Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors

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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 and 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. Here, 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 occurrence of such events in long-term treated patients. (Blood. 2015;125(6):901-906)

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 antileukemic activity in freshly diagnosed patients with CML, with higher rates of complete cytogenetic response (CCyR) and major molecular (MRM) responses compared with 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 nonhematopoietic cells and may therefore be responsible for nonhematologic 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 or pericardial effusions is an issue.13,18,26-28 Several other nonhematologic AEs have also been described for dasatinib,13,27,33 the frequency of AEs is lower in patients receiving 100 mg of dasatinib once daily compared with higher doses.28,34,35 However, even at 100 mg per day, pleural effusions may develop.28,36 Recently, pulmonary hypertension has been reported in patients treated with dasatinib (supplemental Table 1).37,39 However, the frequency of this AE is low17,39 and the same holds true for arterial occlusive events, although VAEs have been reported (supplemental Table 1).40

Nilotinib-treated patients may develop elevated pancreatic enzymes, an increase in serum bilirubin, and/or an increase in fasting glucose levels12,17,29,41 Moreover, the cholesterol level may increase.42,43 Other nonhematologic AEs include constipation, diarrhea, and a folliculitis-like skin rash (supplemental Table 1).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.29-31,44-47 Several of these patients suffer from a rapidly progressive form of PAOD.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.29,30,45,46 In addition to PAOD, nilotinib-treated patients may develop cerebral ischemia and myocardial infarction.29-31 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.12,17

Ponatinib is another novel TKI used to treat patients with drug-resistant CML, including subclones expressing BCR/ABL T315I.16,32

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 1, available on the Blood Web site). In dasatinib-treated patients, the occurrence of pleural and/
First clinical trials have shown that ponatinib is a highly potent agent and useful for the treatment of TKI-resistant CML.\(^1\),\(^6\),\(^3\) However, unfortunately, ponatinib triggers arterial hypertension as well as VAE development.\(^3\) Initially, these events were thought to accumulate in ponatinib-treated patients because of their prior exposure to nilotinib.\(^3\),\(^2\),\(^4\) More recent data suggest, however, that ponatinib can also induce VAEs in patients who had not received nilotinib.\(^5\) As a result, ponatinib was transiently removed from the market in the United States in 2013. Remarkably, both arterial and venous thromboembolic events have been reported in ponatinib-treated patients.\(^3\),\(^2\),\(^4\)

Bosutinib is another novel TKI that has been developed as a third-line BCR/ABL1-targeting drug.\(^4\),\(^1\),\(^5\),\(^2\),\(^4\) Similar to nilotinib or dasatinib, bosutinib inhibits a number of BCR/ABL1 mutants and other kinase targets, but does not block BCR/ABL1 T315I.\(^2\),\(^4\) In contrast to other TKIs, bosutinib does not recognize KIT or PDGFR.\(^2\) The AE profile of bosutinib is also different compared with that of other TKIs. Notably, bosutinib-treated patients may develop diarrhea and an exanthema.\(^5\),\(^2\)\(^9\) In addition, arterial hypertension,\(^5\) pleural effusions, and VAEs have been described in patients receiving bosutinib. However, the frequency of VAEs is much lower compared with patients receiving nilotinib or ponatinib (supplemental Table 1).\(^3\),\(^0\),\(^5\)

### 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 because 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 1 and 2 trials, VAEs were not captured, and therefore, VAE rates were not provided.\(^1\),\(^2\),\(^6\),\(^7\) 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 of exploring 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).\(^2\),\(^9\),\(^3\),\(^1\),\(^4\),\(^4\),\(^7\),\(^5\),\(^2\),\(^4\) It was also found that the numbers (percentage) of patients developing VAEs increase over time (Table 1).\(^3\),\(^5\),\(^5\) 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 of developing VAEs when receiving 2 × 400 mg per day compared with a lower dose (2 × 300 mg per day).\(^4\),\(^5\)

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).\(^3\),\(^2\),\(^4\),\(^9\) 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.\(^5\) 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.\(^8\)

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.\(^5\),\(^6\) In 1 study, <1% of all patients developed PAOD during imatinib.\(^6\) It is noteworthy that in contrast to nilotinib, imatinib is not increasing but may even decrease blood glucose levels.\(^6\) In addition, imatinib may counteract diabetes mellitus–associated atherosclerosis.\(^5\) 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 Data.

### Risk factors predisposing for the development of VAEs

TKI-related side effects may preferentially develop in patients who have preexisting risk factors. Likewise, in most CML patients treated with nilotinib or ponatinib in whom severe recurrent VAEs were
Other well be that the rates of severe VAEs can be decreased substantially clinically relevant AEs, including VAEs, appear to increase in these patients. One such risk factor is the dose of the TKI. Notably, development in patients receiving nilotinib (supplemental Table 2).

tors for both pleural effusion formation under dasatinib and PAOD hypertension, and hypercholesterolemia are considered risk fac-

occurred. It has also been described that nilotinib may cause leading to recanalization and reperfusion once arterial stenosis

recorded, 1 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 2).

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 2).

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. In other words, it may well be that the rates of severe VAEs can be decreased substantially by lowering the TKI dose. 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.

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 3). 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. Indeed, nilotinib may exert direct proatherogenic and antiangiogenic effects on endothelial cells (supplemental Table 3). Where-

vasospasms which may also be relevant and trigger PAOD development. In addition, nilotinib exerts metabolic effects, including an increase in cholesterol and fasting glucose levels (supplemental Table 3). Some patients even develop overt diabetes mellitus. All these drug effects are considered to act together to trigger atherosclerosis and VAE development. Recently, the proatherogenic effects of nilotinib have been confirmed by measuring the ankle brachial index (ABI) in patients with CML. 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 observations from in vitro experiments using human endothelial cells). So far, little is known about molecular targets responsible for nilotinib and ponatinib effects on vascular endothelial cells. Several of these target antigens are major angiogenic receptors, like KDR (a known ponatinib-target) or TEK/Tie-2. 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; eg, 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 comedication may also be required, depending on risk factors and comorbidities. These patients may receive antidiabetic 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 complete molecular response (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 is an additional indication to switch to another TKI. In all of 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 effectively as possible (supplemental Table 4). An unresolved question is whether a slight elevation in the fasting glucose level, which is quite frequently seen in nilotinib-treated patients, should already lead to early intervention with antidiabetic 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, antidiabetic treatment should be considered.

Table 2. Reasons for underreporting of VAEs in CML patients treated with BCR/ABL1 TKIs

<table>
<thead>
<tr>
<th>Reasons</th>
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<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>Relatively high incidence of atherosclerosis and VAEs worldwide.</td>
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<tr>
<td>Relatively low patient numbers per center participating in clinical trials.</td>
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<tr>
<td>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.</td>
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<tr>
<td>The initial clinical trials were not powered for the detection of VAEs.</td>
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<tr>
<td>Most clinical trials excluded patients with severe cardiac and/or metabolic comorbidities.</td>
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<tr>
<td><strong>Secondary</strong></td>
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<tr>
<td>Latency period of several months to years before VAEs develop during TKI therapy.</td>
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<td>CML centers and local experts are not trained to detect and to manage VAEs.</td>
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<tr>
<td>VAEs are not “oncologic”: therefore, VAE patients were neither referred nor referred back to the oncologist by the practitioners.</td>
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<tr>
<td>Also, the patients did not report for the same reason and because of the general incidence.</td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td>Major papers published in top journals did not report on VAE development.</td>
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<tr>
<td>Initially, nilotinib was reported as an extremely safe TKI without side effects.</td>
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<tr>
<td>In major and special meetings, TKIs were long reported as safe without an impact on development of vascular diseases.</td>
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<tr>
<td>Clinically silent vascular events in diabetic patients may be overlooked.</td>
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<tr>
<td>Sudden death before a cerebral or cardiac VAE was detected.</td>
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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 are and/a high ESC score are found should not be exposed to nilotinib or ponatinib or other TKIs can be prescribed. However, even low-risk patients according to the ESC score may develop VAEs during TKI therapy (P.V., personal observation: ESC scoring of CML patients treated at the Medical University of Vienna). 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 2).6,3,64 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 Data.

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 comorbidities and risk factors for AOD development in novel treatment algorithms. It is also important to monitor metabolic and cardiovascular parameters in these patients and to reduce the vascular risk by optimal patient selection, comedication, and early intervention if necessary. Although the mechanisms of drug-induced vascular damage are not well understood, direct proatherogenic 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 of improving 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

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