

CASE REPORT

Rapid and fatal acute heart failure induced by pazopanib

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SUMMARY

Tyrosine kinase inhibitors, represented by sunitinib, sorafenib, axitinib and pazopanib, are emerging molecules harbouring antitumoural efficacy in multiple neoplasia. We report the case of a 51-year-old woman with right thoracic sarcoma who developed fatal heart failure on pazopanib. The patient had no cardiovascular risk factor, except previous exposure to anthracycline, and her cardiac function was normally controlled before initiating the pazopanib. Despite a rapid tumour response, fatigue rapidly appeared, requiring treatment interruption 2 weeks after pazopanib introduction. After clinical improvement, the pazopanib was reintroduced at reduced dose; however, a few days later, our patient was admitted for worsening dyspnoea and fatigue. Pulmonary embolism was excluded as was pleuropericardial effusion. Brain natriuretic peptide was the only laboratory abnormality, and echocardiography revealed acute and severe heart failure. The patient died despite pazopanib arrest and inotropic support.

BACKGROUND

A better understanding of molecular mechanisms in cancer has led to the development of multiple innovative therapeutic agents, such as tyrosine kinase inhibitors (TKIs). These agents have shown promising efficacy in multiple advanced cancers. Pazopanib is an oral inhibitor of multiple tyrosine-kinase receptors including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). Pazopanib is approved for the treatment of patients with metastatic renal cell carcinoma¹ and metastatic non-adipocytic soft-tissue sarcoma after failure of standard chemotherapy.² These treatments are relatively well tolerated, with fatigue, hypertension and gastrointestinal toxicity as the most frequent side effects. TKI-induced heart failure is less frequently reported and is usually easily manageable after treatment adaptation. In this case report, we describe fatal congestive heart failure occurring rapidly during pazopanib treatment. We highlight the importance of carefully monitoring fatigue and dyspnoea when these appear in patients treated with TKI, particularly patients previously treated with anthracycline, even in case of normal cardiac function before TKI introduction. We also suggest that brain natriuretic peptide (BNP) could be helpful in the diagnosis of cardiac damage induced by TKI.

CASE PRESENTATION

A 51-year-old woman developed important fatigue associated with dyspnoea during pazopanib

treatment. The patient had no known cardiovascular risk factor. Her medical history included a synoviosarcoma diagnosed 4 years prior; the tumour was located on the thoracic wall and was associated with unique cerebral metastasis. The tumour had been treated with surgery (right pneumonectomy and cerebral resection) followed by adjuvant cerebral radiotherapy and chemotherapy (ifosfamide, etoposide and adriamycin).

One year prior to the current presentation, the patient had been admitted with large chest wall recurrence. Owing to inoperability, she received systemic therapy with trabectedine, resulting in disease stabilisation. One month earlier, a CT scan showed a disease progression with apparition of right and continuous thoracic pain. Cardiac function was controlled as normal with a left ventricular ejection fraction (LVEF) around 75% and pazopanib was started at 600 mg once daily. Within the first week, despite pain improvement and a decrease in tumour size, the patient developed progressive symptomatic fatigue. She was hospitalised for grade 3 fatigue and grade 2 dyspnoea 15 days after starting pazopanib. At clinical examination, blood pressure was normal (120/60 mm Hg), heart rate was 80 bpm, left auscultation was normal and there were no signs of cardiac overload or abnormal cardiac auscultation. Haemogram was normal (haemoglobin 12 g/dL), as were electrolytes, and renal and liver function. Troponine-I was not elevated; BNP was not tested at this time. ECG was unremarkable (figure 1). CT scan showed a partial tumoural response and excluded pulmonary embolism and pleuropericardial effusion. Pazopanib was interrupted for 7 days resulting in clinical improvement; it was then reintroduced at 200 mg once daily.

Seven days later, the patient was readmitted for grade 3 dyspnoea and worsening fatigue. She denied any cough, thoracic pain, fever, chills or haemoptysis. At clinical examination, blood pressure was 120/70 mm Hg and heart frequency was elevated at 105 bpm. Transcutaneous oxygen

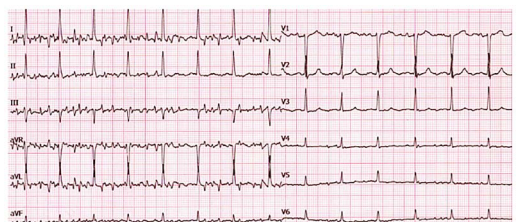


Figure 1 Baseline normal ECG.



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Unexpected outcome (positive or negative) including adverse drug reactions

saturation was normal. Cardiac auscultation revealed a gallop rhythm. Left pulmonary auscultation was normal. There was no hepatjugular reflux and no lower limb oedema.

INVESTIGATIONS

Blood count, renal function, ionogram and hepatic enzymes were in the normal ranges. Troponin-I was slightly elevated at 20 pg/mL (normal range <14), but BNP was over 5000 pg/mL (normal range <100). ECG revealed sinus tachycardia, with diffuse T-wave abnormalities (figure 2). Thoracic CT scan excluded pulmonary embolism and tamponade. Echocardiography revealed diffuse biventricular alteration of the ejection fraction. LVEF was estimated at 10%. There was no sign of pulmonary arterial hypertension or valvular abnormalities. Coronary CT angiography was normal.

TREATMENT

The pazopanib was immediately discontinued; aspirin and a low dose of ACE inhibitor were started.

OUTCOME AND FOLLOW-UP

Although the patient was stable for 3 days, the situation subsequently worsened dramatically. Signs of circulatory insufficiency and ischaemic hepatitis appeared. The patient died, despite inotropic support at the cardiac intensive care unit.

DISCUSSION

We report a case of rapid and fatal heart failure after introduction of pazopanib in a patient without cardiovascular history or risk factors besides previous anthracycline administration. Heart failure in a case of thoracic sarcoma treated with TKI could have multiple potential causes, including disease progression with pericardial and pleural involvement, or prior anticancer treatment such as radiotherapy and anthracycline. In this case, some features led us to consider the hypothesis of pazopanib-induced heart failure, such as the absence of tumour progression, the normal baseline cardiac function and the short time between pazopanib introduction and the onset of symptoms.

Pazopanib belongs to the TKI family, which also includes sunitinib, sorafenib and axitinib, all commonly used in multiple cancers. Pazopanib inhibits the tyrosine kinase receptors VEGFR-1, 2 and 3, the PDGFR α and β , and c-kit, resulting in a significant inhibition of tumour vessel formation. The most frequent side effects of TKI are fatigue, hypertension and gastrointestinal disorders. Cardiac failure induced by TKI appears far less frequently. A meta-analysis of multiple phase II and III trials in different neoplasia demonstrated that the risk of congestive heart failure associated with several approved VEGFR TKI's, such as sorafenib, sunitinib and pazopanib, is 2.39%, with high grade congestive heart failure occurring in

only 1.19% of patients.³ The frequency of cardiac dysfunction seems more important in a study validating the use of pazopanib in patients with advanced sarcoma; in this population previously treated with anthracycline, a LVEF decrease occurred in 16 of the 246 (6.5%) patients treated at a daily dose of 800 mg, but only 3 were symptomatic.² However, whether previous anthracycline treatment increases the risk of TKI-induced cardiotoxicity remains unknown.

Cardiac toxicity is usually easily manageable with TKI interruption and cardiovascular treatment. An observational study evaluated cardiotoxicity in 74 patients with metastatic renal cancer treated with sunitinib or sorafenib. Cardiac events, defined as the occurrence of increased enzymes if normal at baseline, symptomatic arrhythmia, new left ventricular dysfunction, or acute coronary syndrome, appeared in up to 33.8% of patients; half of these patients were totally asymptomatic. All symptomatic patients and some asymptomatic patients underwent cardiovascular treatment, recovered and were considered eligible to resume TKI treatment.⁴

The hypothesis on the underlying cardiotoxicity induced by TKI concerns the physiological role of TKI's targets. VEGF is a growth factor that stimulates cell growth, survival and proliferation through multiple signalling pathways. In a rabbit-model of left ventricular hypertrophy, promoting capillary growth with VEGF reduces apoptosis, preserves myocardial contractile function, and delays the onset of heart failure.⁵ Moreover, PDGFR expressed in cardiomyocytes has been demonstrated to exert a cardioprotective angiogenic function.⁶ This thus suggests that VEGFR and PDGFR inhibition could induce cardiomyocyte apoptosis and prevent correct cardiac remodelling, resulting in ventricular dysfunction. Furthermore, off-target inhibition of AMP-activated protein kinase, a kinase that plays key roles in maintaining metabolic homeostasis in the heart, could account also for the toxicity seen in cardiomyocytes exposed to TKIs.⁷

In our patient, it is important to note that fatigue appeared rapidly with pazopanib. Because fatigue is a frequent TKI symptom, because echocardiography had been recently performed and because there was initially no clinical sign of cardiac failure, complete cardiac examination, including echocardiography and BNP, was not rapidly performed. It is, however, possible that fatigue was already the reflection of arising cardiac decompensation. As the use of TKI's gain clinical indications, there is an urgent need to develop biomarkers in the early

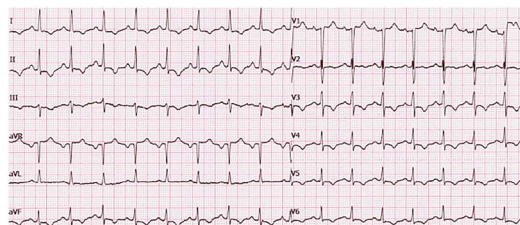


Figure 2 ECG revealing diffuse T wave abnormalities 1 month after pazopanib onset.

Learning points

- ▶ Tyrosine kinase inhibitor (TKI)-induced cardiac failure is real and life-threatening. Cardiac function has to be carefully monitored during the TKI course, particularly in case of previous anthracycline administration and also in cases of baseline normal cardiac function.
- ▶ Although frequently observed with TKI, fatigue could appear as an early clinical sign of cardiac dysfunction. Fatigue developing in a patient with a cardiovascular history or prior anthracycline administration should lead to cardiac monitoring.
- ▶ Brain natriuretic peptide (BNP) could appear as an interesting biomarker of cardiac function, and may be more promising than troponin-T. BNP should thus be evaluated in a clinical trial to find a uniformed non-invasive algorithm in order to monitor TKI-induced cardiotoxicity.

evaluation of cardiotoxicity. As a well-studied marker of myocardial injury, troponin-I has been studied as a surrogate marker of subclinical cardiotoxicity induced by TKI, but this needs to be validated.⁸ BNP is a marker reflecting abnormal filling pressures. In this reported case, BNP was clearly abnormal compared to troponin-I, suggesting that BNP could appear as an interesting marker. To the best of our knowledge, there are no prospective studies regarding its use to assess the risk of VEGFR TKI-induced cardiac dysfunction.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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