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Risk factors and mechanisms contributing to TKI-induced vascular events in patients with CML★

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Abstract

Vascular adverse events (VAE) are an emerging problem in patients with chronic myeloid leukemia (CML) receiving second-generation BCR-ABL1 tyrosine kinase inhibitors (TKI). Relevant VAE comprise peripheral, cerebral, and coronary artery changes in patients receiving nilotinib, venous and arterial occlusive events during ponatinib therapy, and pulmonary hypertension in patients receiving dasatinib. Although each TKI binds to a unique profile of molecular targets in leukemic cells and vascular cells, the exact etiology of drug-induced vasculopathies remains uncertain. Recent data suggest that predisposing molecular factors, pre-existing cardiovascular risk factors as well as certain comorbidities contribute to the etiology of VAE in these patients. In addition, direct effects of these TKI on vascular endothelial cells have

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All authors contributed by joining in vital discussions, by drafting parts of the article, by preparing the Tables, and by critical reading the document. All authors approved the final version of the manuscript.

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been demonstrated and are considered to contribute essentially to VAE evolution. In the current article, we discuss mechanisms underlying the occurrence of VAE in TKI-treated patients with CML, with special emphasis on vascular and perivascular target cells and involved molecular (vascular) targets of VAE-triggering TKI. In addition, we discuss optimal patient selection and drug selection through which the risk of occurrence of cardiovascular events can hopefully be minimized while maintaining optimal anti-leukemic effects in CML, thereby following the principles of personalized medicine.

Keywords

BCR-ABL1-targeting drugs; Vascular adverse events (VAE); Vascular safety; Personalized medicine

1 Introduction

Chronic myeloid leukemia (CML) is a hematopoietic malignancy defined by uncontrolled, clonal expansion of myelopoietic cells carrying the *BCR-ABL1* oncogene [1,2]. The natural course of CML can be divided into a (mostly unrecognized) pre-leukemic (very early) phase with normal blood counts, and 3 clinically relevant phases: a chronic (indolent) phase (CP), an accelerated phase (AP), and a blast phase (BP) [1–3]. In CP, leukemic cells are largely addicted to the kinase activity of BCR-ABL1. As a result, the BCR-ABL1 tyrosine kinase inhibitor (TKI) imatinib is an effective agent in the treatment of patients with CP CML [4–7]. However, not all patients enter long-term disease-free survival with imatinib. Other patients develop intolerance against the drug. Resistance against imatinib often develops in the context of *BCR-ABL1* mutations [8–13]. Other mechanisms of resistance have also been described. These include, among others, pharmacologic resistance, intrinsic stem cell resistance, and *BCR-ABL1* amplifications [9,11,14,15]. In addition, apart from *BCR-ABL1*, the CML clone acquires multiple additional mutations during disease evolution which may (also) contribute to drug resistance [16]. Furthermore, even before *BCR-ABL1* is acquired, clonal hematopoiesis may exist and may contain clinically relevant mutations in various target genes [15–17]. This early clonal (pre-CML) phase may explain the rare occurrence of a BCR-ABL1-negative, TKI-resistant, relapse [17].

The treatment of imatinib-resistant patients with CML is still a challenging problem in clinical hematology. For high-risk patients who are young and fit, stem cell transplantation (SCT) is often recommended [18,19]. In other patients, second- or third-generation BCR-ABL1-targeting TKI, including nilotinib, dasatinib, bosutinib, or ponatinib, can be prescribed. Indeed, it has been reported in various studies that these agents exert major anti-leukemic effects in patients with imatinib-resistant CML [20–25]. In addition, these TKI reportedly induce complete cytogenetic (CCyR) and major molecular (MMR) responses in most patients with freshly diagnosed CML [26–29]. The efficacy of these drugs in newly diagnosed patients apparently exceeds the efficacy of imatinib, which may be explained by the very strong effect of these agents on wild type BCR-ABL1, their effects on various BCR-ABL1 mutants, as well as their effects on additional drug targets [30–33]. However, many of these targets are also displayed by non-hematopoietic cells and therefore may be

responsible for non-hematologic side effects, including vascular adverse events (VAE). In many CML patients treated with second-generation TKI, side effects are mild [20–29]. However, in other patients, severe organ damage is found. Although not recognized in initial studies, VAE have recently been identified as a clinically relevant issue in TKI-treated patients [34–36].

2 Each of the second-generation BCR-ABL1 TKI exhibits a unique profile of adverse events (AE), but most TKI produce VAE

For each of the BCR-ABL1 TKI, specific profiles of AE have been reported (Table 1). Pleural and/or pericardial effusions occur typically and rather specifically in patients treated with dasatinib [21,27,37–39]. The frequency of pleural effusions is lower in cases receiving 100 mg dasatinib per day compared to those treated with 140 mg dasatinib daily [38,39]. However, even at 100 mg daily, pleural effusions develop and accumulate over time [40]. Pulmonary hypertension and VAE have also been reported in patients treated with dasatinib (Table 1) [41–45]. However, the frequency of these AE seems to be rather low [41–45].

In patients treated with nilotinib, a number of non-hematologic AE have been described, including constipation, diarrhea, and a folliculitis-like skin rash [20,26]. Moreover, an increase in pancreatic enzymes, elevated fasting glucose levels, and hypercholesterolemia have been reported during therapy with nilotinib (Table 1) [20,26,46–49]. In addition, more and more data suggest that severe arterial changes develop rather frequently in patients receiving this TKI [34–36,50–53]. It has also been described that VAE accumulate over time during treatment and include coronary artery disease, cerebral ischemic disease (stroke), and peripheral arterial occlusive disease (PAOD) [34–36,50–53]. An interesting aspect is that no increase of venous thromboembolic events was reported in patients receiving nilotinib. In first trials employing nilotinib, VAE were overlooked, which is not surprising since arterial VAE are not 'oncologic AE' and were not reported in previous CML studies [36].

Ponatinib is a multi-targeted TKI that blocks most BCR-ABL1 mutant-forms, including T315I, and is thus often prescribed in patients with multi-resistant CML [25,54]. In first clinical trials, impressive anti-leukemic effects of ponatinib were demonstrated, and the drug was considered a useful new weapon against highly resistant CML [25,54]. However, unfortunately, ponatinib was soon found to produce VAE in a considerable number of patients (Table 1) [54]. These VAE include arterial as well as venous thromboembolic events and may occur relatively quickly (within months) after drug exposure which may point to direct effects of ponatinib on vascular cells [25,54–56].

Bosutinib is another third-generation TKI that has been used successfully in patients with drug-resistant CML [22–24,29]. Unlike nilotinib or dasatinib, bosutinib does not interact with a number of clinically relevant targets such as KIT or platelet-derived growth factor receptor (PDGFR) [32]. Therefore, the hope was that this TKI would produce no or less severe side effects compared to the other available BCR-ABL1 blockers. Indeed, compared to the other second/third-generation TKI, the VAE- and effusion rates are clearly lower in patients receiving bosutinib [22–24,29,57]. However, no safety data from long-term observational studies (> 10 years) are available, and at high doses (500 mg/day), clinically

relevant gastro-intestinal (GI) side effects (diarrhea) have been reported in bosutinib-treated patients (Table 1) [22–24,29,57]. At lower doses of bosutinib (300–400 mg/day), GI tract-involving AE are less frequently seen, and when occurring, these side effects are easily manageable unless the patient is suffering from a concomitant GI tract disease.

3 Frequencies of VAE in TKI-treated patients with CML

The exact incidence of VAE occurring during treatment with TKI is still a matter of debate. As mentioned before, this type of AE was overlooked in early reports of clinical trials – therefore the incidence of VAE in these studies could not be provided [20,26]. In consecutive (mostly retrospective) analyses, the reported incidence of VAE in nilotinib-treated patients with CML varied from study to study, and from center to center. In larger multi-center trials the frequency of VAE observed during nilotinib therapy ranged from about 0.5% to 15% (after 2–4 years observation) [36,50,51,58–63]. In smaller cohort studies conducted in specialized centers, the frequency ranged from roughly 5% to 35% (after 2–4 years observation) [34–36,64–69]. Despite these discrepancies, most studies concluded that: i) the frequency of VAE increases over time, ii) the frequency is higher in patients treated with higher doses of nilotinib (800 vs 600 mg daily) or ponatinib (45 mg vs 30 or 15 mg daily), and iii) there is a certain correlation between pre-existing cardiovascular risk factors and VAE development [34–36,50,51,58–69] (Table 2). The frequency of VAE in patients under imatinib is substantially lower than that reported for patients receiving nilotinib or ponatinib [51,59,67]. In fact, in most studies, less than 1% of all patients developed VAE while on imatinib [51,59,67,70]. It is also noteworthy that in contrast to nilotinib, imatinib is lowering blood glucose levels [71]. In addition, imatinib may suppress diabetes mellitus-associated atherosclerosis [72].

More recent data suggest that VAE can also occur in CML patients treated with dasatinib or bosutinib. However, the VAE rates in CML patients treated with dasatinib or bosutinib appears to be rather low (< 5% of patients) [45,63,65].

4 Risk factors predisposing for the development of VAE

VAE may preferentially develop in those TKI-treated patients who have pre-existing risk factors and co-morbidities. In most CML patients under nilotinib or ponatinib where recurrent VAE were reported, one or more risk factors for the evolution of atherosclerosis were identified [34–36,44,51,52,58–68]. These factors include age, sex, adiposity, arterial hypertension, smoking, diabetes mellitus, and hypercholesterolemia (Table 2). The European Society of Cardiology Score (ESC) is helpful in determining the actual risk [67]. Risk factors predicting the occurrence of pleural effusions during dasatinib have also been reported [73–75]. Interestingly, factors predisposing for dasatinib-induced effusion-formation and nilotinib-induced VAE are in part identical [73–75]. Likewise, age, arterial hypertension, and hypercholesterolemia are established predictive factors for pleural effusionformation under dasatinib and VAE evolution in CML patients treated with nilotinib (Table 2). This observation has obvious clinical implications as many older patients with CML appear to exhibit these risk factors in the Western world. There are also other factors that have to be considered in the context of VAE. One such denominator is the dose of the

TKI applied. Notably, clinically relevant AE, including VAE, appear to increase in frequency with higher TKI doses (45 mg ponatinib daily, 800 mg nilotinib daily) [51,58,59]. Therefore, the risk of development of severe VAE under TKI therapy can be decreased quite substantially by lowering the dose of the drug. In addition, the risk can be lowered by shorting the time of exposure to these TKI. Another important point may be the type of previous therapies. In particular, the risk may be elevated in patients receiving certain TKI sequentially. The VAE-risk may be particularly high when using nilotinib and ponatinib in a sequential manner [55]. Therefore our group recommends that this TKI-sequence is avoided if possible.

Recent data suggest that clonal hematopoiesis (CH) increases with age and that in these patients, the risk for development of both, hematologic neoplasms and severe cardiovascular disorders, increases [76]. Indeed, distinct CH type-mutations may predispose not only for clonal expansion once *BCR-ABL1* has been acquired by neoplastic stem cells, but also for the development of cardiovascular disorders. It is also important to understand that early, BCR-ABL1-negative, CH persists (and expands over time) even after an overt CML has developed, and that TKI therapy is unable to eradicate (all of) this BCR-ABL1-negative CH-portion of the disease or (all) other new CH clones. Whether the CH-mediated risk of occurrence of cardiovascular events also contributes to VAE development in TKI-treated patients with CML is currently under investigation. Preliminary data suggest that CH-related mutations indeed cluster in those patients who developed VAE during therapy with nilotinib (P.V., E.H., G.H., unpublished observation). So far it remains unknown how CH can predispose for VAE in patients with CML. One possibility would be that pluripotent, mutated (CH+) stem cells produce clonal endothelial cells that are more susceptible to proatherogenic stimuli. Another possibility could be that clonal (CH+) leukocytes or platelets induce pro-atherogenic effects on vascular cells. Similar concepts and hypotheses have been developed around JAK2-mutated disorders where CH and clonal (often JAK2-mutated) endothelial cells may (also) contribute to the etiology of VAE [77].

Finally, genetic risk factors may predispose for VAE development in patients treated with nilotinib or ponatinib. However, only little is known about these factors [78]. In fact, the classical genetic determinants of thrombophilia (loss-of-function mutations in genes encoding protein C or S or anti-thrombin; factor V Leiden and prothrombin G20210A variants; non-0 blood groups) have so far not been analyzed in the context of VAE occurring in TKI-treated patients. It may be of interest to examine these factors in affected CML patients in forthcoming studies. All in all, more needs to be learned about genetic and other risk factors contributing to VAE development in TKI-treated patients. Also, little is known about cellular interactions and molecular mechanisms that underlie TKI-induced VAE.

5 Target cells of nilotinib and ponatinib potentially involved in TKI-induced VAE

A number of different target cells may be involved in TKI-induced VAE and TKI-mediated metabolic changes (Table 3). Because of the relatively short time-interval (often within 12 months) between drug exposure and occurrence of VAE, direct TKI effects on vascular cells

have been postulated [36,52,67]. Some experts believe that nilotinib and ponatinib can even provoke vasospasms or rapid stenosis in larger or smaller arteries [50,53]. Based on recent studies, there is now good evidence to suggest that nilotinib and ponatinib exert multiple effects, including pro-atherogenic effects, on vascular endothelial cells [67,79,80]. For example, both TKI may promote the expression of certain pro-atherogenic surface adhesion receptors on human umbilical vein-derived endothelial cells (HUVEC) *in vitro* [67,79,80]. Moreover, studies in Apo-E-deficient mice suggest that nilotinib can promote high-fat-diet-induced atherosclerosis [79]. The pro-atherogenic effect of nilotinib has also been confirmed in CML patients by measuring the ankle brachial index (ABI) during therapy [51]. During and after arterial stenosis, the vascular repair (that includes neo-angiogenesis) is of critical importance. In particular, such repair processes can lead to recanalization of thrombosed vessels and facilitate the survival of the affected larger vessels by protecting the vasa vasorum-mediated nutrition of the vessel wall. In addition, newly generated blood vessels may protect the surrounding tissues from necrosis. However, nilotinib and ponatinib are anti-angiogenic agents and inhibit proliferation and survival of human endothelial cells *in vitro* [67,79–81]. In addition, nilotinib has been described to block neo-angiogenesis and vascular reperfusion (and thus vascular repair) in a model of hind-limb ischemia in mice [67].

Apart from endothelial cells, other cells potentially relevant in the etiology of VAE may also be affected by nilotinib- or ponatinib therapy (Table 3). These cells include, among others, macrophages, muscle cells, and mast cells. For example, both TKI inhibit the kinase activity of KIT and thereby block mast cell activation and differentiation. Since mast cells are important vascular repair cells producing heparin and uncomplexed (bioactive) tissue type plasminogen activator (tPA) [82–84], these TKI effects may be relevant. Mast cell deficiency can also be induced by imatinib (a strong KIT inhibitor) [85], but imatinib-treatment is not associated with increased VAE rates [51,59,67,70]. This observation suggests that other (additional) pro-atherogenic drug effects and metabolic drug effects are required to develop overt VAE. Indeed, it has been described that imatinib is unable to block endothelial cell proliferation or to induce a pro-atherogenic endothelial cell phenotype [67,79–81].

Several different studies have shown that nilotinib produces a number of relevant metabolic changes in patients with CML, including an increase in cholesterol levels and an increase in fasting glucose levels [20,26,34,46–49]. In a few patients overt diabetes mellitus develops. In these patients, peripheral insulin resistance has been identified as a potential mechanism [46]. More recent studies have suggested that nilotinib may also affect insulin production in these patients [86]. However, this hypothesis could not be confirmed by examining insulin production in highly purified human islet cells (P.V., G.H., E.H. unpublished observation). More recently, it has been described that genetic risk factors contribute to nilotinib-induced diabetes mellitus [87]. However, the exact cellular interactions and mechanism underlying nilotinib-induced hyperglycemia and hypercholesterolemia remain unknown. All in all, nilotinib and ponatinib act on a number of different targets cells, and many of these effects may facilitate or trigger metabolic changes and the development of atherosclerosis in patients with CML (Table 3). In the following paragraph, the molecular targets of nilotinib and ponatinib involved in metabolic changes and the evolution of VAE are discussed.

6 Molecular targets and potential molecular mechanisms contributing to TKI-induced VAE

Nilotinib and ponatinib interact with a considerable number of clinically relevant (vascular) targets in endothelial cells. Whereas many of these targets are also identified by imatinib, others are selectively recognized and blocked by nilotinib and/or ponatinib. Molecular nilotinib-targets that are spared by imatinib include Tie-2/TEK, ABL2, JAK1, and several MAP kinases (Table 4) [67,79,80]. Tie-2/TEK is a well-known vascular target that has been implicated in the pathogenesis of vascular disorders. The VEGF receptor KDR is identified by ponatinib but not by nilotinib [79–81,88]. However, nilotinib-induced targeting of ABL2 is followed by downregulation of KDR expression in endothelial cells [79]. Since Tie-2/TEK, KDR, and MAP kinases have been implicated in endothelial cell survival and angiogenesis, these targets may be responsible for TKI-induced inhibition of endothelial cell growth. Other molecular targets primarily detected by nilotinib but not by imatinib include DDR1 and JAK1 [30,79]. However, these molecules have so far not been implicated in the etiology of atherosclerosis or angiogenesis. Other relevant target kinases may be the M-CSF receptor FMS and FMS-related tyrosine kinase-1, both of which are recognized by ponatinib. These targets play a role in macrophage function and have been discussed in the context of atherosclerosis [89,90]. Other targets, like KIT or PDGFR, are recognized not only by nilotinib and ponatinib, but also by imatinib (Table 4) [30]. Whereas KIT is an essential target of mast cells [82–84], PDGFR may play a role in the regulation of growth and function of (peri)vascular cells and perivascular cells during the process of atherosclerosis [91,92]. However, so far it remains unknown what targets of nilotinib and ponatinib are involved in TKI-induced upregulation of pro-atherogenic molecules in endothelial cells. In addition, current research is attempting to identify genetic and somatic factors predisposing for TKI-mediated VAE and the susceptibility (responsiveness) of various target cells to TKI effects. One interesting aspect mentioned before is that endothelial (progenitor) cells may in part be clonal cells in CML and derived from an early (pluripotent) stage of stem cell evolution (pluripotent CH-derived stem cells). Whether clonality of vascular cells predisposes for TKI-induced endothelial damage and development of VAE, remains at present unknown. Another unresolved question is what TKI-targets are involved in the metabolic changes seen during treatment with nilotinib or (less frequently) ponatinib. Potential candidate targets include the insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF1-R) (Table 4) [93,94]. Although several of these receptors may not be directly recognized by nilotinib or ponatinib, several critical down-stream signaling kinases may represent targets of these TKI.

7 Prevention of VAE in patients with CML by applying personalized medicine approaches

Based on the clinical impact of VAE concerning morbidity, mortality, and quality of life as well as the relatively good prognosis in CP CML, it seems of utmost importance to avoid drug-induced development of VAE in all patients, regardless of age and other factors. It is also important to state that VAE can develop at any age and that VAE may be a reason to exclude patients from SCT. A first important step in prevention is proper patient-selection

and selection of the optimal second- or third-line TKI. These TKI should not only be selected on the basis of disease-related variables like *BCR-ABL1* mutations, but also based on patient-related factors, such as comorbidities or risk factors predisposing for VAE development. Indeed, more and more treatment-recommendations and algorithms take patient-related variables into account, thereby following the principles of personalized medicine [11,95–98].

It is almost impossible to detect adult patients in the Western World who have absolutely no risk factors for VAE development. When multiple risk factors are detected, the patient should not be exposed to nilotinib or ponatinib if another TKI can be offered. One unfortunate aspect in this regard is that several VAE-predicting factors are also risk factors for the development of pleural effusions during dasatinib [73–75]. Especially in elderly patients suffering from multiple comorbidities, neither nilotinib nor dasatinib may be a preferred TKI. Whether bosutinib represents a more reasonable alternative in such patients has to be demonstrated in clinical trials. In each case, the potential benefits of these TKI have to be balanced against the potential risk to develop VAE or other relevant AE [11,95–98]. Several strategies have been proposed to keep the risk of severe VAE in TKI-treated patients to a minimum (Table 5). One is to start with imatinib upfront in most patients, and to switch to second-line TKI only when a suboptimal or no response is seen or the patient is at high risk to transform to AP/BP. Indeed, in many centers, imatinib is regarded standard frontline-therapy in 'good-risk' CML. An alternative for high/high risk patients (=high AP/BP-risk and high VAE-risk) may be to start with bosutinib or to switch from imatinib to bosutinib after 3 or 6 months. Another strategy is to induce a stable, deep MR with nilotinib, dasatinib or ponatinib, and to discontinue treatment as soon as possible. The disadvantage of this approach is that it may take months until a deep MR can be reached [99]. Therefore, a more logical strategy may be to switch to imatinib or bosutinib as soon as MR4 is reached and to maintain the patient on such TKI for another 2 years before discontinuation. However, this strategy may still be associated with VAE events because it may take several months to years deep MR is reached. An elegant alternative concept is to introduce rotation therapy, where a potent but 'vasculopathic' TKI (nilotinib or ponatinib) is combined with a less toxic TKI (imatinib or bosutinib) in 1–3 months-intervals [100,101]. All these strategies should be tested in prospective clinical trials as they may indeed combine safety and efficacy and may lead to cures and better treatment-free and AE-free survival in CML.

8 Management of VAE in patients with CML

Once a VAE has been detected in a patient with TKI-treated CML, all relevant organs need to be examined for the presence of vascular changes. Then, the type of pathology and the grade of the arterial occlusive disease (e.g. PAOD grade) has to be determined. Management and treatment of these patients depend on the overall situation in each case. For example, in cases with grade I or II PAOD, optimal anti-PAOD therapy and elimination of cardiovascular risk factors as much as possible (smoking, obesity, diabetes mellitus, arterial hypertension, hypercholesterolemia) may lead to a 'stabilization' of the condition, so that ponatinib or nilotinib can be maintained (often at reduced dose) which is often important since several of these patients have no realistic alternative (e.g. cases presenting with *BCR-ABL1* T315I). For these patients, a cardiovascular follow-up with surveillance of metabolic and angiologic

parameters (including repeated ABI measurements) is recommended [36,51]. Moreover, prophylactic therapy with aspirin should be considered. Other drugs may also be required to prevent the progression of VAE and to keep the metabolic syndrome or blood pressure under control. These patients may receive anti-diabetic drugs (when diabetes mellitus develops), cholesterol-lowering agents, or antihypertensive drugs, like calcium channel blockers that may also be capable of counteracting vasospasm.

In cases suffering from high-grade PAOD (grade III or grade IV) the management is a more challenging task. Several of these patients may still require treatment with ponatinib or nilotinib (e.g. because of certain *BCR-ABL1* mutations) of their CML. In other cases, ponatinib or nilotinib can be replaced by another TKI. In select patients with deep and long-lasting MR (MR4 or deeper), discontinuation of TKI-treatment may be an option. For other patients, the current recommendation remains to change TKI therapy if possible. Peripheral VAE requiring revascularization, cerebral artery occlusive events, and myocardial infarction are also indications to employ a different TKI [36]. In all these cases, the use of platelet aggregation blockers or anticoagulation need to be considered, according to generally accepted guidelines. In addition, it is important to eliminate all identified risk factors and to treat hyperlipidemia, diabetes mellitus, and arterial hypertension in these patients [36].

9 Concluding remarks and future perspectives

During the past few years, the mechanisms that may contribute to the development of cardiovascular events in TKI-treated patients with CML have been examined and have in part been deciphered. Accumulating evidence suggests that multiple mechanisms act together to cause VAE in these patients. Key factors are conventional cardiovascular risk factors, like age, diabetes mellitus, or hypertension; molecular risk factors such as age-related clonal (somatically mutated) hematopoiesis; and pre-existing cardiovascular comorbidities. The hope for the future is that based on this knowledge, the individual risk of patients with CML can be minimized by better selection of patients and optimal TKI-selection, following the principles of personalized medicine. We consider a personalized approach an important point since most TKI-responding patients with CML have a normal life expectancy but still require TKI therapy on a long-term (often life-long) basis, which implies that not only disease-free survival but also long-term safety is an important goal.

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Table 1
The specific profiles of non-hematologic adverse events reported in CML patients treated with BCR-ABL1-targeting tyrosine kinase inhibitors (TKI).^a

Adverse Event	BCR/ABL1-targeting TKI				
	imatinib	nilotinib	dasatinib	bosutinib	ponatinib
Skin rash	+	++	+	+	++
Facial edema	++	+/-	+/-	+/-	-
Peripheral edema	+	+/-	+	+/-	-
Pleural effusion	-	-	+	-	-
Pericardial effusion	-	-	+/-	-	-
Constipation	+	+	-	-	+
Diarrhoea	++	+	+	++	-
Viral (CMV) reactivation	-	-	+/-	-	-
Major bleeding	+/-	-	+/-	-	-
Arterial occlusive disease	-	++	+/-	-	+
Venous thrombosis	-	-	-	-	+/-
Pulmonary hypertension	-	-	+/-	-	-
Muscle cramps/myalgia	++	+	+	+/-	+
Increase in fasting glucose	+	++	-	-	-
Increase in lipase or amylase	+	++	-	-	+
Renal function impairment	+/-	+/-	-	+/-	-

Data from larger and smaller clinical trials and observational trials were screened.

Score of rates of adverse events (any grade) occurring in TKI-treated patients:

++, reported in >20% of patients in at least 2 different studies.

+, reported in >5% of patients in at least 2 different studies.

+/-, reported in 1–5% in at least 1 study.

-, reported in less than 1%.

^a Adopted from Valent et al., Blood 2015 [36] with slight modifications.

Table 2
Clinical risk factors contributing/predisposing to the occurrence of vascular adverse events (VAE) in CML patients treated with nilotinib or ponatinib.

Specific risk factor that may contribute	
Risk factor type	to VAE development during TKI therapy
Predisposing genetic factors	genetic variations predisposing to the occurrence of hypercholesterolemia or the development of diabetes mellitus
Age and sex ^a	advanced age, males > females
Acquired somatic mutations	clonal age-related hematopoiesis; clonal hematopoiesis of indeterminate potential (may predispose for development of CML as well as development of VAE)
Life-style-related risk factors	nicotine consumption ^a , adipositas, refused/irregular drug intake
Pre-existing overt co-morbidities	arterial hypertension ^a , atherosclerosis, hypercholesterolemia ^a , diabetes mellitus, thrombosis, stroke, other arteriopathies
Dose of TKI and TKI sequence	higher doses of nilotinib (800 mg/day) or ponatinib (45 mg/day); sequential exposure to nilotinib and ponatinib (see also below: time of exposure to TKI).
Time of TKI therapy	longer exposure to nilotinib or ponatinib: most VAE occur after 12 months – and VAE continue to accumulate over time

Abbreviations: VAE, vascular adverse event; TKI, tyrosine kinase inhibitor.

^aThese risk factors are included in the European Society for Cardiology (ESC) Score.

Table 3
Target cells of nilotinib and/or ponatinib and their potential role in the etiology of metabolic changes, development of atherosclerosis, and evolution of VAE.

Target cell	Possible effects of the TKI Nilotinib (NI) and Ponatinib (PO)	Potential relevant clinical consequences of TKI effects regarding VAE ^a
Vascular endothelial cells	i) may transform endothelial cells into a 'pro-atherogenic' phenotype with upregulation of various cyto-adhesive molecules (NI > PO) ii) inhibit endothelial cell growth and survival and thus block (neo)-angiogenesis (PO > NI)	may induce/promote atherosclerosis (NI and PO) may counteract vascular regeneration and repair during and after stenosis
Platelets	may inhibit platelet function but do not augment platelet adhesion or aggregation (NI, PO)	–
Macrophages	May inhibit cytokine-induced and FMS-mediated growth	–
Mast cells	i) inhibit SCF/KIT-dependent development of mast cells from their progenitor cells, and thus induce mast cell deficiency ii) block SCF/KIT-mediated release of heparin and tPA from mast cells (NI, PO)	mast cell deficiency after several months of therapy: consecutive loss of heparin and bioactive tPA and thus impaired vascular repair
Insulin-producing islet cells	no inhibitory effects of TKI on insulin production in islet cells reported so far (NI/PO)	– ^b
Tissue cells involved in peripheral insulin-resistance	impaired glucose metabolism (target cells for NI and PO not identified so far; involved potential molecular targets: IGF1-R, IR, others?)	peripheral insulin resistance (NI) ^b

Abbreviations: VAE, vascular adverse event; TKI, tyrosine kinase inhibitor; NI, nilotinib; PO, ponatinib; SCF, stem cell factor; tPA, tissue type plasminogen activator; IGF1-R, insulin-like growth factor-1 receptor; IR, insulin receptor.

^aProposed (hypothetical) clinical consequence of target cell inhibition.

^bIn one study a direct effect of nilotinib on insulin production has been postulated [86].

Table 4
Molecular targets of nilotinib and/or ponatinib and cell types expressing these targets.

Molecular target	IM	NI	PO	Expressed in
KDR (VEGFR)	–	^a	+	Endothelial cells
Tie-2/TEK	–	+	+	Endothelial cells
ABL2	+	+	+	Endothelial cells and other cells
KIT (SCF-R)	+	+	+	Stem cells, progenitor cells, mast cells, melanocytes, Cajal cells
PDGFRA	+	+	+	Stromal cells, megakaryocytes
PDGFRB	+	+	+	Stromal cells, megakaryocytes
FLT3	–	–	+	Myeloid stem and progenitor cells
FMS/CSF1R	+	+	+	Macrophages & their progenitors
FGFRs	–	–	+	Diverse mesenchymal cells
DDR1	+	+	nk	Broadly expressed in tissue cells
MAPK14	–	+	nk	Broadly expressed
IGF1-R	–	–	nk	Broadly expressed
IR	–	–	nk	Broadly expressed

^aNilotinib does not recognize KDR, but is a strong inhibitor of ABL2; blocking ABL2 leads to downregulation of KDR. Abbreviations: TKI, tyrosine kinase inhibitor; IM, imatinib; NI, nilotinib; PO, ponatinib; nk, not known; VEGF-R, vascular endothelial cell growth factor receptor; PDGF, platelet-derived growth factor; SCF1R, colony-stimulating factor-1 receptor; FGFRs, fibroblast growth factor receptors; IGF1-R, insulin-like growth factor-1 receptor; IR, insulin receptor.

Table 5
Proposed strategies to minimize the risk of VAE-evolution in patients with CML.

A: Personalized medicine approaches – patient selection:

Selection of patients and selection of TKI based on co-morbidities, cardiovascular risk factors, and the biology of CML

Exclude patients with cardiovascular co-morbidities from therapy with nilotinib and ponatinib

Exclude patients with cardiovascular risk factors (high ESC score, molecular risk factors) from therapy with nilotinib and ponatinib

B: During treatment: treatment algorithms, schedules and dosing

Frontline use of imatinib in patients with CP CML

Keep nilotinib and ponatinib exposure times to a minimum

Reduce the dose of nilotinib or ponatinib if possible

Avoid sequential application of nilotinib and ponatinib

Switch to other TKI with lower risk concerning VAE development once a deep MR has been reached (prophylaxis)

Switch to other TKI with lower risk concerning VAE development once a VAE has developed

C: Alternative treatment concepts and co-medication

Discontinue TKI therapy after 2 years in deep MR (MR4 or deeper)

Stem cell transplantation = SCT (young and fit patients)^a

Antibody-based CML stem cell eradication followed by TKI discontinuation

Discontinue TKI therapy and introduce immunotherapy or other experimental therapies as maintenance

Prophylactic co-medication with aspirin, gliptins, and statins

TKI rotation therapy: combining more toxic TKI with less toxic TKI

Abbreviation: CP, chronic phase; CML, chronic myeloid leukemia; VAE, vascular adverse event; TKI, tyrosine kinase inhibitor; MR, molecular response; ESC, European Society for Cardiology.

^aIn young and fit patients who are potential candidates for SCT, it is of considerable importance to avoid any occurrence of a VAE before SCT. Therefore, in these patients, it is as important to select optimal and safe therapy as in older patients with comorbidities.