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Coronary Stenosis in a Patient Under Pazopanib Therapy: A Case Study

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Abstract :
Tyrosine kinase inhibitors have transformed therapeutic approaches to cancer, marking a major advance in oncology. This article presents the clinical case of a 59-year-old moroccan patient with metastatic clear cell kidney cancer treated with pazopanib, who developed a cardiac vascular accident through coronary stenosis after 24 months of treatment with pazopanib. The main objective of this article is to illustrate the side effects of anti-angiogenic drugs and the crucial importance of monitoring these toxicities, particularly those of vascular origin, in order to prevent serious complications that could compromise the prognosis of a patient, regardless of the cancer disease itself. This case highlights the need for regular assessment of cardiovascular risk factors in patients receiving treatment with pazopanib, as well as increased vigilance for the appearance of signs or symptoms suggesting hematological or hepatic toxicities. Early and appropriate management of toxicities is essential to optimize the safety and effectiveness of renal cancer treatment with pazopanib, while preserving the patient's cardiovascular health.

Keywords : Tyrosine kinase, Pazopanib, oncocardiology, kidney cancer

I. Introduction:

Targeted therapies have revolutionized cancer treatment, allowing for better therapeutic management. Tyrosine kinase inhibitors (TKIs) have shown significant utility in the treatment of various malignancies and solid tumors, notably non-small cell lung cancers, gastrointestinal stromal tumors, and HER2-positive breast cancers. In clear cell renal cell carcinoma (RCC), they have substantially improved survival. Pazopanib, a tyrosine kinase inhibitor with antiangiogenic activity targeting multiple receptors such as vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), platelet-derived growth factor receptors (PDGFRα and PDGFRβ), and stem cell factor receptor (c-KIT), finds its indication in the treatment of metastatic clear cell renal cancer. [1]

Despite radically altering the natural course of many cancers, these treatments can lead to cardiac and extracardiac complications. This article illustrates the case of a patient monitored for metastatic clear cell renal cancer treated with pazopanib for 24 months, who experienced cutaneous, hepatic, and hematologic toxicities during treatment, complicated by severe cardiac toxicity.

II. Case Study:

The patient is a 72-year-old Moroccan male, hypertensive for 20 years on calcium channel blocker monotherapy, with no surgical history, nonsmoker, followed at the National Oncology Institute of Rabat for renal cancer. He underwent nephrectomy revealing clear cell renal carcinoma grade 2 according to the Fuhrman classification, staged T3a N0 Mx (TNM 2009), invading perirenal fat, adrenal gland, and healthy ureteral margins. Postsurgical evaluation showed pulmonary nodules, and baseline tests were normal. He initiated nephroprotective antihypertensive therapy with an ACE inhibitor before starting pazopanib at 800 mg daily in March 2020. After two months, he developed hepatic cytolysis, followed by grade III hand-foot syndrome and grade 2 thrombocytopenia, leading to dose reduction to 400 mg daily. Radiological evaluation at six months showed stable lesions, with a 20% reduction at 12 months. After 24 months, he developed jaundice and hepatic cholestasis, prompting treatment interruption and subsequent resumption at 200 mg daily. Four months later, he presented progressive general deterioration and abrupt dyspnea, revealing anterior interventricular artery stenosis, requiring coronary angioplasty.

III. Discussion:

Therapeutic progress in anti-cancer treatments has led to improved prognosis for several cancers. The emergence of targeted therapies has significantly increased the life expectancy of patients with metastatic clear cell renal cancer (mRCC), while the increased risk of cardiovascular events proves to be an obvious side effect.[2] These therapies are characterized by the specific inhibition of certain signaling pathways, particularly inhibitors of the vascular endothelial growth factor (VEGF) signaling pathway, hence the vascular side effects. Angiogenesis is a crucial pathway for tumor growth, so its inhibition helps to halt tumor growth and the development of metastases.[3]

Pazopanib (GW786034-Votrient®) is a synthetic indazolylpyrimidine administered orally. It is a protein tyrosine kinase inhibitor with antiangiogenic activity targeting multiple receptors: vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), platelet-derived growth factor receptors (PDGFRα and PDGFRβ), and the stem cell factor receptor (c-KIT). Additionally, albeit to a lesser extent, it also inhibits fibroblast growth factor receptors (FGFR-1 and FGFR-3).[4]

Astudy conducted at the Wexner Medical Center of The Ohio State University evaluating the cardiovascular risk associated with pazopanib suggests that it possesses a multifaceted cardiovascular toxicity profile. This profile includes cardiomyopathy ranging from asymptomatic reduction in left ventricular ejection fraction (LVEF) to fatal cardiogenic shock, cardiac repolarization disorders characterized by prolonged QTc interval, and a striking hypertensive response, primarily within 30 days of pazopanib initiation, associated with pazopanib dose reduction. [5]

Understanding how multikinase inhibitors act, it becomes evident that there is a close relationship between the development or worsening of arterial hypertension, especially if it is present before the start of treatment[6]. In various trials, the incidence of arterial hypertension with single-agent therapy was 42% with pazopanib, 63-68% with ponatinib, 7-43% with sorafenib, 5-24% with sunitinib, 40% with axitinib, and 30-59% with regorafenib [7,8]. Therefore, close monitoring of blood pressure and other cardiovascular risk factors is recommended for a better selection of TKIs adapted to patients' comorbidities. Although this elevation in blood pressure is a high-risk side effect, it has been reported to be an indicator of therapeutic response [9,10]. There is a substantial increase in the risk of cardiac ischemia and a smaller increase in the risk of cardiac dysfunction and arterial thromboembolism.[11]

Small molecule tyrosine kinase inhibitors (TKIs) are associated with an increased incidence of myocardial ischemia or infarction, as well as angina pectoris. In addition to acute coronary syndromes, they exhibit non-targeted vascular pro-atherogenic properties, inducing arterial stenosis and vasospasm. This can be explained by the reduction in nitric oxide (NO) production and mitochondrial superoxide production following VEGF inhibition. [12,13]

IV. Conclusion:

This article highlights cardiac toxicity associated with pazopanib use in renal cancer treatment. While pazopanib effectively controls disease, recognizing and carefully monitoring potential cardiovascular adverse effects in treated patients is crucial. Cardiotoxicity is linked to its antiangiogenic mechanism of action affecting the vascular network. Severe toxicity observed in some patients often correlates with other comorbidities such as age, obesity, and pre-existing cardiovascular diseases, underscoring the importance of early assessment of cardiovascular risk factors and close monitoring throughout treatment. Proper management of treatment-related toxicities is essential to optimize therapeutic benefits while minimizing cardiovascular health risks for patients.

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