



Introduction to Tyrosine Kinase Inhibitors: Pazopanib Cardiotoxicity

5

David P. Dundua, Ana G. Kedrova, Ekaterina V. Plokhova,
Elena A. Zvezdkina, and Olga A. Drobiazko

Key Points

- The understanding of the role of dysregulated tyrosine kinases in cancer has produced a literal explosion in approaches to cancer treatment.
- Multikinase inhibition, although effective for cancer control, increases the likelihood of cardiovascular toxicity.
- TKIs used in cancer care have been associated with heart failure, arterial and venous vascular toxicities including myocardial ischemia and infarction, systemic and pulmonary hypertension, pulmonary embolism, peripheral vascular disease, thrombosis, QT prolongation, ventricular arrhythmias, and atrial fibrillation.

Electronic supplementary material

The online version of this chapter (https://doi.org/10.1007/978-3-030-70998-3_5) contains supplementary material, which is available to authorized users.

D. P. Dundua (✉) · E. V. Plokhova
Cardiology Center, Federal Scientific and Research Center,
FMBA Russia, Orekhovy Bulvar, 28, 115285 Moscow, Russia
e-mail: david.doundoua@gmail.com

E. V. Plokhova
e-mail: evplokhova@gmail.com

A. G. Kedrova
Department of Oncology, Federal Scientific and Research Center,
FMBA Russia, Orekhovy Bulvar, 28, 115285 Moscow, Russia
e-mail: kedrova.anna@gmail.com

E. A. Zvezdkina · O. A. Drobiazko
Department of Radiology, Federal Scientific and Research Center,
FMBA Russia, Orekhovy Bulvar, 28, 115285 Moscow, Russia
e-mail: zvezdkina@yandex.ru

O. A. Drobiazko
e-mail: droa@mail.ru

5.1 Introduction

Tyrosine kinases are mediators of critical signal transduction processes, leading to cell proliferation, differentiation, migration, metabolism, and programmed cell death. Using adenosine triphosphate, these enzymes catalyze phosphorylation of tyrosine residues in target proteins. They are primarily classified as either receptor tyrosine kinase, e.g., endothelial growth factor receptor (EGFR) or non-receptor tyrosine kinase, e.g., ABL. Tyrosine kinases are implicated in several steps of neoplastic development and progression. Normally the level of cellular tyrosine kinase phosphorylation is tightly controlled by the antagonistic effects of tyrosine kinases and tyrosine phosphatases. There are several mechanisms by which the normal homeostasis might be transformed, but the ultimate result is the constitutive activation of normally controlled pathways leading to the activation of other signaling proteins and secondary messengers which in turn initiate and perpetuate cancer development by hampering regulatory functions in cellular responses like cell division, growth, and cell death [1].

The understanding of the role of dysregulated tyrosine kinases in cancer has produced a literal explosion in approaches to cancer treatment through the development of tyrosine kinase inhibitors (TKI) in the form of monoclonal antibodies and small molecules. Ideally, these TKIs should only inhibit the dysfunctional tyrosine kinase driving the cancer. However, many TKIs are multi-kinase inhibitors by virtue of targeting the adenosine triphosphate (ATP) pocket which is a commonly shared feature among TKIs. Multi-kinase inhibition, although effective for cancer control, increases the likelihood of cardiovascular toxicity [2]. With the success of these agents has come the realization that recognizing and managing cardiovascular toxicity is essential if these drugs are to realize their potential. TKIs used in cancer care have been associated with heart failure, arterial and venous vascular toxicities including myocardial ischemia and infarction, systemic and pulmonary hypertension, pulmonary embolism, peripheral vascular disease,

thrombosis, QT prolongation, ventricular arrhythmias, and atrial fibrillation [2, 3].

In this atlas, it is not possible to effectively illustrate all the reported cardiovascular effects of TKIs. The cases in this chapter and the chapters that follow illustrate the effectiveness of TKIs as anticancer agents, their adverse effects on the cardiovascular system, and the thoughtful risk/benefit compromises that are the cornerstones of best practices in cardio-oncology.

Soft tissue sarcoma (STS) is an uncommon malignant disease represented in less than 1% of diagnosed malignancies in the Western world [4]. Although STS may occur anywhere in the human body it most often can be found in the extremities and chest wall. Treatment of STS includes surgical resection of the tumor with adjuvant and neoadjuvant therapy with anthracyclines, radiation, or both [5]. Long-term survival is quite stable after timely administered combination therapy, the mean metastasis-free survival being 11 years [6]. But synovial sarcoma may grow slowly and can be associated with late metastases after more than 10 years [7]. Pazopanib is an oral medication active against many kinases by virtue of its ability to inhibit ATP-mediated phosphorylation. It has exhibited inhibition of vascular endothelial growth factors (VEGFR-1, -2, and -3), platelet-derived growth factor receptors (PDGFR- α and - β), fibroblast growth factor receptors (FGFR-1 and -3), stem cell factor receptor (c-Kit), interleukin-2 receptor-inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (sc-Fms). Pazopanib has been shown to be effective for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma in patients previously treated with chemotherapy earning FDA approval for these indications [8].

A common cardiovascular side effect of the drug is the induction of hypertension [8, 9]. In patients who had systematic left ventricular ejection fraction (LVEF) assessment, myocardial dysfunction may occur in up to 11%, although congestive heart failure is very rare and is evident in about 0.5% of patients treated with this drug. When cardiotoxicity is related to pazopanib, interruption or dose reduction is usually required [8].

5.2 Case

Pazopanib: Cardiotoxicity during pazopanib treatment in a patient with a sarcoma metastatic to the mediastinum.

A 33-year-old woman was referred to the cardio-oncology service for the evaluation of right-sided heart failure. She first presented with a synovial sarcoma of the middle third of the diaphysis of the left tibia in 2006. Two courses of neoadjuvant chemotherapy with doxorubicin and

cisplatin were administered, followed by amputation of the distal third of left thigh. She then received four courses of adjuvant chemotherapy with doxorubicin, ifosfamide, Mesna, and dacarbazine administered from 2006 until 2007. The anthracycline infusions were accompanied by dexrazoxane for cardiac protection because the total dose of doxorubicin well exceeded 450 mg/m². The patient was free of relapses, became pregnant in 2008, and delivered a healthy child in 2009. She was stable for 7 years. However, progression of disease was noted on a surveillance chest CT performed August 2016 with metastases in the left lung and tumor growth in the mediastinum. Extended lower left lobectomy with resection of pericardial segments was performed in March 2017. The tumor material was typical for synovial sarcoma. In the postoperative period, four courses of adjuvant chemotherapy were administered according to the IE-VAC regimen (includes anthracyclines).

The patient presented to the cardio-oncology service with right heart failure manifest as jugular vein distention, ankle edema, ascites, and massive left hemothorax in September 2018. She was found to have a large and metabolically active mediastinal tumor on chest CT (Fig. 5.1) and PET CT (Fig. 5.2). Compression of the right branch of main pulmonary artery (Fig. 5.3) with right ventricular and right atrial dilatation also noted on contrast CT angiography (Fig. 5.4). Chest MRI demonstrated that the whole heart was surrounded by the tumor (Fig. 5.5).

Echocardiography (not shown) revealed right ventricular (RV) and right atrial dilatation, a pulmonary artery (PA) trans stenotic gradient of 70 mmHg with LVEF of 46%. Surgical treatment and percutaneous balloon angioplasty for PA stenosis was discussed by a multidisciplinary

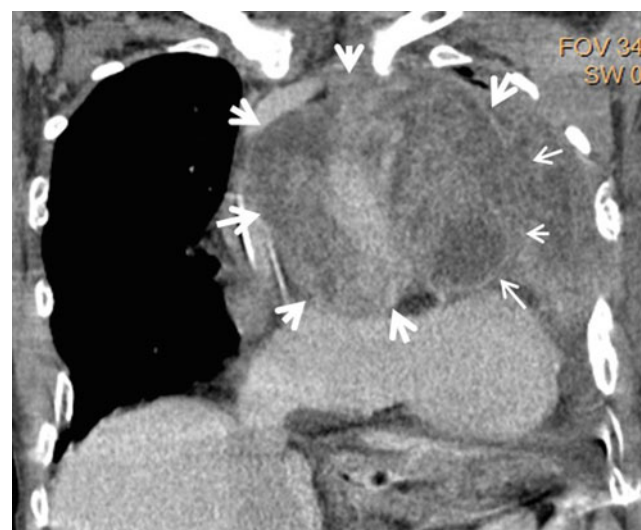


Fig. 5.1 CT pulmonary angiogram (coronal plane) shows a tumor (arrows) surrounding the heart and large vessels

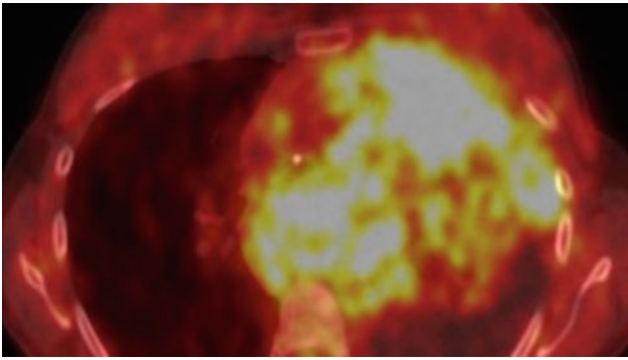


Fig. 5.2 PET-CT demonstrating a large tumor with active metabolism before treatment

team but was rejected as a therapeutic option because of the high risk and frankly unknown efficacy. Therapy with the tyrosine kinase inhibitor pazopanib was chosen.

After left thoracentesis pazopanib 800 mg once daily and spironolactone 100 mg daily were started in September 2018. Alleviation of peripheral edema and symptomatic improvement was achieved over three weeks of observation. Echocardiography in December 2018 revealed reduction of the PA gradient, the estimated PA pressure dropped to 30 mmHg and the right PA artery compression disappeared (Fig. 5.6). However as the RV size returned toward normal, the LV became dilated and globular on contrast CT (Fig. 5.7) confirmed by subsequent echocardiography where the LVEF was measured at 25%. Low dose enalapril and bisoprolol were started with gradual dose escalation. The dilated

Fig. 5.3 Left panel: CT pulmonary angiogram before treatment with pazopanib: Severe right pulmonary artery (PA) stenosis. Right panel: 3D reconstruction of heart and great vessels. Severe right pulmonary artery obstruction (arrow)

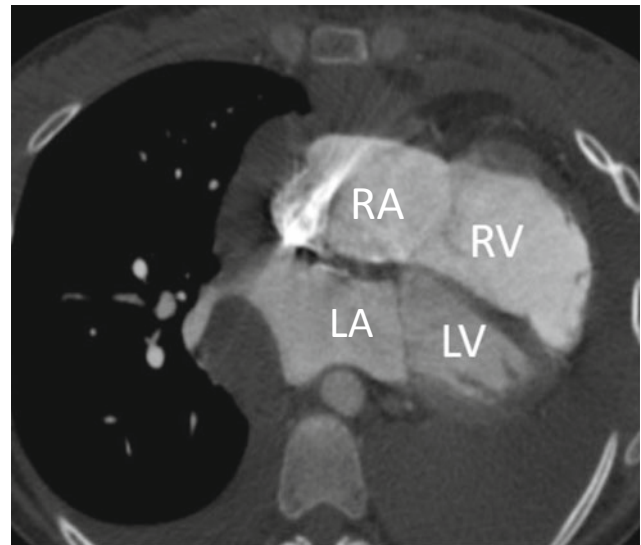
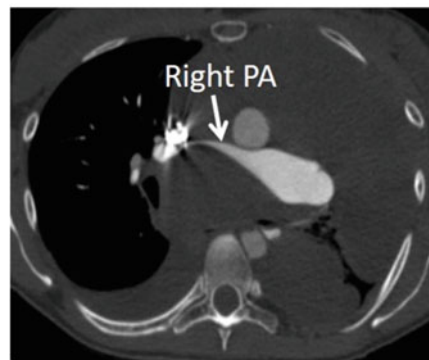
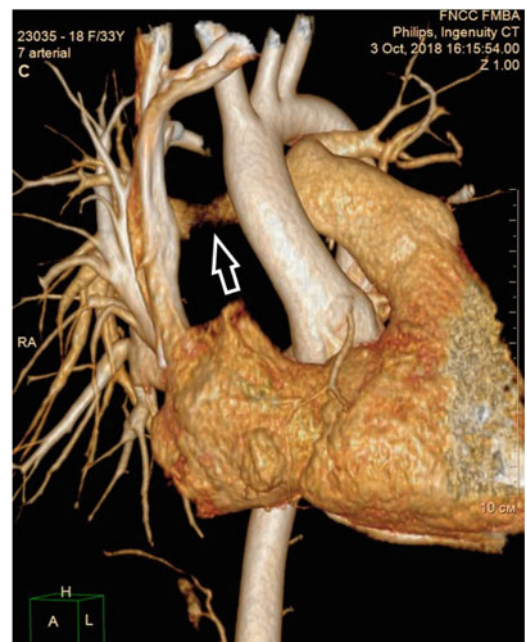


Fig. 5.4 CT contrast angiography—right ventricular (RV) dilatation. RV dimension exceeds the left ventricular (LV) dimension

cardiomyopathy was attributed to pazopanib therapy in the setting of pretreatment with high doses of anthracyclines. Pazopanib dose interruption was deemed inappropriate since it was a very effective anti-tumor option for this patient. The drug was continued but at a reduced dose of 400 mg daily.

Further reduction of mediastinal tumor metabolism was documented on PET CT at the end of January 2019 (Fig. 5.8). LVEF by echocardiography improved up to 40%. The daily dose of pazopanib was increased back again to



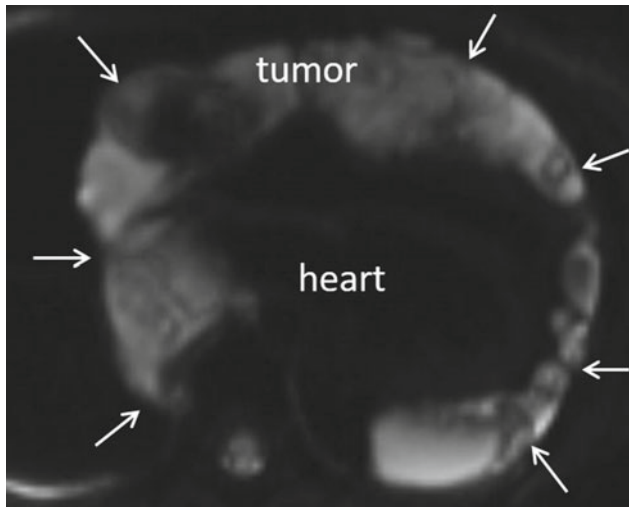


Fig. 5.5 Chest MRI (diffusion weighted imaging) of the patient demonstrating the tumor embracing the heart and great vessels

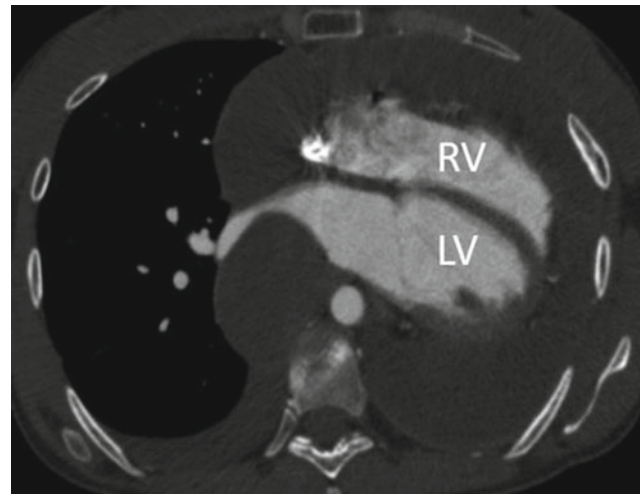


Fig. 5.7 CT contrast angiography after 8 months of pazopanib treatment demonstrating dramatic reduction in right ventricular size but the left ventricle is somewhat dilated and globular

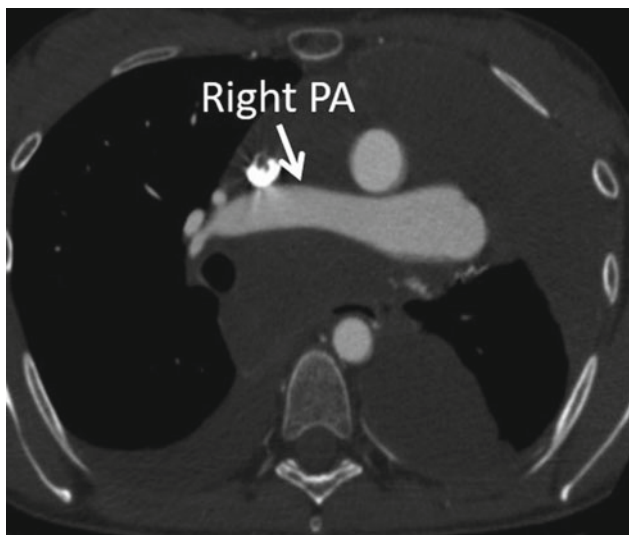


Fig. 5.6 CT pulmonary angiogram after 8 months of pazopanib treatment shows alleviation of the right pulmonary artery obstruction

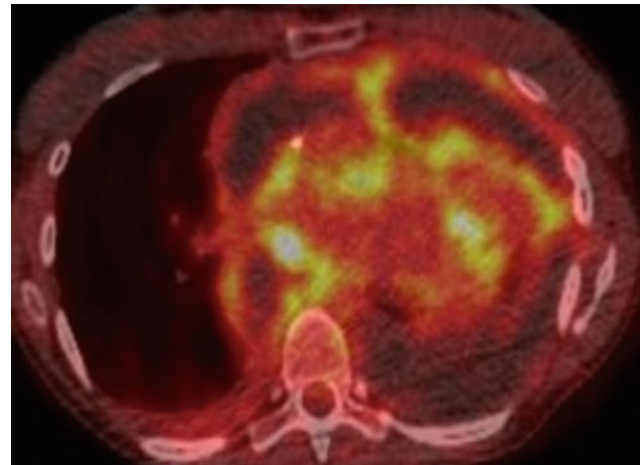


Fig. 5.8 PET-CT after eight months of pazopanib shows reduction in the size and metabolism of the sarcoma

800 mg/day without significant adverse effects. The cardiac status of the patient was stable for 10 months while on cardioprotective therapy.

Unfortunately, her condition worsened at the end of August 2019 with further spread of the disease and tumor

ingrowth into the right atrium (Fig. 5.9, Video 5.1). Anti-coagulation was started as pulmonary embolism prophylaxis but was complicated by an intracranial hemorrhage associated with brain metastases. She underwent emergency evacuation of an intracranial hematoma but was left with a residual focal neurologic deficit. Four weeks later in September 2019 the patient died while in palliative care.

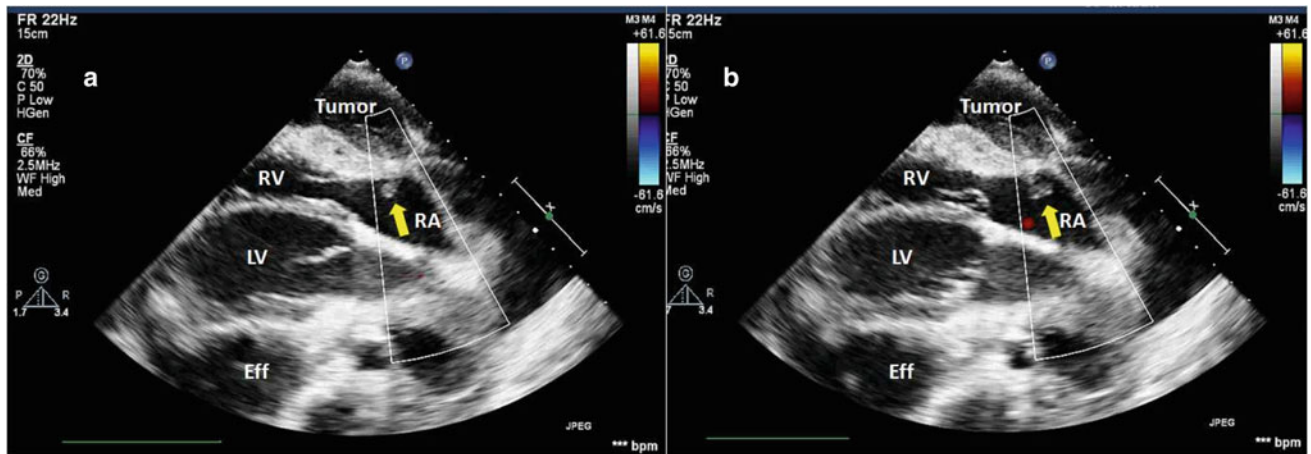


Fig. 5.9 A. Diastolic frame from echocardiogram parasternal long axis view demonstrating mass ingrowth (arrow) to the right ventricle. B. Systolic frame. The left ventricle appears mildly hypokinetic. Eff—pleural effusion, LV—left ventricle, RA—right atrium, RV—right ventricle

5.3 Conclusion

Pazopanib is an effective TKI for soft tissue sarcoma. Although hypertension is common, other cardiotoxic effects of pazopanib are rare and likely related to prior cardiotoxic treatments and abnormal ventricular function at the beginning of therapy. With an abnormal pretreatment LVEF and further reduction during pazopanib treatment, dose reduction or interruption of the TKI is indicated. In this instance, treatment with guideline directed medical therapy for left ventricular dysfunction stabilized the patient and allowed for continued anti-cancer therapy.

Reference

1. Paul MK, Mukhopadhyay AK. Tyrosine kinase—role and significance in cancer. *Int J Med Sci.* 2004;1(2):101–115. <https://doi.org/10.7150/ijms.1.101>. PMID: 15912202; PMCID: PMC1074718.
2. Cheng H, Force T. Why do kinase inhibitors cause cardiotoxicity and what can be done about it? *Prog Cardiovasc Dis.* 2010;53(2):114–20. <https://doi.org/10.1016/j.pcad.2010.06.006>. PMID: 20728698.
3. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. *J Am Coll Cardiol.* 2017;70(20):2536–51. <https://doi.org/10.1016/j.jacc.2017.09.1096>.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *Cancer J Clin.* 2020;70(1):7. PMID: 31912902.
5. Casali P.G., Abecasis N, Bauer S., et al. Soft tissue and visceral sarcomas: ESM-EURACA clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29(4):iv51–iv67. <https://doi.org/10.1093/annonc/mdy096>.
6. Krieg AH, Hefti F, Speth BM, et al. Synovial sarcomas usually metastasize after >5 years: a multicenter retrospective analysis with minimum follow-up of 10 years for survivors. *Ann Oncol.* 2011;22(458). PMID: 20716627.
7. Rothermundt C, Whelan JS, Dileo P, et al. What is the role of routine follow-up for localized limb soft tissue sarcomas? A retrospective analysis of 174 patients. *Br J Cancer.* 2014;110(2420). PMID: 24736584.
8. Votrient [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017. <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/votrient.pdf>. Accessed 19 Aug 2017.
9. Pinkhas D., Ho T., Smith S. Assessment of pazopanib-related hypertension, cardiac dysfunction and identification of clinical risk factors for their development. *Cardiooncology.* 2017;3(5). MCID: PMC5828231. <https://doi.org/10.1186/s40959-017-0024-8>.