Review article

Tyrosine kinase inhibitors – should we worry about cardiovascular complications?

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ABSTRACT

Small-molecular tyrosine kinase inhibitors constitute an effective therapeutic option in patients with hematologic malignancies and solid tumours. On the other hand, the significance of cardiovascular adverse events associated with their use is often emphasised. The events include arterial hypertension, heart failure, coronary disease/acute coronary syndromes, and long QT syndrome. The paper discusses the underlying mechanisms behind cardiovascular events associated with the treatment that involves tyrosine kinase inhibitors, and presents preventive and therapeutic options available in clinical practice. Awareness of the potential cardiovascular complications, regular follow-up, early diagnosis and initiation of appropriate treatment, combined with close collaboration with cardiology specialists, may enhance the benefits of long-term TKI therapy.

Key words: small-molecular tyrosine kinase inhibitors, cardiotoxicity, anti-angiogenic therapy, cardiovascular events

INTRODUCTION

Targeted therapies including tyrosine kinase inhibitors (TKI) contributed to important advance in oncology and have improved the prognosis for many patients with wide range of cancers which previously had few therapeutic options. TKI are small molecules that interfere with the kinase activity switching "on" or "off" many cellular processes including proliferation, apoptosis, metabolism and transcription [1]. They were expected to be less toxic than conventional chemotherapy as their action mechanism is more specific for tumor cells. However, after their widespread use, many clinical studies have demonstrated off target effects and increased risk of cardiac damage related to these compounds. This have been also addressed in recently published ESC position paper on cancer treatments and cardiovascular toxicity [2].

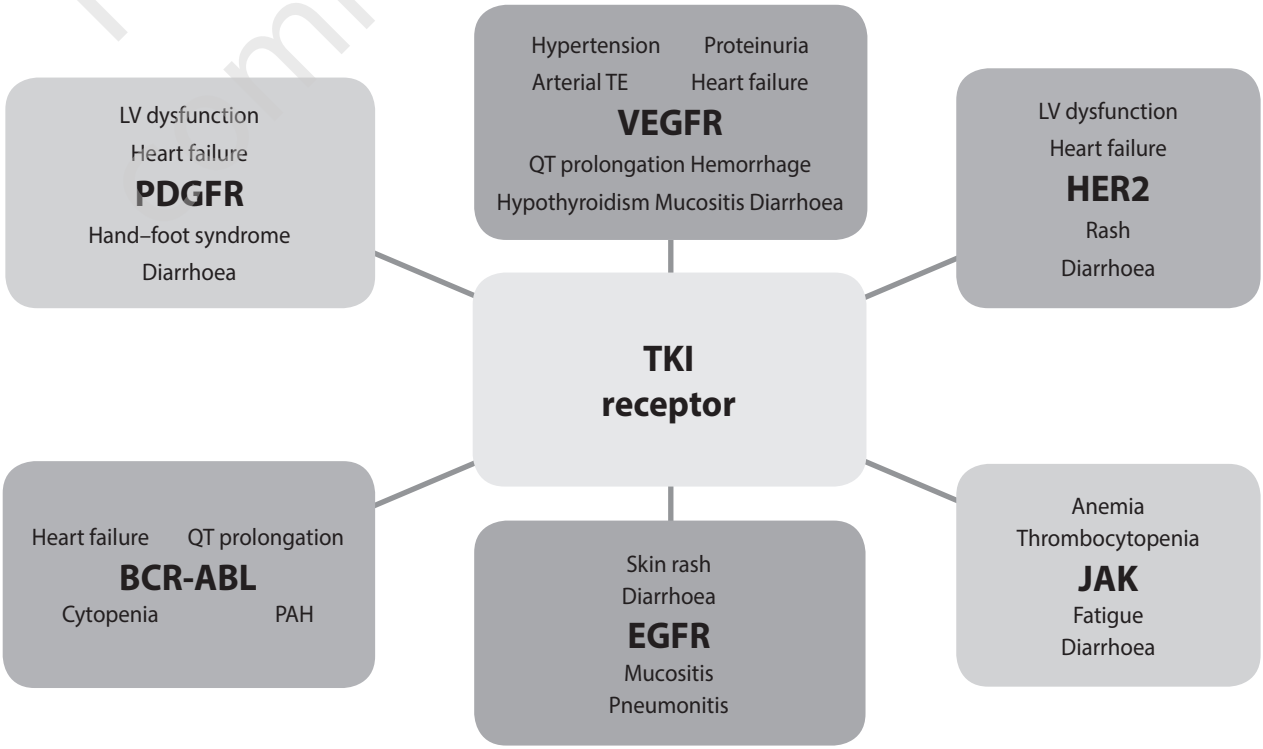
Not all TKI exert the same cardiotoxicity effects, indicating that this should not be considered as only a class toxic effect. On the other hand different classes of TKI targeting specific receptors are reported to be typically associated with particular toxicities (fig. 1). Among them cardiovascular complications including hypertension, heart failure, myocardial ischemia/acute coronary syndrome (ACS) and QT prolongation have emerged particular interest due to their importance and consequences for further patient therapy.

HYPERTENSION

Pathophysiology

High blood pressure is an established risk factor for cardiovascular events including myocardial infarction, heart failure, stroke and renal failure. It has been demonstrated that TKI that interfere with the vascular endothelial growth factor (VEGF) signalling pathway exert blood pressure raising effect [3]. This may lead to substantial risk of inducing new hypertension or worsening previously controlled hypertension. The frequency of these adverse events varies between 11% and 45% patients treated with VEGF-inhibitors [2] and suggested mechanisms are presented in table 1. The most frequently described in clinical trials TKI causing hypertension are sunitinib and sorafenib but blood raising

FIGURE 1.
TKI target receptors and associated toxicities.



TKI – Tyrosine Kinase Inhibitor; PDGFR – Platelet-Derived Growth Factor Receptor; VEGFR – Vascular Endothelial Growth Factor Receptor; HER2 – Human Epidermal Growth Factor Receptor 2; EGFR – Epidermal Growth Factor Receptor; JAK – Janus Kinase, TE – thromboembolism.

effect has been also reported for other TKI involving VEGF pathway signaling inhibition e.g. axitinib, vandetanib, regorafenib [2].

TABLE 1.
Mechanisms of blood pressure raising effect of VEGF-inhibitors.

1.	Nitric oxide pathway inhibition favouring vasoconstriction
2.	Vascular rarefaction (reduced number of vessels)
3.	Oxidative stress
4.	Glomerular injury
5.	Suppression of nephrine leading to proteinuria

The onset of TKI-related hypertension is variable – it may occur within 24 h or it can be delayed even 1 year after treatment onset. The available data shows also that the risk of hypertension depends substantially on tumor type. The risk of developing hypertension is significantly higher in patients with renal cell carcinoma (RCC) compared to non-RCC tumors. This could be due to the fact that patients with RCC have higher baseline blood pressure, higher VEGF level and worse renal function after nephrectomies compared to non-RCC subjects. Also the dosing schedule seems to be associated with the increased hypertension risk. Patients being treated with continuous daily dosing of sunitinib are at the increased risk of hypertension development when compared to intermittent dosing schedule. It is postulated that two weeks off therapy may favour better vascular endothelial recovery from the damage of sunitinib than the continuous daily dosing [4].

Above risk factors have been also the case for sorafenib – the data showed also that the risk of high-grade hypertension is substantially higher for patients with RCC and for patients treated with sorafenib for a long duration. Recently published paper by Hamnik et al. identified several clinical risk factors for development of hypertension in patients receiving various anti-VEGF therapies for many types of malignancies (RCC hepatocellular carcinoma, gastrointestinal stromal tumors and other sarcomas). The patients with pre-existed hypertension, age ≥ 60 years old and/or with a BMI of ≥ 25 kg/m^2 were at increased risk of anti-VEGF therapy-induced blood pressure raise, especially if all risk factors were present [5].

Management of hypertension

As hypertension is the established determinant of cardiovascular complications affecting significantly prognosis also in cancer patients, it should be managed in line with the current guidelines [6, 7]. According to them, the initial evaluation of patient with hypertension should first start with confirmation of the hypertension diagnosis which implies correct office blood pressure measurement using validated devices. Out-of-office blood pressure in turn could be assessed by ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) providing more reliable assessment of actual blood pressure than office measurements. The cut-off points for diagnosis of hypertension with these various methods are shown in table 2. The next step should be evaluation of cardiovascular risk, organ damage and concomitant clinical conditions which influence the patients prognosis. This requires except from blood pressure measurement also medical history, physical examination, laboratory tests and sometimes further diagnostic tests e.g. echocardiography, peripheral artery ultrasonography, ankle–brachial index etc.

TABLE 2.
Definitions of hypertension by office and out-of-office blood pressure levels [6].

Category	Systolic blood pressure [mmHg]		Diastolic blood pressure [mmHg]
Office blood pressure	≥ 140	and/or	≥ 90
Ambulatory blood pressure			
24-h	≥ 130	and/or	≥ 80
daytime	≥ 135	and/or	≥ 85
nighttime	≥ 120	and/or	≥ 70
Home blood pressure	≥ 135	and/or	≥ 85

The classification in low, moderate, high and very high risk is based on blood pressure category, cardiovascular risk factors, organ damage and presence of diabetes, symptomatic cardiovascular disease or chronic kidney disease. It is recommended that decisions on treatment strategies should depend on the initial level of total cardiovascular risk. The goal should be lowering systolic blood pressure below 140 mmHg except from elderly patients in whom higher blood pressure values are acceptable. Diastolic blood pressure target of < 90 mmHg is recommended, except from patients with diabetes, in such case values < 85 mmHg are indicated.

An adequate blood pressure control should be obtained before beginning of VEGF-inhibitor therapy as the blood pressure rais-

ing effect may occur very early, sometimes within hours since the treatment is started. Next, antihypertensive drugs should be titrated to obtain recommended blood pressure values as VEGF--inhibitor therapy proceeds. Given the high rate of hypertension related to anti-VEGF therapy, even in case of prehypertensive subjects presenting with cardiovascular risk factors, antihypertensive treatment is recommended before initiation of VEGF-inhibitors [3].

The position paper [2] does not indicate exactly the frequency rate of blood pressure monitoring however other data suggests weekly measurements during the first cycle of anti-VEGF therapy [3] and then at least every 2–3 weeks during the following treatment. Also, after completion of first cycle therapy and stabilisation of blood pressure, the control could be done using home monitoring method. In case of hypertensive crisis temporary discontinuation of anti-VEGF drugs must be considered. Once blood pressure is under control, VEGF-inhibitors can be reinstituted.

Currently there is no evidence that antihypertensive therapy impairs oncology responses. On the other hand, the hypertension development during VEGF therapy may be considered as marker of oncological treatment efficacy. In the study of Rini et al. [8] patients with metastatic RCC treated with sunitinib who developed hypertension continued to survive longer than patients without blood pressure raise effect.

Along with antihypertensive agents, one should not forget about lifestyle modification being the cornerstone for the prevention and treatment of hypertension. Clinical data show that the blood pressure lowering effects of these interventions can be equivalent to drug monotherapy although the major drawback is the low level of adherence over time [6]. Another advantage could be that lifestyle changes contribute to better control of other cardiovascular risk factors. The recommended lifestyle modification include salt restriction, moderation of alcohol consumption, increased consumption of vegetables and fruits, weight reduction, regular physical exercise and smoking cessation. However these strategies are not always easy and possible to be introduced in patients with metastatic cancer disease.

The choice of the antihypertensive therapy must be individualized considering the patients' medical history and specific indications/contraindications of different antihypertensive agents [6, 7]. ACE-inhibitors, angiotensin receptor blockers (ARBs) and non-dihydropyridine calcium channel blockers (preferable amlodipine or felodipine) are suggested as the first line treatment [2]. In case of concomitant heart failure or left ventricle (LV) dysfunction preferred are ACE-inhibitors and β-blockers. The choice of β-blocker should be made basing on the pathogenesis of anti-VEGF-induced hypertension involving nitric oxide pathway (nebivolol) or vasodilatory effect (carvedilol). Antihypertensive efficacy of nitrates or phosphodiesterase inhibitors described in several publications may derive also from pathophysiology of anti-VEGF-induced hypertension. Another interesting option for increasing the antihypertensive effect without adding another agent is using the combinations of two antihypertensive drugs at fixed doses in a single tablet. It has been demonstrated that reducing the number of pills to be taken daily improves adherence, which in turn increases the rate of blood pressure control [6, 7].

On the other side there are some antihypertensive class agents that are not recommended during anti-VEGF therapy. As dihydropyridine derived calcium channel blockers (dilatizem and verapamil) interfere with cytochrome P450 3A4 and many VEGF-inhibitors are substrate of this isoenzyme, this combination should be avoided as it increases drug plasma level. In case of diuretics use there is increased risk of electrolyte depletion and further QT prolongation especially in presence of diarrhoea frequently occuring during anti-VEGF therapy. Patients with resistant hypertension should be referred to cardiologists consultation to minimalize the risk of anti-VEGF therapy suspension.

HEART FAILURE AND LV DYSFUNCTION

Pathophysiology

Heart failure and LV dysfunction usually described with the term "cardiotoxicity" are not so common concern in patients receiving TKI therapy as compared to hypertension. According to the ESC position paper published last year [2] LV dysfunction may occur most frequently in case of sunitinib (2.7–19 %), sorafenib (4–8%), pazopanib (7–11%), less frequently during therapy with imatinib (0.2–2.7%) and lapatinib (0.2–1.5%). However, at the same time it is underlined that TKI-related cardiotoxicity may result not only in complications during cancer therapy but it can also cause increase in patients morbidity and mortality many years later. Lately a large meta-analysis including over 10,000 patients from phase II and III randomized trials using various VEGF TKI (sunitinib, sorafenib, vandetanib, pazopanib, axitinib, cabozantinib, ponatinib and regorafenib) revealed 2.69-fold increased risk of all grade heart failure compared to controls not receiving TKI. However the risk of severe heart failure was not increased according to this data [9].

Yet, molecular mechanism of cardiotoxicity caused by TKI remains poorly understood. Proposed mechanisms of sorafenib- and sunitinib-induced cardiotoxicity include [10]: inhibition of angiogenic growth factors, inhibition of platelet-derived growth factor (PDGFR) signalling, impaired prosurvival signalling, inhibition of c-Kit signalling, alterations in AMPK activity resulting in energy compromise and mitochondrial dysfunction.
In case of lapatinib which has lower rate of heart failure complications, the cardiac toxicity is due to the fact that this TKI targets human epidermal growth factor receptor 2 (HER2) which plays important role in cardiomyocytes survival. Risk factors associated with TKI-related cardiotoxicity include mainly prior cardiac disease and pre-existing hypertension [2].

Management

The first step should start from careful assessment of cardiovascular risk factors, aiming at identification of patients with increased risk of cardiotoxicity. None of the guidelines [2, 11] provides risk scores or algorithms for such assessment and this should be done by individual clinical judgement taking in consideration medical history, examination, baseline measurement of cardiac function (echocardiography, nuclear cardiac imaging, cardiac magnetic resonance) and cardiac biomarkers (troponin, B-type natriuretic peptide – BNP). Although baseline risk assessment usually is performed by the oncology team, it is recommended that high risk patients should be referred for cardiologic evaluation [2].

In case the baseline risk is high, it is recommended [2] that patients should undergo early clinical follow-up in the first 2–4 weeks after starting TKI therapy with e.g. sunitinib, sorafenib, pazopanib. The same guidelines do not indicate the rate of periodic re-assessment, they state only that periodic echocardiography may be considered every 6 months until stability in left ventricle ejection fraction (LVEF) is achieved. In case of significant decrease in LVEF > 10% to above value that is not below lower cut-off point of normal (which is 50%) patients should have repeated assessment of LVEF shortly after and during the cancer therapy. If drop of LVEF > 10% will be lower from 50%, such patients are considered at high risk of developing heart failure and should receive preventive therapy with ACE-inhibitors (or ARBs) and β-blockers.

In turn, the Stanford monitoring algorithm for targeted therapies proposed by Hall et al. [12] suggests LVEF assessment and NT-proBNP at baseline, 1 month and every 3 months on treatment. According to this algorithm, in case of 10% fall in LVEF, elevated NT-proBNP, or 100% increase in previously elevated NT-proBNP the patient should be referred to heart failure specialist.

As the guidelines on specific management of TKI-induced heart failure is lacking, it is commonly accepted to consult the general population standards [11]. The progression of heart failure may be delayed through interventions aimed at treatment of risk factors for heart failure including lifestyle modifications (salt and fluid restriction – if not contraindicated, weight management, increased physical activity, alcohol reduction, smoking cessation) and pharmacotherapy (ACE-I, β-blockers, another antihypertensive drugs, statins, etc). One should also be careful to exclude another non-drug related causes of cardiac dysfunction such as ischemic heart disease, valvular dysfunction or hypertension, and in case they are confirmed – treat them appropriately.

Both guidelines [2, 11] recommend use of ACE-inhibitors (or ARBs) and β-blockers in patients with symptomatic heart failure or asymptomatic cardiac dysfunction which in case of TKI-related cardiotoxicity may improve myocardial energetics and therefore attenuate the cardiomyocyte death. Diuretics are recommended in case of presence of signs and symptoms of congestion but their effects on mortality and morbidity is not confirmed. Other drugs such as spironolactione, digoxin, ivabradine and nitrates are reserved for still symptomatic patients despite of optimal therapy with ACE-I/β-blocker and should be administrated in consultation with cardiologist. As LV dysfunction caused by TKI is likely to improve through early and appropriate treatment, the implantable devices should be reserved only for patients with persistent dysfunction and prognosis allowing on achieving benefit from such device.

Another possibility of cardioprotection although with less evidence compared to conventional therapy with ACE-inhibitors/β-blockers is use of agents promoting favourable myocardial energetics. One of the examples may be use of metformin to augment AMP-activated protein kinase (AMPK) activity and therefore attenuate sunitinib-induced cardiotoxicity. Although treatment with metformin was proven to attenuate LV dysfunction after myocardial infarction, in experimental studies concerning the sunitinib cardiotoxicity the beneficial effect of this agent was not confirmed. Also addition of thalidomide to sunitinib therapy through increase of PDGFR signalling was suggested to inhibit cardiotoxicity in some experimental studies.

MYOCARDIAL ISCHEMIA/ACUTE CORONARY SYNDROME

Pathophysiology

The mechanisms of myocardial ischemia and as a consequence acute coronary syndrome (ACS) have a wide range [2, 13]. They

may result from direct proatherogenic and antiangiogenic effect on endothelial cells (nilotinib, ponatinib), vasospasm (sorafenib, nilotinib), acceleration of aterosclerotic process (sorafenib, nilotinib), procoagulant effect including platelet activation (sorafenib, sunitinib, nilotinib). On the other side must be remembered that ACS could be the result of tachycardia, hypotension, hypoxia, and anemia in cancer patients with significantly reduced myocardial reserve because of e.g. frequently preexisting coronary artery disease (myocardial infarction type II – according to third universal definition of myocardial infarction).

The risk of arterial thrombosis was estimated for 1.7% in case of sorafenib and 1.4% for sunitinib [2]. Currently there is growing evidence that newer generation of TKI (nilotinib, ponatinib, dasatinib), that have improved prognosis of some hematologic cancers, in contrast to initial reports and older TKI like imatinib, are associated with a broad spectrum of cardiovascular toxic effects. In recently published study of Dahlen et al. [14] the event rate for myocardial infarction was higher in patients treated with nilotinib or dasatinib (29 and 19 per 1000 person-years, respectively) than in those receiving imatinib (8 per 1000 person-years). Of notice, among patients treated with TKI who had myocardial infarction, 84% had at least 1 major cardiac risk factor before the event occurred. In another paper [15], most patients with chronic myeloid leukemia (CML) treated with nilotinib or ponatinib in whom vascular adverse events were reported, 1 or more risk factors for the development of atherosclerosis were found.

Management

In order to prevent ACS, baseline assessment of cardiovascular history and risk should be the key first step, and any potentially modifiable risk factor and disease should be optimized before proceeding with cardiotoxic TKI therapy. During such treatment, attention should be paid to the potential occurrence of coronary artery disease and thus patients should be carefully monitored for the development of coronary ischemia/ACS symptoms.

The diagnostic algorithms to identify myocardial ischaemia and ACS related to TKI therapy are the same as in subjects without cancer, although for example patients who develop ACS and simultaneously are thrombocytopenic due to chemotherapy constitute demanding challenge for optimal treatment with antiplatelet agents.

Current cardiology guidelines [16] recommend a stepwise approach for decision making in patients with suspected stable coronary artery disease. The process begins with a clinical assessment of the probability of coronary angina. The next step involves non-invasive testing (exercise testing, stress imaging e.g. echocardiography) in order to establish the diagnosis. After that optimal medical therapy should be introduced that combines angina relief agents (β-blockers, nitrates, calcium channel blockers) with event prevention strategy (lifestyle modification, risk factors control, acetylsalicylic acid, statins and ACE-inhibitors/ARBs). The last step is stratification of subsequent event risk and selecting patients who may benefit from revascularisation procedures.

Initial assessment of patients with suspected ACS is shorter and adequately simplified as this is emergency situation. It is based on the integration of the clinical presentation assessment (seeking for high-likelihood features of ACS e.g. pain characteristics, previous cardiovascular history), 12-lead ECG and cardiac troponin measure. In patients with suggestive signs and symptoms, the finding of persistent ST elevation even without troponin testing indicates ST-elevation myocardial infarction (STEMI), which mandates immediate reperfusion. Of note, in patients on TKI therapy who develop symptoms of ACS the best initial diagnostic and simultaneously therapeutic step may be administration of nitroglycerin or calcium channel blocker (if not contraindicated) to alleviate any possible coronary vasoconstriction [2].

In reality, presented algorithms in the background of overall cancer disease context, frequently accompanying anemia, thrombocytopenia and other coagulation abnormalities, various mechanisms of TKI-related ACS, constitute a particular challenge for cardiologists especially in case requiring urgent revascularisation. In patients treated with percutaneous coronary intervention the risk of dual antiplatelet therapy (sometimes requiring also combination with anticoagulants) causing potential bleeding complications, should be evaluated before the procedure. Another issue to be raised, is that ACS event should be considered as additional indication to switch to another TKI/anticancer agent which may again shift the balance towards worse patients prognosis.

QT PROLONGATION

Pathophysiology

Cancer therapies including TKI may be associated with a variety of arrhythmias but most notable can prolong QT interval, potentially leading to ventricular arrhythmias including the most severe in consequences – torsade de pointes (TdP) [2]. These arrhythmias may be due to the direct TKI electrophysiological effects on myocytes or indirect influence through ischemia/ACS or LV dysfunction (which also may be associated with TKI therapy) leading to an

arrhythmic substrate. Ventricular arrhythmias predominantly are considered to be more dangerous than atrial arrhythmias, and are typically due to abnormalities in ventricular repolarization which leads to electrical heterogeneity resulting in TdP.

Several factors such as electrolyte imbalance, hypothyroidism, cardiovascular diseases, age, impaired renal and hepatic function, concurrent use of QT-prolonging drugs may affect the duration of QT interval. A significant QT-prolongation has been reported especially in case of vemurafenib, vandetanib, sunitinib, sorafenib, nilotinib and cabozantinib [2, 17].

Management

As mentioned above, multiple TKI are known to prolong the QT interval, however without translating it into significant risk of TdP. Nevertheless, the QT interval and associated risk factors for QT prolongation are recommended to be assessed before and during treatment with TKI. The re-assessment should take place 7–15 days after therapy initiation or change in dose, monthly during the first 3 months and then, the frequency depends on chemotherapy drug and patient status [2].

Since increase in heart rate results in shortening of the QT interval, a correction for heart rate (corrected QT – QTc) should be applied using commonly Bazett or Fridericia formula. The upper limit of normal QTc interval is 450 ms for men and 460 ms for women. It is recommended to consider treatment discontinuation or turning into alternative agent if QTc is > 500 ms, QTc prolongation compared to baseline exceeds 60 ms or significant arrhythmias are observed [2]. Of note is that, the risk of developing life-threatening arrhythmias from QTc prolongation is difficult to quantify and the degree of prolonged QTc interval does not reliably correlate with the incidence of TdP and sudden death.

According to the available guidelines [2, 19] the treatment of TdP is based mainly on correction of predisposing factors (e.g. electrolyte abnormalities treatment, avoidance of concomitant QT-prolonging drugs, agent dose correction in patients with impaired renal and hepatic function, etc.) [18]. In critical situation when the patient develops TdP, administration of magnesium sulphate, overdrive transvenous pacing or titration of isoprenaline to prevent new events may help. In case of ventricular arrhythmia with accompanying haemodynamic instability defibrillation should be performed to stop the event.

CONCLUSIONS

TKI provide an effective therapeutic option in patients with hematologic malignancies and solid tumors. However in the background of currently available data, the use of TKI is associated with increased risk of developing cardiovascular complications including hypertension, heart failure, myocardial ischemia/ACS and QT prolongation. As these drugs are now frequently used in the routine cancer treatment, oncologists should be aware of potential adverse events and diagnose them through close monitoring and cooperation with cardiologists. On this cardio-oncology backgroud we will be ready to offer the patients optimal balance between clinical benefit from TKI therapy and life-threating cardiovascular events.

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