grade 2 fatigue, grade 2 anorexia, grade 3 stomatitis, grade 2 hand–foot syndrome and grade 2 diarrhea. Her lab results showed a decrease in renal function with a creatinine of 117 umol/l and raised liver enzymes (Table 1). The adverse events were considered as pazopanib related and therapy was discontinued. She did not use any other medication.

Two days later, she presented critically ill at the emergency department with progressive dyspnea and severe fatigue since one day. Physical examination revealed that she had a low blood pressure of 67/49 mmHg with a heart rate of 125/min. Her respiratory rate was 24/min and oxygen saturation with room air was 99%. Auscultation of heart and lungs was unremarkable, her liver was not palpable, there was no edema or raised central jugular vein pressure. The electrocardiogram showed a sinus tachycardia with a left axis and left bundle branch block. We had no previous electrocardiograms.

Lab results showed a hemoglobin of 11.3 mmol/l, leukocytes of 8.7 10^9/l and trombocytes of 41 10^9/l. Her liver enzymes had tripled compared to the results two days earlier (Table 1). CRP was 29 mg/l, lactate 7.3 mmol/l. Coagulation parameters showed a PT of 36 sec, APTT 45 sec, D-dimer 26,920 ng/ml and fibrinogen 1050 mg/l.

A CT scan excluded pulmonary embolism and showed stable disease, without pulmonary or new intrahepatic abnormalities. Cardiac ultrasound showed a dilated left and right ventricle with an ejection fraction of 20–25%.

Upon admission, nearly 72 hours after the last dosage of pazopanib, the patient still had high concentrations of pazopanib in her blood (Table 1). Pazopanib half-life was determined based on a second serum level on day two, corresponding with a half-life of 63.5 hours (population average is ~31 hours). This implied that the serum levels on admission corresponded with at least a trough level (a level that is taken at 24 hours after a drug is taken OD) of 65 mg/l. Extrapolation of the serum level on admission to the trough level should be interpreted with caution, since the elimination might have decreased in the course of time, due to worsening of metabolic capacity as a consequence of worsening of liver impairment. Nevertheless, even with the most conservative approach the trough level on admission can be regarded as toxic. Serum levels >20.5 mg/l are associated with more efficacy, while levels >46mg/l are associated with more toxicity [3].

She was admitted to the intensive care unit with serious and most likely pazopanib induced heart failure. She received

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Table 1. Pazopanib serum levels and course of liver enzymes.

	First presentation Day −2	Emergency department Day 0	Day 2	Day 7
Pazopanib (mg/l)	–	37.70	25.23	–
ALT (<35 U/l)	272	1050	3292	716
AST (<30 U/l)	537	2138	10390	532
LDH (<250 U/l)	758	2211	8860	948
gGT (<40 U/l)	20	25	20	26
AF (<100 U/l)	125	126	94	86
Bilirubin (17 umol/l)	22	48	37	127

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vasopressive treatment and treatment with N-acetylcysteine [4]. Viral causes of acute liver failure were excluded. A second cardiac ultrasound showed a non-dilated left ventricle with an ejection fraction of 10–15%, despite high levels of inotropic medication.

Unfortunately, despite maximal supportive treatment on the IC unit, including hemodynamic and ventilatory support, the patient died seven days after admission.

Discussion

We described a 27-year-old patient without cardiovascular history or risk factors, except for previous doxorubicin administration, who developed fatal congestive heart failure during treatment with pazopanib in conjunction with unexplained high trough levels.

A meta-analysis of 10,647 patients treated with several tyrosine kinase inhibitors (TKI) including pazopanib, showed a 2.4% risk of congestive heart failure versus 0.75% in the non-TKI group [5]. High-grade (3 and 4, no fatal cases reported) congestive heart failure occurred in 1.19% of patients receiving TKI, versus 0.65% in the non-TKI group. The relative risk of all grade congestive heart failure was 2.69 ($p \leq .001$) and for high-grade 1.65 ($p = .227$). Median therapy duration was 23 weeks for all TKIs, and 7.4 months and 16.4 weeks for the two pazopanib trials. Remarkably, the congestive heart failure in our patient developed as early as 4 weeks after start of pazopanib.

Hypothetically the previous treatment with doxorubicin could contribute to the occurrence of heart failure, although the PALETTE trial showed a 1% rate of symptomatic left ventricular systolic dysfunction in people treated with pazopanib, while 99% of patients had received anthracyclines [1].

This severe heart failure has not been reported for pazopanib before. The absence of highly increased bilirubin levels and encephalopathy plead against toxic hepatitis. In combination with the rapid recovery, it is most likely this was hypoxic hepatitis secondary to cardiac failure after treatment with pazopanib and doxorubicin. As the liver enzymes were only slightly raised on day −2, we do not think that liver dysfunction explains the prolonged high serum trough levels of pazopanib.

Hepatotoxicity is a well-known adverse event of pazopanib. A meta-analysis of all pazopanib containing trials showed a 42% incidence of all grade ALT increase, and an 9.4% incidence of high-grade ALT increase [6]. There has been little understanding of the underlying mechanism. One case series of two patients showed mild active cholestatic hepatitis with inflammation that predominantly involved portal tracts [7]. However, in this case we concluded that liver failure most likely had a hypoxic origin and was secondary to cardiac failure, although a direct hepatoxic effect of pazopanib due to high trough levels cannot be excluded.

Conclusions

This case shows a fatal outcome of heart failure in a young female patient who had unexplained, high exposure to pazopanib. Next to monitoring left ventricular ejection fraction, therapeutic drug monitoring may be helpful in the future to adapt pazopanib dosages in a timely fashion.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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