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### Cover Page Footnote

None acknowledgments.

# Fatal Heart Failure Induced by Pazopanib in a Sarcoma Patient Previously Treated with Gemcitabine

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## Abstract

Gemcitabine is commonly used for various solid organ malignancies with rarely reported cardiac side effects such as cardiomyopathy. Pazopanib usually can cause arterial hypertension but cases of heart failure have recently been reported. We describe a case of fatal heart failure after treatment with gemcitabine and pazopanib in a 55-year-old female with sarcoma. Patient developed left ventricular dysfunction after gemcitabine treatment and acute heart failure after 22 days of pazopanib treatment which led to death. Physicians should be aware of the cardiotoxicity risk when managing the use of pazopanib especially in patients previously treated with other cardiotoxic drugs.

**Keywords:** cardio-oncology, cardiotoxicity, heart failure, pazopanib, gemcitabine

## 1. Introduction

Gemcitabine is a nucleoside analog and pyrimidine antimetabolite that inhibits RNA synthesis [1]. The most common adverse effects of its use being myelosuppression, elevated liver enzymes, edema, and dyspnea [2]. In regards to cardiac complications, gemcitabine is associated with venous thromboembolisms, digital ischemia or necrosis, systemic capillary leak syndrome, vasculitis, arrhythmias and thrombotic microangiopathy [3]. Although rare, gemcitabine therapy can cause cardiotoxicity in the form of acute congestive heart failure [4]. On the other hand pazopanib is an oral multi-targeted tyrosine kinase inhibitor (TKI), targeting vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and stem cell factor (c-KIT)

receptors [5,6]. It is approved for the treatment of metastatic renal cell carcinoma (RCC) and soft tissue sarcoma [5,6]. It is usually a well-tolerated oral agent. The main side effects are fatigue, nausea, diarrhoea and arterial hypertension. The increased use of TKI agents has been associated with recognition of a potentially fatal spectrum of toxicities, including cardiotoxicity, sometimes even fatal [6,7].

Here, we present a complex case of a female patient with mesenchymal tissue neoplasm, previously treated with gemcitabine, with a fatal pazopanib induced heart failure.

## 2. Case Report

A 55-year-old woman presented with persistent right hip pain, hypotonia and paresthesia on the right leg, for ten months in March 2019. The patient had a smoking history of ten pack-year until her

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diagnosis, no other cardiovascular risk factor. The patient had no other systemic disease history. Pelvic magnetic resonance imaging (MRI) showed bone edema and hypodense/hypointense streak on the right hip. A guided computed tomography (CT) tract biopsy was performed, the histopathological examination of the tissue sample diagnosed a mesenchymal tissue neoplasm with myofibroblastic differentiation spindle cell sarcoma. Furthermore, diffuse lytic bone metastases and multiple pulmonary nodular-like lesions were found at 18 F-fluorodeoxyglucose positron emission tomography (PET) - CT. The mass was considered unresectable, and gemcitabine-based systemic chemotherapy after localized radiotherapy at lytic bone metastases was planned. Before the systemic treatment, transthoracic echocardiography (TTE) was performed in March 2019 and left ventricular ejection fraction (LVEF) was measured as 60%. Gemcitabine and zoledronic acid treatment was started. After six months, at second follow up visit, a control TTE showed a mild decrease in left ventricular ejection function measured as 48%. Therefore gemcitabine was stopped and medical therapy was optimized by starting ramipril 2.5 mg orally once daily and bisoprolol fumarate 1.25 mg orally once daily. After one month at follow up, considering stability of cardiologic and echocardiographic status and for detection of tumor progression at control CT, pazopanib was planned as a second line treatment. Pazopanib was started at a dose of 800 mg once daily in October 2019. On the 22<sup>nd</sup> day of treatment, she presented with palpitation, fatigue and exertional dyspnea for one week. The blood pressure was measured as 120/60 mmHg, the heart frequency was 112 beats per minute, the respiration rate was 18 breaths per minute, and there was no high fever. Bilateral pretibial pitting edema was noted. There was a third heart sound on the auscultation of the heart and were bilateral basal crackles on the auscultation of the lungs. She was hospitalized, and blood tests including complete blood count, kidney and liver function tests, C-reactive protein (PCR), thyroid stimulating hormone, coagulation parameters, Troponin-T (two values at 0 and 2 h), N-terminal (NT)-pro hormone BNP (NT-proBNP), arterial blood gases were obtained. Blood analyses showed: mild normochromic normocytic anemia (hemoglobin: 10.5 g/dl), NT-proBNP markedly increased (10,860 pg/ml). All the other blood analyses were in normal values. The electrocardiogram showed sinus tachycardia, nonspecific ST-T changes. Pulmonary embolism was ruled out by considering clinical findings, arterial blood gas analysis, and electrocardiogram findings as a whole.

Echocardiography was performed, and LVEF was measured as 20%. As a result, patient was admitted to the sub intensive care unit, pazopanib-induced heart failure (HF) was considered and pazopanib was stopped immediately. Medical therapy has been optimized as follows: ramipril 2.5 mg orally once daily has been confirmed, bisoprolol fumarate has been increased to 2.5 mg orally once daily, and spironolactone 50 mg orally once daily, furosemide 20 mg intravenous twice a day were started. The patient's symptoms partially improved. Second echocardiography was performed after two days, and LVEF was measured as 30%. After an initial apparent stabilization, the patient died during hospitalization for cardio-respiratory arrest.

### 3. Discussion

Our case describes a rare but fatal cardiovascular complication of gemcitabine and pazopanib treatment. Few cases are reported in the literature about cardiac dysfunction caused by isolated treatment with gemcitabine [1]. Some cases reported cardiomyopathy induced by gemcitabine after treatment with cardiotoxic anticancer drugs such as anthracyclines [8]. Generally treatment with gemcitabine can cause supraventricular tachycardia including atrial fibrillation, especially after 18–24 h of infusion [8]. In addition, several case reports have demonstrated acute myocardial infarction post-gemcitabine injection secondary to drug-induced vascular injury or endothelial damage [9–10].

Also pazopanib usually causes arterial hypertension and in a few cases heart failure [11]. Especially several case of fatal heart failure after pazopanib are reported [12].

In our case, gemcitabine caused left ventricular dysfunction in a patient without cardiovascular risk factors (only smoking); after gemcitabine treatment, pazopanib caused fatal heart failure. Cardioprotective treatment (beta blockers and ramipril) was started during the first reduction of LVEF during gemcitabine treatment; gemcitabine treatment was discontinued for 1 month in accordance with guidelines and it was restarted 1 month later, considering the stable value of LVEF and the necessity of oncological treatment in a patient with advanced cancer.

Thus, gemcitabine and pazopanib-induced HF are not very frequent but unfortunately may be fatal. Physicians and patients should be aware of the cardiotoxicity risk when managing the use of pazopanib, especially in patients previously treated with other cardiotoxic drugs such as gemcitabine. This highlights the importance of performing a complete

cardiac workup before starting this type of treatments and during follow-up.

### Author Contribution

Di Lisi: Conception; Design; Supervision; Fundings; Materials; Data collection and/or processing; Analysis and/or interpretation; Literature review; Writer; Critical review.

Manno: Conception; Design; Supervision; Fundings; Materials; Data collection and/or processing; Analysis and/or interpretation; Literature review; Writer; Critical review.

Novo: Conception; Design; Supervision; Fundings; Materials; Data collection and/or processing; Analysis and/or interpretation; Literature review; Writer; Critical review.

Russo: Conception; Design; Supervision; Fundings; Materials; Data collection and/or processing; Analysis and/or interpretation; Literature review; Writer; Critical review.

Filorizzo: Conception; Design; Supervision; Fundings; Materials; Data collection and/or processing; Analysis and/or interpretation; Literature review; Writer; Critical review.

Santanelli: Supervision.

Guarino: Supervision.

Lunetta: Fundings.

Badalamenti: Materials.

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