Case Report

Pazopanib-Induced Reversible Left Ventricular Systolic Dysfunction

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Pazopanib is a tyrosine kinase inhibitor used for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma. The authors describe a patient with advanced renal cell carcinoma who developed severe hypertension and severe left ventricular systolic dysfunction after starting pazopanib therapy with subsequent recovery of left ventricular ejection fraction upon treatment interruption.

Keywords: Pazopanib, Cardiotoxicity, Heart failure

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Pazopanib is an oral inhibitor of multiple tyrosine kinase receptors including vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR). It is approved for the treatment of patients with advanced renal cell carcinoma (RCC)[1] and advanced soft-tissue sarcoma after failure of standard chemotherapy[2]. It is relatively well-tolerated, with fatigue, nausea, diarrhea and hypertension as the most frequent side effects. There is less evidence about pazopanib-induced cardiotoxicity. Only rare cases of cardiac dysfunction have been reported in association with pazopanib including apical ballooning and rapid fatal cardiac decompensation[3-7].

The case illustrates congestive heart failure (CHF) occurring during pazopanib treatment. The authors highlight the adverse cardiovascular effects of tyrosine kinase inhibitor (TKI) including severe hypertension and cardiomyopathy regardless of prior exposure to anthracyclines. Immediate discontinuation of a potential agent, blood pressure control, and optimizing medical treatment can lead to recovery of left ventricular systolic function with normalization of ejection fraction.

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Case Report

A 66-year-old man suffered from dyspnea and orthopnea. His medical history was significant for clear cell RCC with lung metastasis and hypertension treated with losartan. Owing to inoperability, he was recently started on pazopanib for systemic treatment of metastatic RCC. The starting dose was 800 mg daily. Within the third week of starting pazopanib, the patient developed dyspnea and orthopnea. His blood pressure was 178/122 mmHg, heart rate was 110 beats per minute, respiratory rate was 22 breaths/min, and oxygen saturation was 96% on room air. Physical examination was unremarkable. His electrocardiography (ECG) showed sinus tachycardia, left axis deviation, left atrial enlargement and poor R progression. His troponin-I was 2,042 ng/L without significant serial changes. NT-pro BNP rose to 21,235 pg/mL. Thyroid function test was normal. A transthoracic echocardiography (TTE) revealed dilated left atrium and left ventricle with global left ventricular systolic dysfunction and left ventricular ejection fraction (LVEF) of 15%. Grade II diastolic dysfunction was found. Right ventricular systolic function was borderline reduced.

Furosemide was initiated to relieve his symptoms. The pazopanib was immediately discontinued as it might be a potential cause of cardiomyopathy. The patient had been treated with sacubitril/valsartan, bisoprolol, digitalis, isosorbide dinitrate and hydralazine. He underwent cardiac catheterization which revealed non-significant coronary lesion. Cardiac magnetic resonance imaging was scheduled two weeks later and revealed LVEF of 40% with global hypokinesis and normal right ventricular systolic function, possibly reflecting the recovery of ventricular systolic dysfunction. Neither evidence of myocardial scar nor myocarditis was detected. The patient subsequently underwent repeat TTE three weeks after pazopanib discontinuation, which revealed recovery of LVEF to 60%. No differences were observed in the computed tomography appearances of lung metastases comparing to the prior study.

He was subsequently started on immunotherapy with nivolumab.

Discussion

Cardiovascular risk increases with age even in healthy adults given the higher prevalence of comorbid conditions such as hypertension, diabetes, and atherosclerotic disease. Cancer and cardiovascular disease share many common risk factors. This could in part explain why cardiovascular comorbidities are common in patients with RCC. The cardiovascular side effects of pazopanib should be especially concerned.

Pazopanib has a multimodal mechanism of action, including inhibiting cell surface VEGF, PDGF, fibroblast growth factor receptors, and decline in mitochondrial function. VEGF plays a central role both in maintaining a well-vascularized myocardium and in developing a robust neovascular response to chronic ischemic changes or pressure overload[8]. In a rat-model of left ventricular hypertrophy, promoting capillary growth with VEGF reduces apoptosis, preserves myocardial contractile function, and delays the onset of heart failure[9]. Moreover, PDGF expressed in cardiomyocytes, also a target of pazopanib, has been demonstrated to exert a cardioprotective angiogenic function[10]. Thus, VEGF and PDGF receptor inhibition could induce cardiomyocyte apoptosis and prevent cardiac remodeling, resulting in ventricular dysfunction. Hypertension is also an important risk of HF.

A recent meta-analysis of 10,647 patients treated with different kinds of TKI, including pazopanib, found a significantly increased risk of CHF), 2.4% (138 of 5,752 patients, RR 2.69, 95% CI: 1.86 to 3.87, p<0.001) versus

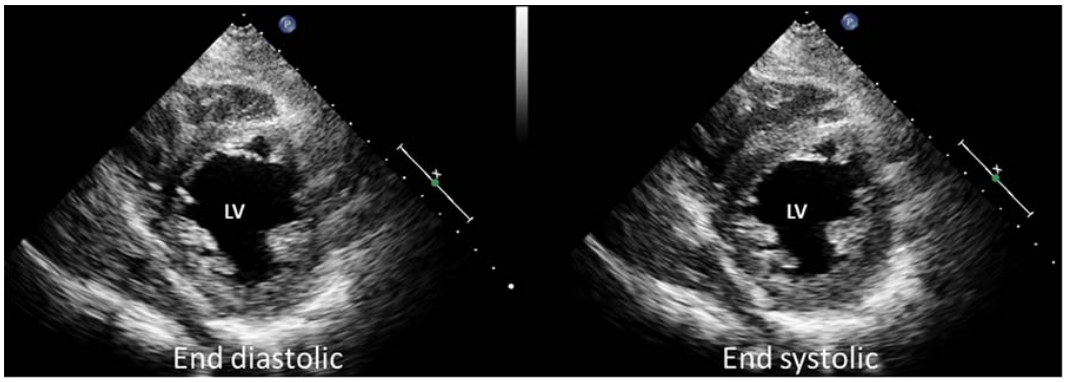

Figure 1. Showed the end-systolic and end-diastolic frames of the left ventricular (LV) short-axis view from initial transthoracic echocardiography, which revealed severe LV systolic dysfunction (ejection fraction 15%).

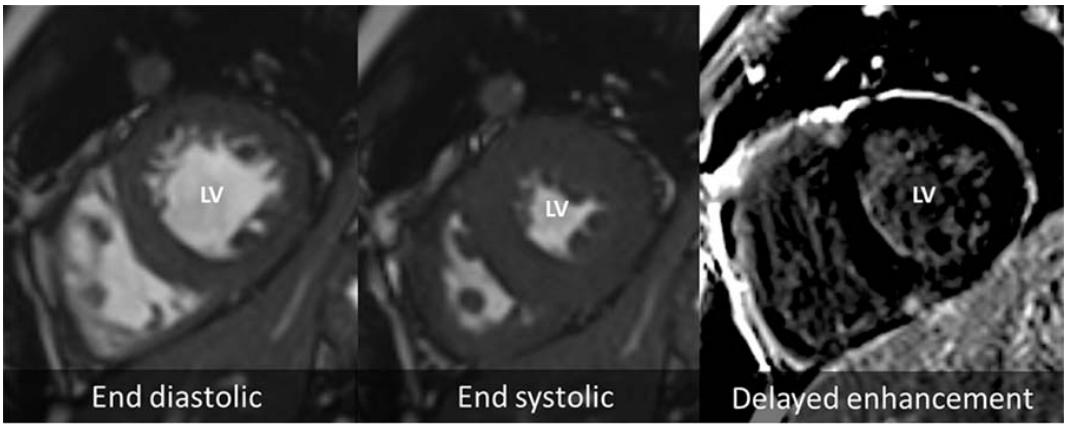

Figure 2. Demonstrated the end-systolic and end-diastolic frames of the left ventricular (LV) short-axis view from cardiac magnetic resonance performed at two weeks after the onset of symptom. There was a significant interval improvement of LV systolic function without scar detected from the delayed enhancement image.

0.75% (37 of 4,895 patients) in the non-TKI group. High-grade CHF occurred in 1.19% (17 of 1,426 patients) receiving VEGFR TKIs and 0.65% (8 of 1,232 patients) in the non-TKI group[11]. A comprehensive meta-analysis of 10,553 patients from 36 clinical trials unveiled the use of VEGFR-TKIs significantly increased the risk of developing all grade (OR 2.37, 95% CI 1.76 to 3.20, p<0.001) and high grade (OR 3.51, 95% CI: 1.74 to 7.05, p<0.001) CHF. Notably in three trials of pazopanib found 6.1% incidence of CHF (21 of 353 patients) OR 2.40, 95% CI 1.01 to 5.69, p=0.047[12]. In the pazopanib for metastatic soft tissue sarcoma (PALETTE) trial of 372 patients, left ventricular systolic dysfunction occurred in three patients (2.4%) in the placebo group and 16 patients (6.5%) in the pazopanib group, of which three were asymptomatic during or after treatment. Notably in this trial, 99% of patients had previously received anthracyclines. Interestingly, 88% of the patients who developed cardiac dysfunction also had concurrent hypertension, which was probably a contributing factor. LVEF had improved in eight patients, of whom, five continued pazopanib and three discontinued for other reasons[2]. In a phase III trial of 362 RCC patients treated with pazopanib, 1% incidence of symptomatic HF and 9% incidence of an absolute LVEF decline of 15% or greater was observed[13]. Hall et al evaluated 159 patients receiving TKIs including pazopanib for the treatment of advanced RCC and showed that the cardiotoxicity related to all study drugs when hypertension was excluded varied from occurrences of asymptomatic drops in LVEF to severe HF was 33%, and the rate of decreased LVEF related only to pazopanib was 7%, which are higher than the general reports in the literature[14].

Although most patients with soft tissue sarcoma had received doxorubicin as first-line treatment, which is known for its cumulative cardiotoxicity, the incidence of pazopanib-induced cardiotoxicity was not higher than patients with RCC. Thus, whether previous anthracycline treatment increases the risk of TKI-induced cardiotoxicity remains unknown.

The timing between initiation of treatment and onset of cardiac dysfunction is variable. In the current case, the patient developed heart failure and severe left ventricular systolic dysfunction within three weeks of starting pazopanib, regardless of previous anthracycline administration. Symptoms were substantially resolved. LVEF returned to normal within three weeks after interruption of pazopanib. Considering life-threatening adverse effect, pazopanib was permanently discontinued. A previous case reported of a young patient without any cardiovascular history apart from previous treatment with doxorubicin, who presented with fatal heart failure 4 weeks after initiating treatment with pazopanib has been recently published[4]. Another report of a patient without cardiovascular risk factors besides previous treatment with anthracycline, who presented with fatigue and dyspnea two weeks after starting pazopanib and initially improved following interruption of pazopanib for a week. Subsequently, a lower dose of pazopanib was reintroduced which caused recurrence of patient's dyspnea and fatigue and reduced LVEF at 10%. Despite immediate discontinuation of the pazopanib, the patient died.[5] It remains unclear whether the cardiomyopathy induced by pazopanib is reversible or not.

Interestingly, a recent report of a 47-year-old male patient with metastatic RCC with no significant past medical history showed an improvement in his LVEF from 20% to 25% to 43% within 7 months after starting a low dose of pazopanib 400 mg daily titrated up to 800 mg daily[15]. CHF could represent a paraneoplastic phenomenon, as improvement was noted in the patient's LVEF after systemic treatment, accompanied with resolution of anemia and thrombocytosis. There has been a report of patient with RCC who presented with heart failure[16], which has been hypothesized as due to catecholamine-mediated myocardial stunning[17]. This generates the dilemma of whether pazopanib use should be precluded in low ejection fraction states or could be used in gradually uptitrated doses.

The actual incidence of pazopanib-induced cardiotoxicity is uncertain. Given the widespread use of this agent, there might be increased incidence of CHF in future. Proper cardiovascular monitoring methods are needed to accurately measure asymptomatic and symptomatic cardiac dysfunction. Cardiotoxicity should always be kept in mind in the management of patients using pazopanib. However, the optimal screening method and interval are unclear. Although, recommendations of careful clinical assessment, routine ECG and TTE have been made for all patients exposed to TKIs, sequential monitoring may be reserved for selected elderly patients or high-risk patients with cardiovascular comorbidities such as preexisting hypertension or cardiomyopathy, preceding treatment with anthracycline[18]. Additionally, decreases in the left ventricle longitudinal strain may indicate early subclinical cardiac dysfunction as marker of cardiotoxicity[19]. Brain natriuretic peptide (BNP) could appear as an interesting biomarker of cardiac function. BNP should thus be evaluated to find a uniformed non-invasive algorithm in order to monitor TKI-induced cardiotoxicity. When HF develops, pazopanib should be discontinued immediately, and it should be managed with standard HF therapies, whereas for grades 1 to 2 cardiotoxicity, pazopanib could be continued at the current dose or restarted at a lower dose while treating the cardiotoxicity[20].

Conclusion

This current case will add to the available literature about this potentially life-threatening complication associated with TKI therapy while demonstrating the potential reversibility of cardiotoxicity with normalization of LVEF by cessation of therapy along with optimizing medical treatment. There may be a spectrum of the severity of cardiotoxicity whether the cardiomyopathy induced by pazopanib is reversible or not.

What is already known on this topic?

There is limited evidence of pazopanib-induced

cardiotoxicity and spectrum of disease severity. Only rare cases of cardiac dysfunction have been reported in association with pazopanib including apical ballooning and rapid fatal cardiac decompensation.

What this study adds?

This current case will add to the available literature of a life-threatening complication associated with pazopanib while demonstrating the potential reversibility of cardiotoxicity with normalization of LVEF by cessation of therapy along with optimizing medical treatment.

Potential conflicts of interest

The authors declare no conflict of interest.

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