Targeted therapies for chronic myeloid leukemia and cardiovascular system

Sebastian Szmit, MD, PhD[1],
Wiesław Wiktor Jędrzejczak, MD, PhD[2],
Adam Torbicki, MD, PhD[1]

[1] Department of Pulmonary Circulation and Thromboembolic Diseases, Centre of Postgraduate Medical Education
[2] Chair and Department of Haematology, Oncology and Internal Diseases, Medical University of Warsaw

ABSTRACT

Morbidity of chronic myeloid leukemia is recorded in elderly population, in patients with coexisting significant risk factors for atherosclerosis and heart diseases. Molecularly targeted therapy, imatinib, dasatinib and nilotinib, improve significantly the prognosis. However, the similar molecular targets in the form of different kinases are essential for cardiovascular system and blocking their pathways may have adverse effects. There is evidence about risk of systolic heart failure related to imatinib, pulmonary arterial hypertension induced by dasatinib and ischemic events associated with peripheral arterial disease and observed during nilotinib therapy. Some groups of patients with defined risk factors need appropriate cardiac monitoring.

KEY WORDS: imatinib, heart failure, dasatinib, pulmonary arterial hypertension, nilotinib, peripheral arterial occlusive disease

INTRODUCTION

Tyrosine kinase inhibitors (TKIs): imatinib, nilotinib, dasatinib, constitute currently the basis for treatment of chronic myeloid leukaemia (CML) with Philadelphia (Ph) chromosome presence. All above mentioned TKIs affect BCR-ABL, a fusion oncoprotein encoded by the Philadelphia chromosome, and affect also, in a diverse way, c-KIT (receptor for Steel factor), α and β receptors for PDGF (platelet-derived growth factor) and a number of other similar enzymes, which can play an important role in the cardiovascular system (Table 1) [1]. Looking at the demographic data of CML patients it is obvious that CML incidence increases with age and is significantly higher after the age of 50 years. The median age of patients with newly diagnosed CML is 66 years [2]. However the clinical trials of new drugs enrol as a rule patients 10–20 years younger on the average [3]. Moreover, significant cardiovascular diseases are usually regarded as a criterion of exclusion from clinical trials.

Parallel epidemiological data show that in the general population aged over 65 years arterial hypertension occurs in 76.6% of women and 63.0% of men [4], lipid disorders are diagnosed in 60.3% of the population (71.1% of women and 59.1% of men), while diabetes mellitus is found in 21.2%. All the above mentioned diseases are significant risk factors of atherosclerosis and heart failure development, their presence is associated with a high risk of serious cardiovascular events [5]. Besides that, age, arterial hypertension and diabetes are significant risk factors of renal diseases [6], the prevalence of which increased recently from 10% to 13.1% (comparison of the years 1988–1994 with the period 1999–2004) [7] and which are also associated with a poor cardiovascular prognosis. Age increases not only the risk of progressing atherosclerosis [8] but also of heart failure [9]. Intravascular ultrasound examinations demonstrate that asymptomatic atherosclerosis is diagnosed in at least 85% of people aged over 50 years [10].

TABLE 1.
Molecular targets for tyrosine kinase inhibitors used in the treatment of chronic myeloid leukaemia – modified from Swords et al.

Imatinib Nilotinib	Dasatinib		
ABL	ABL	TXK	LIMK2
ARG	ARG	DDR1	MYT1
BCR-ABL	BCR-ABL	DDR2	PTK6/Brk
KIT	KIT	ACK	QIK
PDGFR	PDGFR	ACTR2B	QSK
DDR1	SRC	ACVR2	RAF-1
NQ02	YES	BRAF	RET
	FYN	EGFR/ERBB1	RIPK2
	LYN	EPHA2	SLK
	HCK	EPHA3	STK36/ULK
	LCK	EPHA4	SYK
	FGR	EPHA5	TA03
	BLK	FAK	TESK2
	FRK	GAK	TYK2
	CSK	GCK	ZAK
	BTK	HH498/	
	TEC	TNNI3K	
	BMX	ILK	
		LIMK1	

The real scale of cardiovascular complications during treatment of chronic myeloid leukaemia remains unknown. However, the age of that population, high probability of coexistence of significant risk factors of atherosclerosis and heart failure development and in many cases even the occurrence of asymptomatic disease of the heart or blood vessels, combined with the molecular profile of the drugs discussed, can cause an increased cardiotoxicity.

MOLECULAR TYPES OF CARDIOTOXICITY

The frequency of cardiotoxicity development after tyrosine kinase inhibitors is in fact not known, since the definition of cardiotoxicity itself has not been clearly specified neither in phase II/III clinical trials, nor in observational studies. Peripheral oedema is one of the most frequent complications of TKI therapy, described even in 70% of patients [11] but it is difficult to unequivocally demonstrate its origin and the causal connection with heart function.

Only those tyrosine kinase inhibitors which exert effects on the kinases expressed in the heart and vascular system, cause cardiotoxicity. Unfortunately, very few prospective trials assessed that problem in detail. Two types of molecular mechanisms of cardiotoxicity associated with TKIs have been described [12]:

1. Toxicity associated with the primary molecular target of the drug (on-target toxicity). That toxicity results directly from the mechanism of drug action. Kinase, which is the target point for those drugs is present both in the malignant cells and in the cells of the heart and blood vessels [13]. The classic examples of that type cardiotoxicity include the complications after trastuzumab and lapatinib.
2. Toxicity not associated with the primary molecular target of the drug (off-target toxicity). That toxicity is associated with limited selectivity of the majority of TKIs, which additionally inhibit those kinases, which have not been assumed to be the primary target point [14]. If the additionally blocked kinases

and metabolic pathways play an important role in the cardiomyocytes, that can result in cardiotoxicity. A typical example is the cardiotoxicity of sunitinib, which blocks over 50 kinases, including some of those important for ATP production in the cardiomyocytes.

The studies are pending, the aim of which is to synthesize more selective inhibitors in order to maximally reduce toxicity not associated with the main blocked pathway. Unfortunately, the development of cancer is connected with appearance in it of cells with mutations in genes for more than one kinase.

CHARACTERISTICS OF IMATINIB CARDIOTOXICITY

The first report on cardiotoxicity associated with therapy of chronic myeloid leukaemia with low molecular weight tyrosine kinase inhibitors was a series of 10 cases of congestive heart failure development during treatment with imatinib [15]. All the patients described had significant atherosclerosis risk factors. Later retrospective analyses demonstrated that congestive heart failure during imatinib treatment developed in about 0.5–1.1% of cases [16] and was more frequent in elderly patients with coexistent diseases.

The most frequently occurring known adverse effects of imatinib therapy include: peripheral oedema, effort dyspnoea and fatigue, i.e. the symptoms and signs typical of heart failure [17]. In the mentioned paper, Kerkela et al. reported that acute heart failure developed in isolated cases of imatinib treatment [18]. During the treatment LVEF reduction was observed, by almost 2% compared with the values from before the beginning of imatinib therapy. In myocardial biopsy in two out of ten patients with acute heart failure cardiomyocyte cell membrane lesions were found – the picture was typical of toxin-induced myopathies. Additional findings described included pleomorphic mitochondria with damaged crests, lipid droplets scattered in the cytosol, numerous vacuoles and accumulation of glycogen. The authors of the discussed paper prepared also a cardiomyocyte culture, in which they found endoplasmic reticulum activation effect in response to stress, loss of mitochondrial membrane potential, cytochromec release in the cytosol and reduction of ATP in the cell. Classic morphological features of apoptosis and necrosis were also found. The authors explained in the discussion that they were possibly caused by a loss of ATP. Apoptosis is a process requiring energy, therefore when ATP concentration decreased to about 65% due to mitochondrial damage, the cardiomyocytes were dying in the process of necrosis and not due to activation of the apoptosis pathway. However, imatinib certainly causes an increase of activity of protein kinase Cd (PHCd), a kinase exerting proapoptotic effect in the heart [18], although its role in promoting heart dysfunction has not been unequivocally established.

In another study it was observed that in a group of 103 patients with chronic myeloid leukaemia, peripheral oedema developed more frequently if they were treated with imatinib. Four of the patients had BNP > 100 pg/ml (possible diagnosis of heart failure) and one had reduced LVEF [19]. In another study the possibility of imatinib cardiotoxicity was assessed through BNP concentration measurement but no significant relationship was found [20].

A modification of imatinib molecule, so that it could additionally block the JNK pathway, has lead to a significant reduction of cardiotoxicity without any negative influence on drug efficacy [21]. JNK activation may be responsible for the toxic effects in the myocardium, and inhibition of JNK pathway significantly reduces the loss of mitochondrial membrane potential and death rate of cardiomyocytes [22].

It has been also documented that the occurrence of acute heart failure during imatinib therapy is reversible. Owing to cardiologic treatment a complete normalization of cardiac systolic function can be achieved, but heart failure recurs during consecutive lines of treatment with dasatinib or nilotinib [23].

CARDIOTOXICITY OF DASATINIB AND NILOTINIB

High percentages of peripheral oedema [24] and pleural effusion [25] were noted in clinical trials with dasatinib, but the incidence of congestive heart failure and also cardiac arrhythmia (including tachycardia) was only 2%. Isolated cases of asymptomatic QT prolongation and pericardial effusion were reported [26]. Fluid retention seems to be the most serious complication of dasatinib treatment [27]. Pleural effusion is also a frequent complication – it affects 20–55% of the patients and is most likely an effect of PDGFR blockade [28], but that complication is significantly less frequently observed during treatment with other TKIs [29, 30]. The treatment of pleural effusion usually includes dasatinib dose reduction, administration of diuretics and glucocorticosteroids. The way of dasatinib posology seems to be the most important predictive factor of that complication – twice daily administration increased the risk [31], daily dose reduction from 140 to 100 mg very significantly decreased the incidence of that complication. Among other risk factors the following are recognized: cardiologic treatment of heart diseases in history data, arterial hypertension, phase of the disease (BP > AP > CP, i.e. blast phase [blast crisis] > accelerated phase > chronic phase)

and respiratory system diseases: chronic obstructive pulmonary disease and even cigarette smoking or respiratory infections in history [29]. In some cases pleural effusion may be accompanied by pericardial effusion [32, 33], and increased right ventricular pressure is also noted. The risk of excessive fluid retention and cardiotoxicity should call for close cardiologic monitoring of patients, particularly those with significant heart failure risk factors [34].

In the preclinical trials with nilotinib, changes in ECG record were reported, including QT prolongation effect [35]. In the ENESTnd study [36], heart dysfunction was a criterion of exclusion – patients qualified for nilotinib therapy were not allowed to have QTcF > 500 ms; during the active treatment the mean QTcF prolongation was 6 ms. Cardiac deaths occurred rarely, with 0.6% incidence. They were most likely a consequence of ventricular repolarization disorders. It has been noted that significant QT prolongation can take place when nilotinib is administered together with CYP3A4 inhibitors or other QT-prolonging drugs [37, 38].

Recently papers were published, documenting new cardiovascular complications in patients treated with dasatinib or nilotinib [39, 40]:

- pulmonary arterial hypertension (PAH) during dasatinib therapy
- progressing peripheral arterial occlusive disease (PAOD) during nilotinib treatment.

DASATINIB AND PULMONARY ARTERIAL HYPERTENSION

The development of precapillary pulmonary arterial hypertension (PAH) during dasatinib therapy has been documented in literature. It is supposed that PAH, apart from pleural effusion, is a specific complication of dasatinib therapy [41]. In addition, pleural effusion is probably a positive predictive factor for occurrence of PAH. Quintas-Cardam et al. [29] published a report, according to which increased right systolic ventricular pressure (RSVP) in 18 patients (results from 29 mmHg to 42 mmHg) was normalised (to the initial value) after dasatinib withdrawal. The results of the clinical trials did not suggest that the complication could have been a significant clinical problem. In a large retrospective analysis including over 2800 patients treated with dasatinib in clinical trials, only one case of PAH was diagnosed [42]. In the DASISION study [43], in which dasatinib was administered in 100 mg dose, PAH symptoms and signs were diagnosed only in three patients, i.e. in 1.2%, but none of them discontinued the treatment for that reason.

Nine cases of PAH were described in a French register [44], from November 2006 to September 2010 (Table 2). In all cases moderate to severe precapillary pulmonary hypertension was diagnosed, clinical and haemodynamic improvement was obtained within four months after dasatinib withdrawal. Three patients required PAH-specific treatment: two – with endothelin receptor antagonists and one with a calcium antagonist. Alarming was the fact

TABLE 2.
Clinical characteristics of patients with precapillary pulmonary arterial hypertension (PAH) induced with dasatinib – modified based on the data from the French register (Montani D. et al. Circulation 2012; 125: 2128-2137).

Patients	Age	Sex	Time between dasatinib treatment beginning and the diagnosis of PAH (months)	NYHA functional class	Pleural effusion	Pericardial effusion
1	74	F	33	III	bilateral	-
2	51	F	30	III	bilateral, clinically insignificant	clinically insignificant
3	64	F	28	IV	-	clinically insignificant
4	28	F	45	III	-	-
5	59	F	45	III	bilateral	-
6	29	F	36	IV	bilateral	-
7	17	F	8	II	bilateral	-
8	39	F	34	IV	bilateral	clinically insignificant
9	68	M	48	II	-	-

that after nine months of follow-up (median with range from 3 to 36 months) after dasatinib withdrawal, most patients experienced no complete normalization, neither clinical nor haemodynamic, and none patient had normal mean pulmonary arterial pressure (≤ 20 mmHg). Unfortunately, two patients died: one due to unexplained sudden death, one due to heart failure in the course of sepsis.
Besides the French register many case reports were published [45–49], in which the diagnosed PAH was a relatively late complication (8–48 months following dasatinib therapy beginning), it coexisted with pleural effusion or peripheral oedema. The fact is optimistic that in all cases a haemodynamic and clinical improvement was noted after dasatinib withdrawal, and a part of the patients were later treated with nilotinib without recurrence of PAH manifestations, with the exception of one case described by Philibert et al. In some patients sildenafil was used – observations by Sano et al., Dumitrescu et al., Hennings et al., Orlandi et al. A pessimistic result, however, was the fact that only in three cases a complete regression of PAH was observed: observations by Orland et al., Sano et al., Dumitrescu et al. In the remaining cases, similarly as in the French register, only a partial PAH regression was found – Mattei et al., Hennings et al., Rasheed et al., Philibert et al.
In a Polish observation, Patkowska et al. [50] documented PAH induced by dasatinib therapy and confirmed by right heart catheterization. Lymphocytic exudate in the pleural cavity was diagnosed as an accompanying complication. In effect, dasatinib was withdrawn and sildenafil therapy was recommended. After almost 18-month follow-up, in control right heart catheterization examinations normal pressure was found in the pulmonary artery, both at rest and during exercise, in spite of sildenafil withdrawal, what confirmed complete PAH regression. It is worth stressing that after dasatinib withdrawal the patient was given nilotinib, what led to a greater molecular CML response.
The pathogenesis of PAH during dasatinib treatment is not known. The mechanism is discussed of off-target inhibition of kinases associated with the function of pulmonary vessel myocytes, which results in an increase of the resistance in the pulmonary circulation. The cause lies probably in blocking of kinases from the SRC family and ephrin receptor kinases by dasatinib [51]. In some studies it has been proven that SRC activation influences the mechanisms of proliferation, contraction and relaxation of myocytes in the pulmonary vessel walls [44, 52]. The kinases from the SRC family are involved in the regulation of the function of ion channels, mainly calcium channels responsible for vasospasm and production of nitric oxide and prostaglandins responsible for relaxation.
The mechanism associated with metabolism of oestrogens is also taken into account, since, as a rule, iatrogenic PAH develops definitely more frequently in women (Table 2) [53, 54]. Some importance is also ascribed to other molecular pathways dependent on the function of RTKs (receptor tyrosine kinase), including platelet-derived growth factor receptors [55, 56], fibroblast growth factor receptors [57, 58] and c-KIT [59] and epidermal growth factor receptor [60, 61] – all these receptors may be involved in normal regulation of the pulmonary vessels, what has been confirmed in experimental models.
It should be stressed that in CML patients pulmonary hypertension of unclear or multifactorial aetiology may develop – that is the fifth group in pulmonary hypertension classification (Table 3) [62–68]. Chronic myeloproliferative diseases can induce a number of mechanisms that can lead to pressure increase in the pulmonary artery. These mechanisms include increase of left ventricular stroke volume, direct pulmonary vasospasm, thromboembolic episodes, portal hypertension or congestive heart failure [62, 63].
The paradox is that clinical and haemodynamic improvement can be achieved due to administration of imatinib in patients with CML and coexistent precapillary pulmonary hypertension [69]. The efficacy of imatinib in such cases depends on PDGF receptor and c-KIT receptor blockade [55, 56, 59]. Studies and discussions are pending, concerning imatinib efficacy in pulmonary arterial hypertension [70].

THE PREVALENCE OF PULMONARY ARTERIAL HYPERTENSION IN THE GENERAL POPULATION

Pulmonary hypertension (PH) is defined as increased mean pulmonary artery pressure ≥ 25 mmHg at rest (normal value is 14 ± 3 mmHg) [71]. PH is always suspected when the right systolic ventricular pressure (RSVP) on echocardiography exceeds 35 mmHg. Typical clinical manifestations include reduced effort tolerance and dyspnoea. The objective diagnosis is possible after right heart catheterization, since that examination enables differential diagnosis to exclude venous postcapillary pulmonary hypertension caused by coexistent left ventricular diseases, frequently occurring in elderly people. Pulmonary hypertension develops in: up to 60% of patients with severe left ventricular systolic dysfunction, up to 70% of patients with isolated diastolic dysfunction [72], 65% of patients with symptomatic aortic stenosis and practically all patients with severe symptomatic mitral valve disease [73].
The newest clinical classification of pulmonary hypertension (developed during the Dana Point meeting) is presented in Table 3 [74]. Precise determination of the incidence of individual forms of pulmonary hypertension is difficult, differential diagnosis also presents a significant clinical challenge. In a questionnaire

survey conducted in an echocardiography laboratory [75] the prevalence of pulmonary hypertension among 4579 patients was 10.5%. In the group of 438 patients with diagnosed pulmonary hypertension the following causes were found:

- left heart disease (group 2) – 78.8%
- lung diseases and hypoxia (group 3) – 9.7%
- thrombo-embolic complications in the pulmonary vessels (group 4) – 0.6%.

TABLE 3.
Clinical classification of pulmonary hypertension (clinical groups, clinical categories) (Dana Point 2008) – modified from: Simonneau G. et al.: J. Am. Coll. Cardiol. 2009; 54: S43-S54.

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drugs and toxins induced
1.4. Associated with (APAH)
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1.4.6. Chronic haemolytic anaemia
1.5. Persistent pulmonary hypertension of the newborn
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2. Pulmonary hypertension due to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear and/or multifactorial mechanisms
5.1. Haematological disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

In this study, only 4.2% of the patients were identified as group 1 (Table 3), while in 6.8% making the diagnosis and establishing the aetiology of pulmonary hypertension were not possible (probably group 5).

Pulmonary arterial hypertension (PAH) includes non-homogenous clinical conditions, the common feature of which are similar clinical and haemodynamic manifestations and, in principle, identical pathomorphological changes in the pulmonary microcirculation. Secondary pulmonary vascular resistance (PVR) increase leads to right ventricle overloading, hypertrophy and dilatation and, finally, to right ventricular failure and death. The haemodynamic changes and prognosis in PAH are associated with combined pathophysiological interactions between the rate of progression (or regression) and the obliterative changes in the pulmonary microcirculation and reaction of the overloaded right ventricle. These factors can be also genetically determined [76].

The prevalence of PAH is within the range of 15–50 cases per one million in the European population [77]. In the French register 39.2% of patients had the idiopathic form and 3.9% had PAH in family history, while a high percentage of patients had PAH associated with administration of anorectic drugs [78].

Many risk factors of PAH development were found. They were defined as any factor or clinical condition, which may predispose to the disease or facilitate its development. The risk factors were classified as **definite, likely, possible** or **unlikely**, based on the strength of their relationship with PAH and the probability of their causal role:

1. **Definite** association – e.g. frequent PAH development during treatment with appetite-suppressant medications, or epidemiological data from multicentre trials showing the association of a disease or drug with PAH development.
2. **Likely** association – demonstrated in a monocentre clinical-control trial or in the material from many patients.

NILOTINIB AND ARTERIAL ATHEROSCLEROSIS

The data from clinical trials, post-registration studies and spontaneous reports show that during nilotinib treatment ischaemic vascular events can occur, associated with atherosclerosis and possible atherosclerotic plaque rupture. They are manifested as: acute coronary syndromes, cerebral ischaemic stroke and most frequently acute ischaemia of the limbs, which is a complication of peripheral arterial occlusive disease (PAOD). The question remains open, to what extent they are a clinical manifestation of the progression of atherosclerosis present in CML patients, and to what extent endothelial damage due to nilotinib.

Kim et al. in their observation identified seven cases of coronary

events, which occurred during nilotinib therapy, several months following therapy beginning – median time 14.5 months. One case ended up with cardiac death, while in the remaining cases further treatment with nilotinib was possible [79]. As a potential explanation the authors proposed overlapping on the existent atherosclerosis risk factors and coexistent diseases of most likely the molecular effect of nilotinib (with its off-target effect on the vascular wall through a specific receptor – discoidin domain receptor 1 [DDR1]) [80] or its metabolic effect associated with insulin resistance [81, 82].

A chronological analysis of reports on PAOD during nilotinib therapy shows that initially they were descriptions of series of cases. **Aichberger et al.** [81] described three cases of progressing PAOD among 24 patients with CML from one centre in Austria, which developed after therapy switching from imatinib to nilotinib – all patients had initially significant risk factors, such as diabetes mellitus or neuropathy. **Tefferi et al.** [83] described the case of a patient with CML refractory to imatinib treatment, who experienced PAOD during nilotinib therapy, requiring invasive angioplasty treatment. **Quintás-Cardama et al.** [84] identified five cases of PAOD among 233 CML patients taking nilotinib, who participated in phase I and II studies at M.D. Anderson Cancer Centre. All reports suggested the need for considering atherosclerosis risk factors in patients qualified for nilotinib therapy.

The comparison of the results of two-year follow-up in ENESTnd study patients, who were given nilotinib in 300 mg or 400 mg dose twice daily with the results in patients treated with imatinib, demonstrated that the incidence of complications associated with PAOD was 1% what meant three patients in each of nilotinib trial arms [36]. In four-year analysis of that trial nine cases of PAOD were observed in both nilotinib arms (four patients received nilotinib in 300 mg dose twice daily, five patients – in 400 mg dose twice daily). In the imatinib arm no complications were observed [85].

Le Coutre et al. [86] performed a **retrospective** analysis of 179 patients receiving nilotinib in four centres, 151 of whom were included into clinical trials. Most patients were treated for CML (n = 175) and four patients were treated for other diseases (hypereosinophilic syndrome, acute lymphoblastic leukaemia, systemic mastocytosis). Out of 179 patients included in the analysis, in 11 (6.15%) complications of PAOD type developed, which required surgical treatment. Ten out of 11 mentioned patients had cardiovascular risk factors, such as nicotinism, diabetes mellitus, obesity and hypercholesterolaemia. Most of them were treated for drug-resistant CML or were intolerant of previous treatment (nine – intolerance of treatment or drug-resistant CML, one – newly diagnosed CML, one – hypereosinophilic syndrome). During nilotinib treatment all 11 patients had at least cytogenetic remission. The mean time from CML diagnosing to nilotinib therapy beginning was 347 weeks (range: 8–651 weeks) and the mean time from nilotinib treatment institution to the first episode of PAOD type was 105.1 weeks (range: 16–212 weeks). Lower limb involvement occurred in all 11 patients, and in nine of them the disease involved the external iliac artery. The treatment included angioplasty (n = 8), stent implantation (n = 8) or amputation (n = 4).

Levato et al. [87] in a **retrospective** analysis of 82 patients with CML found PAOD or another vascular episode in four out of 27 (14.8%) patients receiving nilotinib as first- or second-line therapy and in one out of 55 patients treated with imatinib monotherapy. The estimated probability of absence of PAOD development over 10 years was 100% in the group of imatinib monotherapy and 67% in the group of patients treated with nilotinib (HR = 14.6; p = 0.0008). In the group treated with nilotinib (median treatment duration 24 months) all four patients with vascular complications were aged over 60 years, three were males, two were cigarette smokers, two had arterial hypertension, two had dyslipidaemia. Vascular complications included: two episodes of limb ischaemia, one myocardial infarction and one cerebral stroke. Among the patients treated exclusively with imatinib, one had myocardial infarction (after 135 months of treatment).

Labussiere-Wallet et al. [88] assessed the clinical and metabolic parameters in a group of 54 patients with CML-CP treated with nilotinib. After the mean time of 2.6 years of nilotinib administration, abnormal ankle-brachial index (ABI) values (ABI < 1.0) were found in the total number of 13 patients. In seven of them Doppler ultrasound examination confirmed arteriopathy. The authors observed a correlation between the duration of nilotinib therapy and development of confirmed arteriopathy (p = 0.07), and also total cholesterol and LDL fraction concentrations. A relationship was demonstrated between the vascular events and patients' age at the time of nilotinib therapy beginning.

In the first **prospective** study, **Kim et al.** [89] carried out an assessment of PAOD among patients treated with nilotinib or imatinib for CML in chronic phase (study period: August 2011 – November 2012). During the study the clinical and biochemical risk factors of cardiovascular events were assessed in 159 patients. Advanced PAOD was assessed based on non-invasive ankle-brachial index (ABI) tests and Doppler ultrasound examination. Abnormal ABI values were found in 24 out of 129 prospectively assessed patients (18.6%), significantly more frequently in patients receiving nilotinib as the first-or second-line therapy (7 out of 27 cases, i.e. 26%, and 10 out of 28 cases, i.e. 34.7%,

respectively). The patients receiving imatinib had significantly less frequently abnormal ABI values (three out of 48 cases, i.e. 6.3%). Besides that, in patients treated with nilotinib significantly higher total cholesterol and LDL concentrations were found. In the second phase of the study clinically significant PAOD events, i.e. those causing limb ulcerations or acute ischaemia were assessed. These events were assessed in several cooperating CML--treating centres; 27 cases were diagnosed (Table 4).

Six out of these patients were earlier described by Le Coutre et al., and three by Levato et al. or Giles et al. Only one patient was not treated with nilotinib (was given imatinib) but had a number of significant atherosclerosis risk factors: 77 years of age, arterial hypertension, nicotinism, obesity and dyslipidaemia. As a rule, PAOD clinical events occurred only in patients with atherosclerosis and cardiovascular disease risk factors (Table 4). Ischaemia in most cases concerned either the femoral artery (12 cases, i.e. 44.4%), or the peroneal artery (10 cases, i.e. 37%). In most cases invasive treatment was necessary. PAOD manifestations development was the basis for nilotinib treatment termination, dose reduction or therapy switch to other TKI (ponatinib).

Giles et al. [90] carried out a retrospective analysis of **PAOD incidence in patients treated in phase III clinical trials**. The analysis included 2390 patients from three clinical trials: ENESTnd, IRIS, TOPS [91–93]. Three large subgroups of patients were created:

1. The first – 533 TKI-naïve patients. PAOD was diagnosed in three patients (0.6%).
2. The second – 556 patients treated with nilotinib (300 mg or 400 mg doses administered twice daily). PAOD was diagnosed in seven patients (1.3%).
3. The third: 1301 patients treated with imatinib (400 mg or 800 mg daily doses). PAOD was diagnosed in two patients (0.2%).

It should be stressed that 10–12% of patients in each subgroup were at the age of ≥ 65 years and 33–36% of patients had at least one atherosclerosis risk factor. When the first subgroup was assumed as control, then, taking into account treatment duration, it was found that PAOD risk was **RR = 0.9 (95% CI: 0.2–3.3) for the subgroup treated with nilotinib and RR = 0.1 (95% CI: 0.0–0.5) for the imatinib-treated subgroup**. Besides that, almost all patients with PAOD (except one case) initially had significant atherosclerosis risk factors – arterial hypertension, diabetes mellitus or nicotinism.

TABLE 4.
Clinical characteristics of patients with lower limb ischaemia in the course of peripheral arterial obliterative disease (PAOD) during nilotinib or imatinib therapy – modified from Kim et al. Leukemia 2013; 27: 1316-1321.

	Characteristics in subgroups	**PAOD clinical events N = 27 (100%)**
TKI treatment line	imatinib as first-line treatment nilotinib as first-line treatment nilotinib as second-line treatment nilotinib as third-line treatment previous nilotinib treatment	1 (3.7) 9 (33.3) 11 (40.7) 1 (3.7) 5 (18.5)
Nilotinib treatment duration	36 months (6-72)	
Age at the time of PAOD diagnosis	68 years (38-87)	
Coexistent atherosclerosis risk factors	0 1–2 3–4 > 4	0 8 (29.6) 15 (55.6) 4 (14.8)
Administered treatment	angioplasty stent implantation limb amputation surgical revascularization non-invasive treatment	9 (33.3) 6 (22.2) 6 (22.2) 5 (18.5) 11 (40.7)

Multifactorial logistic regression analysis demonstrated that the patients receiving nilotinib as compared with the subgroup not treated with TKI were at no increased risk of PAOD: OR = 0.906 (95% CI: 0.206–5.453) (Table 5). The result of that analysis was clinically interesting, showing that patients receiving imatinib compared with the subgroup not treated with TKI were at statistically significantly reduced risk of PAOD: OR = 0.062 (95% CI: 0.005–0544). The authors tried to explain that result with a more specific effect of imatinib on PDGFR [94, 95] and a more favourable effect on glucose metabolism [96, 97].

PAOD seems to be a rare cardiologic complication and to a significant extent associated with the presence of atherosclerosis risk factors in patients with chronic myeloid leukaemia. Detailed pathogenesis remains unknown. No cause-and-effect relation-ship between the mechanism of nilotinib action and the potential mechanism of atherosclerosis progression was unequivocally demonstrated. It is assumed that older age, arterial hypertension and hypercholesterolaemia are the risk factors of both pleural effusion during dasatinib therapy and PAOD during nilotinib treatment. It has been proven that compared with imatinib, the therapy with nilotinib is associated with such biochemical abnormalities as hyperglycaemia and hypercholesterolaemia [98].

INCIDENCE OF OBLITERATIVE ATHEROSCLEROSIS IN LOWER LIMBS IN THE GENERAL POPULATION

Peripheral arterial obliterative disease (PAOD), despite the fact that it usually involves the lower limbs, is associated with a high risk of acute arterial events, such as cerebral strokes and myocardial infarctions [99, 100]. From the clinical point of view, it is understood as a marker of subclinical coronary artery atherosclerosis. It is assumed that 75% of PAOD cases are asymptomatic. However, the symptoms and signs of limb ischaemia causing intermittent claudication are the cause of significant impairment of the patients' quality of life [101]. The first epidemiological studies demonstrated that PAOD developed in about 3–4% of people at middle age and 13–14% of elderly people [102–105], the individual studies reported the following incidence of PAOD:

- the Cardiovascular Health Study – 12.4% [106]
- the Rotterdam Study – 19%, range from about 12% in the 60–64 years of age group to over 55% among people aged ≥ 85 years [107].

Elizabeth Selvin and Thomas Erlinger conducted an analysis of the data from The National Health and Nutrition Examination Survey from the years 1999-2000 [108]. The essence of the study method was an assessment of results of a representative group of 2174 United States citizens aged over 40 years. Based on the data it was estimated that POAD incidence increases significantly with age. Assuming the ankle-brachial index < 0.90, PAOD was diagnosed in 4.3% of the subjects (95% CI: 3.1–5.5%), what corresponded to about 5 million patients in the USA (95% CI: 4 000 000–7 000 000). In the 40–49 years age group PAOD incidence was 0.9% (95% CI: 0.1–1.7%), in the 50–59 years group it was 2.5% (95% CI: 0.5–4.5%) and in the 60–69 years group it was as high as 4.7% (95% CI: 2.5–6.9%), reaching 6.7% in males. However, in the population aged over 70 years, PAOD incidence was 14.5% (95% CI: 10.8–18.2%), 13.7% in males and 15% in females. A great majority of patients (over 95%!) had at least one risk factor of cardiovascular diseases, which should have been the target of cardiologic therapy. It should be stressed that 72% of patients had at least two risk factors. Over 60% of patients with PAOD had hypercholesterolaemia, 74% had arterial hypertension, 26% had diabetes mellitus and 33% were active cigarette smokers. In logistic regression analysis, after taking into account the age and

TABLE 5.
Multifactorial logistic regression analysis, presenting PAOD risk factors – modified from Giles F.J. et al. Leukemia 2013; 27: 1310-1315.

Risk factor		OR	95% confidence interval
Age (years)	≥ 65 vs < 65	2.753	0.632–11.184
Hyperlipidaemia	yes vs no	4.349	0.979–20.743
History of vascular disease	yes vs no	7.962	1.777–36.950
Exposure to TKI	nilotinib vs no TKI	**0.906**	**0.206–5.453**
	imatinib vs no TKI	**0.062**	**0.005–0.544**
	nilotinib vs imatinib	14.587	2.732–145.64

gender, the following risk factors were proven:

1. Cigarette smoking habit: **OR = 4.46** (95% CI: 2.25–8.84).
2. Diabetes mellitus: **OR = 2.71** (95% CI: 1.03–7.12).
3. Renal dysfunction (GFR <60 ml × min^{-1} × 1.73 m^{-2}): **OR = 2.00** (95% CI: 1.08–3.70).
4. Arterial hypertension: **OR = 1.75** (95% CI: 0.97–3.13).
5. Hypercholesterolaemia: **OR = 1.68** (95% CI: 1.09–2.57).

In the analysis, similarly as in previous studies, the importance was proven of additional risk factors associated with inflammatory condition, i.e. the role was noted of increased concentrations of fibrinogen and C-reactive protein (CRP) [109, 110]. That confirmed the importance of inflammatory condition for the progression of atherosclerosis. Importantly, among the patients with already diagnosed coronary artery disease, heart failure, or those who experienced a stroke, the observed PAOD incidence was 12.9% (95% CI: 7.6–18.2%); in the logistic regression analysis, after taking into account the age and gender, a statistically significant risk concerned the patients with coronary artery disease (OR = 2.54; 95% CI: 1.52–4.25).

In the more recent issue of The National Health and Nutrition Examination Survey from the years 1999–2004 only older patients, i.e. aged ≥ 60 years were included in the analysis [111]. The population assessed consisted of 3947 patients. No significant differences were proven in PAOD development depending on gender: 12.5% in males and 12% in females. In spite of the fact that the population was 20 years older than that in the former analysis, the influence of age on PAOD development was proven again. The incidence in the whole population was 12.2% (95% CI: 10.9–13.5%). Among the youngest subjects, i.e. in the 60–69 years age group, PAOD was diagnosed in 7.0% (95% CI: 5.6–8.4%) of the studied patients, in the 70–79 years group – in 12.5% (95% CI: 10.4–14.6%), and among the oldest, aged ≥ 80 years, even in 23.2% (95% CI: 19.8–26.7%). Similarly as in the former study it was demonstrated that black race was a significant risk factor of PAOD development, moreover it was proven that Latin American origin, particularly in women, was associated with a higher incidence of PAOD. In a logistic regression model taking into account the risk associated with age, sex and ethnic origin, it has been proven that the remaining significant PAOD risk factors include those, which can be controlled with adequate protective activities:

1. Active cigarette smoking: **OR = 5.48** (95% CI: 3.60–8.35).
2. Cigarette smoking in the past: **OR = 1.94** (95% CI: 1.39–2.69).
3. Diabetes mellitus: **OR = 1.81** (95% CI: 1.12–2.91).
4. Renal failure: **OR = 2.69** (95% CI: 1.58–4.56).
5. Mild renal dysfunction: **OR = 1.71** (95% CI: 1.22–2.38).
6. CRP concentration > 3.0 mg/l: **OR = 2.69** (95% CI: 1.24–5.85).
7. Non-optimally treated arterial hypertension: **OR = 1.95** (95% CI: 1.40–2.72).
8. Untreated arterial hypertension: **OR = 1.68** (95% CI: 1.13–2.50).

SUMMARY

The effect of the antitumour drug on specific molecular pathways, important for cardiac or vascular cells, is the main factor determining the development of cardiovascular complications. The aim of the research is to develop such targeted drugs, which would exert effects only on the target tissue, that is the tissue of the tumour with minimization of the influence on other tissues, including the heart. Another way is the search for a specific cardioprotection.

It is interesting that during the treatment of CML, drugs similar in molecular respect cause very diverse cardiovascular complications, from systolic heart failure to pulmonary arterial hypertension and obliterative arterial atherosclerosis. It is supposed that the presence of atherosclerosis risk factors is the common clinical denominator. It seems that they should be taken into account when starting successive lines of CML therapy. Patients with two or more atherosclerosis risk factors should remain under particularly careful cardiologic supervision.

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Address:
Sebastian Szmit, MD, PhD
Department of Pulmonary Circulation and Thromboembolic Diseases,
Centre of Postgraduate Medical Education
05-400 Otwock, ul. Borowa 14/18,
tel.: (22) 710-30-52
e-mail: s.szmit@gmail.com