Spotlight Article

Vascular Safety Issues in CML Patients treated with BCR/ABL1 Kinase Inhibitors

Peter Valent1,2, Emir Hadzijusufovic1,2,3, Gerit-Holger Schernthaner4, Dominik Wolf5, Delphine Rea6, Philipp le Coutre7

1Department of Internal Medicine I, Division of Hematology & Hemostaseology, Medical University of Vienna, Austria; 2Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Austria; 3Department/Clinic for Companion Animals and Horses, Clinic for Small Animals, Clinical Unit of Internal Medicine, University of Veterinary Medicine Vienna, Austria; 4Department of Internal Medicine II, Division of Angiology, Medical University of Vienna, Austria; 5Medical Clinic III for Oncology, Haematology and Rheumatology, University Hospital Bonn (UKB), Bonn, Germany; 6Service d’Hématologie Adulte, Hôpital Saint-Louis, Paris, France; and 7Medical Clinic for Hematology and Oncology, Campus Virchow, Charité, Medical University of Berlin, Germany

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Correspondence:
Peter Valent, M.D.
Department of Internal Medicine I
Division of Hematology & Hemostaseology and
Ludwig Boltzmann Cluster Oncology
Medical University of Vienna
Waehringer Guertel 18-20
A-1090 Vienna, Austria
E-mail: peter.valent@meduniwien.ac.at

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Abstract

Vascular safety is an emerging issue in patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs). Whereas imatinib exhibits a well-documented and favorable long-term safety profile without obvious accumulation of vascular events, several types of vascular adverse events (VAEs) have been described in patients receiving second- or third-generation BCR/ABL1 TKIs. Such VAEs include pulmonary hypertension in patients treated with dasatinib, peripheral arterial occlusive disease as well as other arterial disorders in patients receiving nilotinib, and venous and arterial vascular occlusive events during ponatinib. Although each TKI interacts with a unique profile of molecular targets and has been associated with a unique pattern of adverse events, the mechanisms of drug-induced vasculopathy are not well understood. In this spotlight-article, recent data and concepts around VAEs in TKI-treated patients with CML are discussed, with special reference to potential mechanisms, event-management and strategies aimed at avoiding the occurrence of such events in long-term treated patients.
Introduction

Chronic myeloid leukemia (CML) is characterized by uncontrolled expansion of myeloid cells and the *BCR/ABL1* oncogene.\(^1,2\) The BCR/ABL1 tyrosine-kinase inhibitor (TKI) imatinib is considered a ‘gold-standard’ of treatment of patients with newly diagnosed CML.\(^3-6\) However, resistance against imatinib may occur, often in association with *BCR/ABL1* mutations.\(^5,7\) Treatment of TKI-resistant CML is an emerging challenge. For these patients, more effective TKIs, including nilotinib, dasatinib, bosutinib and ponatinib, have been developed and are successfully used in clinical trials and daily practice.\(^6-16\)

Novel TKIs also exert major anti-leukemic activity in freshly diagnosed patients with CML, with higher rates of complete cytogenetic (CCyR) and molecular (MMR) responses compared to imatinib.\(^17-20\) Superior efficacy of these TKIs may result from stronger effects on BCR/ABL1, effects on various BCR/ABL1-mutants, and suppression of additional drug-targets.\(^21-25\) However, several targets are also expressed in non-hematopoietic cells and may therefore be responsible for non-hematologic adverse events (AEs). Whereas in many cases, side effects are mild and manageable\(^12-20\), some of these patients develop severe organ damage.\(^26-30\) One emerging type of clinically relevant AEs in patients receiving second- or third-generation BCR/ABL1 TKIs are vascular AEs (VAEs).\(^29-32\)
The unique profiles of AEs seen with BCR/ABL1 TKIs

A unique spectrum of AEs has been reported for each TKI used to treat CML (Supplemental Table S1). In dasatinib-treated patients, the occurrence of pleural and/or pericardial effusions is an issue.\textsuperscript{13,18,26-28} Several other non-hematologic AEs have also been described for dasatinib.\textsuperscript{13,27,33} The frequency of AEs is lower in patients receiving 100 mg dasatinib once daily compared to higher doses.\textsuperscript{28,34,35} However, even at 100 mg/day, pleural effusions may develop.\textsuperscript{28,36} Recently, pulmonary hypertension has been reported in patients treated with dasatinib (Supplemental Table S1).\textsuperscript{37-39} However, the frequency of this AE is low\textsuperscript{37-39} and the same holds true for arterial occlusive events, although VAEs have been reported (Supplemental Table S1).\textsuperscript{40}

Nilotinib-treated patients may develop elevated pancreatic enzymes, an increase in serum bilirubin and/or an increase in fasting glucose levels.\textsuperscript{12,17,29,41} Moreover, the cholesterol level may increase.\textsuperscript{42,43} Other non-hematologic AEs include constipation, diarrhea and a folliculitis-like skin rash (Supplemental Table S1).\textsuperscript{17,41} During the past few years more and more data suggest that severe peripheral arterial occlusive disease (PAOD) and other cardiovascular events develop in patients receiving nilotinib.\textsuperscript{29-31,44-47} Several of these patients suffer from a rapidly progressive form of PAOD.\textsuperscript{29-31} Unfortunately, PAODs were also found to accumulate over time, and were recorded not only in patients in whom cardiovascular risk factors were present, but sometimes also in younger patients.
without risk factors concerning PAOD.\textsuperscript{29,30,45,46} In addition to PAOD, nilotinib-treated patients may develop cerebral ischemia and myocardial infarction.\textsuperscript{29-31,47} In contrast, no increase in venous thromboembolic events has been reported for these patients. A remarkable aspect is that VAEs were not reported in initial clinical trials testing nilotinib.\textsuperscript{12,17}

Ponatinib is another novel TKI used to treat patients with drug-resistant CML, including subclones expressing BCR/ABL T315I.\textsuperscript{16,32} First clinical trials have shown that ponatinib is a highly potent agent and useful for the treatment of TKI-resistant CML.\textsuperscript{16,32} However, unfortunately, ponatinib triggers arterial hypertension as well as VAE-development.\textsuperscript{32} Initially, these events were thought to accumulate in ponatinib-treated patients because of their prior exposure to nilotinib.\textsuperscript{32,48,49} More recent data suggest, however, that ponatinib can also induce VAEs in patients who had not received nilotinib.\textsuperscript{40} As a result, ponatinib was transiently removed from the market in the US in 2013. Remarkably, both arterial and venous thromboembolic events have been reported in ponatinib-treated patients.\textsuperscript{32,40,49}

Bosutinib is another novel TKI that has been developed as a third-line BCR/ABL1-targeting drug.\textsuperscript{14,20,24,50} Similar to nilotinib or dasatinib, bosutinib inhibits a number of BCR/ABL1 mutants and other kinase-targets, but does not block BCR/ABL1 T315I.\textsuperscript{20,24} In contrast to other TKIs, bosutinib does not recognize KIT or PDGFR.\textsuperscript{24} The AE profile of bosutinib is also different compared to that of other TKIs. Notably, bosutinib-treated patients may develop diarrhea
and an exanthema.\textsuperscript{20,50} In addition, arterial hypertension\textsuperscript{51}, pleural effusions and VAEs have been described in patients receiving bosutinib. However, the frequency of VAEs is much lower compared to patients receiving nilotinib or ponatinib (Supplemental Table S1).\textsuperscript{51,52}

**Reported frequencies of VAEs in TKI-treated patients with CML**

So far, little is known about the exact incidence of VAEs in long-term TKI-treated patients with CML and about factors predisposing for VAE-development. From a clinical point of view, these are essential questions since many of these patients are candidates for long-term treatment or may be young and thus potentially transplantable, so that comorbidities must be kept to a minimum. In initial Phase I and II trials, VAEs were not captured, and therefore, VAE-rates were not provided.\textsuperscript{12,16,17} Later, several centers recognized a potential relationship between drug-intake and VAE-development, and therefore started to record VAEs systematically. In addition, several retrospective analyses were started, with the aim to explore the frequency of VAEs in clinical trials. However, the rates of VAEs in these surveys varied considerably. After an observation time of about 2 years the numbers (percentage) of CML patients developing VAEs during nilotinib ranged between 1% and 29% (Table 1).\textsuperscript{29-31,44-47,53-60} It was also found that the numbers (percentage) of patients developing VAEs increase over time (Table 1).\textsuperscript{54,55} By contrast, in retrospective analyses of larger clinical trials, the numbers
of patients with documented VAEs remained low (<5%). However, in first prospective analyses, the frequency of VAEs in these trials is again higher and increases over time. There is also some indication that TKIs trigger VAE-development in a dose-dependent manner. Likewise, nilotinib-treated patients may be at higher risk to develop VAEs when receiving 2x400 mg/day compared to a lower dose (2x300 mg/day).44,51

The frequency of all VAEs in patients treated with ponatinib in the PACE trial was 8.9% after 11 months and 17.1% after 24 months (Table 1).32,40,49 As mentioned before, many of these patients had received nilotinib prior to their inclusion in the PACE trial. However, VAEs were also recorded in patients who did not receive nilotinib prior to ponatinib.40 On the other hand sequential treatment with nilotinib and ponatinib may be associated with a particularly high risk as recently documented in single case reports.48

Although no long-term data from prospective trials are available, retrospective studies suggest that the frequency of VAEs in patients receiving imatinib is significantly lower than that observed with nilotinib or ponatinib.54,61 In one study, less than 1% of all patients developed PAOD during imatinib.61 It is noteworthy that in contrast to nilotinib, imatinib is not increasing but may even decrease blood glucose levels.62 In addition, imatinib may counteract diabetes mellitus-associated atherosclerosis.63 Similar to imatinib, the frequency of VAEs in patients treated with dasatinib or bosutinib appears to be rather low.
Why did we initially overlook VAEs in our patients with CML?

A number of different factors may explain why we did initially overlook the VAE-triggering potential of nilotinib and ponatinib (Table 2). This is an important issue and needs attention in the era of TKI therapy. Specific factors and potential explanations are discussed in the Supplemental Appendix.

Risk factors predisposing for the development of VAEs

TKI-related side effects may preferentially develop in patients who have pre-existing risk factors. Likewise, in most CML patients treated with nilotinib or ponatinib in whom severe recurrent VAEs were recorded, one or more risk factors for the development of atherosclerosis were found. These include obesity, arterial hypertension, smoking, diabetes mellitus and hypercholesterolemia. Similarly, several risk factors for the development of pleural effusions during dasatinib-therapy have been described (Supplemental Table S2). Interestingly, some of the risk factors predisposing for dasatinib- and nilotinib-related AEs are the same. For example, age, arterial hypertension and hypercholesterolemia are considered risk factors for both pleural effusion-formation under dasatinib and PAOD-development in patients receiving nilotinib (Supplemental Table S2).
There are several other factors that have to be considered in these patients. One such risk factor is the dose of the TKI. Notably, clinically relevant AEs, including VAEs, appear to increase in frequency with higher TKI-doses.\textsuperscript{27,34,35,53,65} In other words, it may well be that the rates of severe VAEs can be decreased substantially by lowering the TKI-dose.\textsuperscript{53} In addition, the risk may decrease with shorter exposure-times. Another important point is previous therapy. In fact, the risk may be higher in patients receiving certain TKIs in a sequential manner.\textsuperscript{48}

**Potential mechanisms underlying VAEs in TKI-treated patients**

Several different factors may contribute to the development of VAEs in patients treated with nilotinib or ponatinib (Supplemental Table S3).\textsuperscript{54,66,67} Because of the relatively short time-interval between drug exposure and occurrence of VAEs, a direct effect of these TKIs on vascular and/or perivascular cells has been postulated.\textsuperscript{54} Indeed, nilotinib may exert direct pro-atherogenic and anti-angiogenic effects on endothelial cells (Supplemental Table S3).\textsuperscript{54} Whereas the pro-atherogenic effect may lead to arterial stenosis, the anti-angiogenic effect of the drug may block repair mechanisms leading to recanalization and reperfusion once arterial stenosis occured.\textsuperscript{54} It has also been described that nilotinib may cause vasospasms which may also be relevant and trigger PAOD-development.\textsuperscript{47} In addition, nilotinib exerts metabolic effects, including an increase in cholesterol and fasting glucose levels (Supplemental Table S3).\textsuperscript{17,29,43,68,69} Some patients
even develop overt diabetes mellitus.\textsuperscript{29,68} All these drug effects are considered to act together to trigger atherosclerosis and VAE-development.\textsuperscript{52,68} Recently, the pro-atherogenic effects of nilotinib have been confirmed by measuring the ankle brachial index (ABI) in patients with CML.\textsuperscript{31} So far, no data on ponatinib-effects on vascular cells are available. Preliminary data suggest that ponatinib also counteracts endothelial cell growth and survival (P.V. and E.H., unpublished observation). So far, little is known about molecular targets responsible for nilotinib and ponatinib effects on vascular endothelial cells.\textsuperscript{54} Several of these target-antigens are major angiogenic receptors, like KDR (a known ponatinib-target) or TEK/Tie-2.\textsuperscript{54} The impact of these targets in VAE-development is under investigation.

**Management of VAEs in patients with CML**

In patients developing VAEs during treatment with nilotinib or ponatinib, management depends on the overall situation in each case. In patients with low grade (grade I and II) PAOD, optimal therapy of PAOD and the elimination of all risk factors (smoking, obesity, diabetes mellitus, arterial hypertension, hypercholesterolemia) may lead to a stabilization of the condition, so that treatment can be continued which is important as some of these patients may have no other therapeutic options (e.g. those with BCR/ABL1 T315I). For these patients a thorough follow-up regarding cardiovascular and metabolic parameters
(including vascular ultrasound investigations, ABI, cholesterol and fasting glucose levels, HbA1c) and PAOD-related risk factors (age, obesity, arterial blood pressure, smoking habits) is recommended. In addition, prophylactic treatment with aspirin should be considered. Additional co-medication may also be required, depending on risk factors and comorbidities. These patients may receive anti-diabetic and/or cholesterol-lowering drugs.

In patients with high grade PAOD (grade III or IV) the situation is more difficult to manage. Some of these patients may still need to be treated with nilotinib or ponatinib based on the biology (mutation-status) of their CML. In other patients, the drug should be discontinued or replaced by another TKI. In select cases with stable CMR, discontinuation of TKI-therapy may be considered. For all other patients, a general recommendation is to switch to another TKI if possible. PAOD requiring interventional revascularization procedures, central (cerebral) ischemia and myocardial infarction are additional indications to switch to another TKI. In all these patients, platelet aggregation inhibitors or anticoagulation should be considered following generally accepted guidelines. In these patients it is also essential to eliminate all risk factors and to treat hyperlipidemia, diabetes mellitus and arterial hypertension early and as effective as possible (Supplemental Table S4). An unresolved question is whether a slight elevation in the fasting glucose level that is quite frequently seen in nilotinib-treated patients, should already lead to early intervention with anti-diabetic therapy. At least repeated testing of glucose and HbA1c, and an oral glucose tolerance test (OGTT) seems justified;
when the fasting glucose level permanently increases to >125 mg/dL or the OGTT is clearly pathologic, anti-diabetic treatment should be considered.

How to prevent the development of VAEs in TKI-treated patients

Based on the severity of VAEs, the relatively good prognosis of CML patients even in the second- and third-line setting, and the impact of VAEs on overall morbidity and transplant-eligibility, it is of utmost importance to avoid VAEs in all CML patients, regardless of age and other factors. A first important step in prevention is patient-selection for second- and third-line TKIs. Such TKIs should be selected not only on the basis of disease-related parameters such as \( BCR/ABL1 \) mutations, but also based on patient-related variables, including comorbidities and overt risk factors for AE-development. Indeed, more and more guidelines and treatment-algorithms take patient-related factors into account, thereby fulfilling the criteria of personalized medicine.\(^5,11\)

Based on the frequent detection of risk factors for PAOD-development in the general population (adults) in the Western World, it is important to determine the individual risk in each case using validated scores, such as the European Society of Cardiology (ESC) score. This score should indeed be applied in order to select optimal and safe TKIs for all patients with CML. Patients in whom multiple risk factors or/and a high ESC are found should not be exposed to nilotinib or ponatinib if other TKIs can be prescribed. However, even low-risk patients
according to the ESC score may develop VAEs when treated with Nilotinib or Ponatinib (P.V., personal observation). Another unfortunate aspect is that several risk factors for PAOD development are also independent risk factors for the development of pleural effusions during dasatinib-therapy (Supplemental Table S2).\textsuperscript{64,65} Especially in elderly patients, neither nilotinib nor dasatinib may be an optimal TKI. Whether bosutinib may be a better choice for these patients remains to be determined in clinical trials. In contrast, ponatinib should not be considered as an alternative drug in these patients, unless leukemic cells express BCR/ABL1 T315I. In each case, the potential benefit of ponatinib has to be balanced against the potential AE-risk. Several other strategies may keep the risk of severe VAEs in TKI-treated CML patients to a minimum. These strategies are described in the Supplemental Appendix.

**Concluding Remarks and Future Perspectives**

Vascular safety has become an emerging challenge in the treatment of CML patients with second- and third-generation BCR/ABL1 TKIs. Whereas the vascular safety of imatinib is well documented, exposure to nilotinib and ponatinib is associated with an increased rate of arterial occlusive events. Therefore, it is of great importance to consider the overall risk profile before starting therapy and to include co-morbidities and risk factors for AOD development in novel treatment algorithms. It is also important to monitor metabolic and cardio-vascular
parameters in these patients and to reduce the vascular risk by optimal patient-selection, co-medication and early intervention if necessary. Although the mechanisms of drug-induced vascular damage are not well understood, direct pro-atherogenic and growth-inhibitory effects on endothelial cells as well as metabolic drug-effects seem to contribute. Currently, novel TKIs that spare critical vascular targets but retain full anti-CML activity are developed, with the hope to improve safety in long-term treated patients. Alternative options might be to discontinue or to ´switch back´ to less toxic TKIs once a stable deep response has been reached.
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Authorship

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.

Disclosures

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References


45. Levato L, Cantaffa R, Kropp MG, Magro D, Piro E, Molica S. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib


### Tables

**Table 1**

Reported numbers of CML patients developing vascular occlusive events (VAEs) and peripheral occlusive VAEs (PAOD)* during treatment with nilotinib or ponatinib

<table>
<thead>
<tr>
<th>First Author</th>
<th>Number of pts (n)</th>
<th>TKI</th>
<th>VAE %</th>
<th>PAOD %</th>
<th>observation time (months)</th>
<th>Ref #</th>
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<tbody>
<tr>
<td>Aichberger</td>
<td>24</td>
<td>NI</td>
<td>25.0</td>
<td>16.5</td>
<td>24</td>
<td>29</td>
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<tr>
<td>Le Coutre</td>
<td>179</td>
<td>NI</td>
<td>n.r.</td>
<td>6.2</td>
<td>n.r.</td>
<td>30</td>
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<tr>
<td>Quintás-Cardama</td>
<td>233</td>
<td>NI</td>
<td>2.0</td>
<td>1.3</td>
<td>n.r.</td>
<td>47</td>
</tr>
<tr>
<td>Larson</td>
<td>556</td>
<td>NI</td>
<td>4.9</td>
<td>1.3</td>
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<td>51</td>
</tr>
<tr>
<td>Labussiere-Wallet</td>
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<td>NI</td>
<td>n.r.</td>
<td>13.0</td>
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<td>54</td>
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<tr>
<td>Kim</td>
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<td>NI</td>
<td>n.r.</td>
<td>6.0</td>
<td>n.r.</td>
<td>31</td>
</tr>
<tr>
<td>Rea</td>
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<td></td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Hiwase</td>
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<td>NI</td>
<td>n.r.</td>
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<td>17.1</td>
<td>11.8</td>
<td>24</td>
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</table>

The patients described in the above listed investigations were in part from identical cohorts: patients reported in Aichberger et al29 were also included in the report by Le Coutre et al30 and data reported by Giles et al44, Larsen et al51 and Saglio et al55 were mostly from patients included in the ENESTnd trial. CML, chronic myeloid leukemia; PAOD, peripheral arterial occlusive disease; pts, patients; TKI, tyrosine kinase inhibitor; NI, nilotinib; PO, ponatinib; n.r., not reported.
Table 2
Reasons for under-reporting of vascular adverse events (VAEs) in CML patients treated with BCR/ABL1 tyrosine kinase inhibitors (TKIs)

Primary Reasons
- Relatively high incidence of atherosclerosis and VAEs worldwide
- Relatively low patient numbers per center participating in clinical trials
- Only a very few drugs are known to promote atherosclerosis; and only a very few drugs used to treat hematologic neoplasms may promote VAE development
- The initial clinical trials were not powered for the detection of VAEs
- Most clinical trials excluded patients with severe cardiac and/or metabolic co-morbidities

Secondary Reasons
- Latency period of several months to years before VAEs develop during TKI therapy
- CML centers and local experts are not trained to detect and to manage VAEs
- VAEs are not ´oncologic´ - therefore VAE patients were neither reported nor referred back to the oncologist by the practitioners; and also the patients did not report for the same reason and because of the general incidence.

Other Reasons
- Major papers published in top journals did not report on VAE development
- Initially, nilotinib was reported as an extremely safe TKI without side effects
- In major and special meetings, TKIs were long reported as safe without an impact on development of vascular diseases
- Clinically silent vascular events in diabetic patients may be overlooked
- Sudden death before a cerebral or cardiac VAE was detected

CML, chronic myeloid leukemia; TKI(s), tyrosine kinase inhibitor(s)
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