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Should vascular effects of newer treatments be addressed more completely?



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KEYWORDS

• cardio-oncology • cardiotoxicity • dasatinib • imatinib resistance • leukemia • nilotinib • peripheral arterial disease • ponatinib • tyrosine kinase inhibitors • vascular toxicity

For over half a century, the development of groundbreaking chemotherapeutic agents have resulted in prolonged survival outcomes and more treatment options for patients with hematologic and oncologic malignancies. In the shadow of these achievements, cardiovascular toxicities have been documented with most agents, including newer, so-called 'targeted therapies', which were initially considered to be have minimal cardiovascular adverse effects [1]. However, concern has arisen over a number of alarming vascular adverse events (VAEs) with the advent of second- and third-generation BCR-ABL tyrosine kinase inhibitors (TKIs), including agents such as nilotinib and ponatinib [2].

The *BCR-ABL* fusion gene arises from a balanced translocation between chromosome 9 and 22 that generate a constitutively active tyrosine kinase that can lead to development of myeloproliferative disorders such a chronic myeloid leukemia (CML) and acute lymphoblastic leukemia. Imatinib was the first tyrosine kinase inhibitor approved and became the poster child for targeted therapy. [3] Initial reports on cardiotoxicity arose but from a vascular standpoint it was deemed to be safe, and actually shown to decrease atherosclerosis in experimental models. However, an estimated 20–30% rate of resistance to imanitib [4] prompted the development of alternative agents with the goal of achieving superior cytogenetic, molecular and clinical responses compared with imatinib. Second-generation TKIs such as dasatinib and nilotinib have been US FDA approved for the treatment of imatinib-resistant patients, as well as for first-line therapy. Dasatinib, a piperazinyl derivative TKI, has been demonstrated to be 325-times more potent than imatinib against cells expressing wild-type *BCR-ABL*. Nilotinib, an orally active phenylaminopyrimidine derivative of imatinib, is 30-times more potent than imatinib in *BCR-ABL* inhibition. Finally, ponatinib was developed as a pan-*BCR-ABL* inhibitor that would shown high potency across all *BCR-ABL* mutations in patients with CML that has been resistant to prior TKI therapy. More agents are in the pipeline, including XL228 (protein kinase inhibitor), bafetinib (dual

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BCR-ABL/Lyn kinase inhibitor) as well as aurora kinase inhibitors (i.e., danusertib) that have completed or are entering Phase I clinical trials [5].

Initial trials of these newer generation TKIs did not appear to demonstrate major VAEs, with predominantly hematologic, gastrointestinal or dermatologic adverse effects being reported [6–9]. Subsequently, however, reports emerged on the development of pulmonary arterial hypertension and pleural effusions with dasatinib. Most of these rare cases were reversible, although a few deaths were reported; it is unclear if these complications were related [10]. No significant association with VAEs has been reported for dasatinib. This is distinctly different for nilotinib, for which multiple studies have documented an increased incidence of VAEs [11–16]. One particular striking example comes from Aichberger *et al.* who reported a combined cardiac and vascular ischemic event rate of about 33% in a consecutive series of 24 CML patients. Three patients developed peripheral arterial occlusive disease (PAOD) during treatment within months to 3 years, requiring a range of significant interventions, including peripheral angioplasty and stenting, lower extremity bypass and even amputation for gangrene in one patient after bypass graft failure and infection occurred [11]. A prospective screening trial using ankle-brachial index (ABI) and duplex ultrasonography for PAOD screening showed a significantly higher incidence of abnormal ABI results in patients on first-line and second-line nilotinib therapy (26 and 35.7%, respectively) compared with patients on first-line imatinib therapy (6.3%) [17]. A cumulative analysis of various studies done by Valent *et al.* showed an incidence of VAEs of up to 29.4% [12], which is significantly different from initial safety data.

> "...while initial trials of newer generation tyrosine kinase inhibitors may have underdetected vascular adverse events, they have shown significant clinical benefit in patients who have limited therapeutic options due to imatinib resistance."

The mechanisms surrounding this association of nilotinib and VAEs are not fully understood; kinase targets that are bound by nilotinib include KIT, PDGFR, and discodin domain receptor 1 – although imatinib also binds to these targets as well, albeit likely to a lesser degree. Discodin domain receptor 1 has been implicated in plaque formation in animal models, although there is conflicting data on whether inhibition promotes or protects against this. KIT and PDGFR also have been implicated in regulation of vascular and perivascular cells, and KIT also regulates the function and survival of mast cells – which include repair molecules such as heparin, histamine and tissue type plasminogen activator. It may be possible that inhibition of these kinase targets may interfere with the vascular repair system and predispose certain patients to thromboembolic and accelerated atherosclerotic events. There are likely other unknown kinase targets involved that are responsible for this mechanism [11].

While an initial Phase I trial in refractory CML did not report any significant VAEs [9], a subsequent Phase II trial revealed an incidence of 17.1% of arterial thrombotic events with ponatinib [18]. This led to the termination of a randomized trial comparing ponatinib to imatinib in newly diagnosed CML, temporary suspension of ponatinib and subsequent reintroduction with a FDA mandated boxed warning, citing significantly high rates of VAEs. As a significant proportion of patients had a history of prior nilotinib exposure, it is unclear if ponatinib was the sole culprit, whether nilotinib was the triggering offending agent, or if there was some 'syngergistic' effects that led to this high incidence of VAEs. Furthermore, the adjudication of events was not as uniform and included a spectrum of more benign to very severe complications.

Why were VAEs not seen in initial trials? First of all, cardiovascular disease remains one of the top causes of morbidity and mortality in both developed and developing countries where these studies were conducted; therefore, the link of TKI-induced vascular toxicity in patients with cardiovascular comorbidities may not have been identified during initial evaluation. Other possible explanations include that these clinical trials were underpowered or did not monitor patients long enough for the detection of VAEs, and patients with significant cardiac comorbidities were excluded from many initial trials, which may not reflect 'real-life' practice. In addition, VAEs was not an expected safety endpoint, and may not have been regarded as an 'oncologic' issue; as a result, these events may have not been reported by the patient's primary care and/or cardiovascular physician to their hematologist. Finally, symptoms of claudication or other lower extremity complaints may have been attributed to more common causes such as metabolic derangements, musculoskeletal side effects or neuropathy and PAOD may have been underdiagnosed [12].

At present, many unanswered questions remain about which patients are at elevated risk

of developing peripheral artery disease with TKI exposure, particularly agents such as nilotinib and ponatinib. Peripheral arterial disease has been well established as an independent risk factor predictive of elevated cardiovascular morbidity and mortality [19], and even if a successful clinical response is obtained with TKI therapy, close follow-up, baseline screening and yearly surveillance for peripheral arterial disease in the absence of symptoms is warranted until further data are available. ABI testing and duplex ultrasonography are relatively inexpensive tests and can provide valuable information in determining if further imaging workup and pharmacologic and/or invasive intervention may be needed.

As some studies have indicated, there is also a need for a risk stratification score and/or algorithm to predict risk of VAEs to evaluate patients prior to TKI therapy. However, on the other hand, cases of VAEs have occurred in patients without known prior risk factors, which may make such an analysis difficult. Breccia *et al.* applied global cardiovascular risk assessment scores to their patients undergoing nilotinib therapy and uniformly found a high incidence of VAEs in their intermediate and high-risk population **(Figure 1)** [20]; this requires study on a larger scale for further validation. The question of whether these toxicities are dose dependent also warrants further study. Further randomized studies are also indicated to see if potential pharmacologic therapies used in peripheral arterial disease (i.e., antiplatelet therapy, statins and antihypertensive therapy) in patients at elevated risk for VAEs prior to initiating TKI therapy could potentially be beneficial, although patients developed events despite being on such PAOD therapy.

To be able to provide the best patient care from a cardio-oncologic perspective, it is essential to have a multidisciplinary team of hematology/oncologists, cardiovascular, vascular and radiology specialists who are cognizant of the potential for these VAEs to occur, and when to refer for urgent imaging and treatment. Finally, in the event of a VAE likely to arise from TKI administration, an ongoing multidisciplinary discussion over the risk–benefit ratio of ongoing vascular toxicity and benefits of TKI therapy must be held.

In conclusion, while initial trials of newer generation TKIs may have underdetected VAEs,

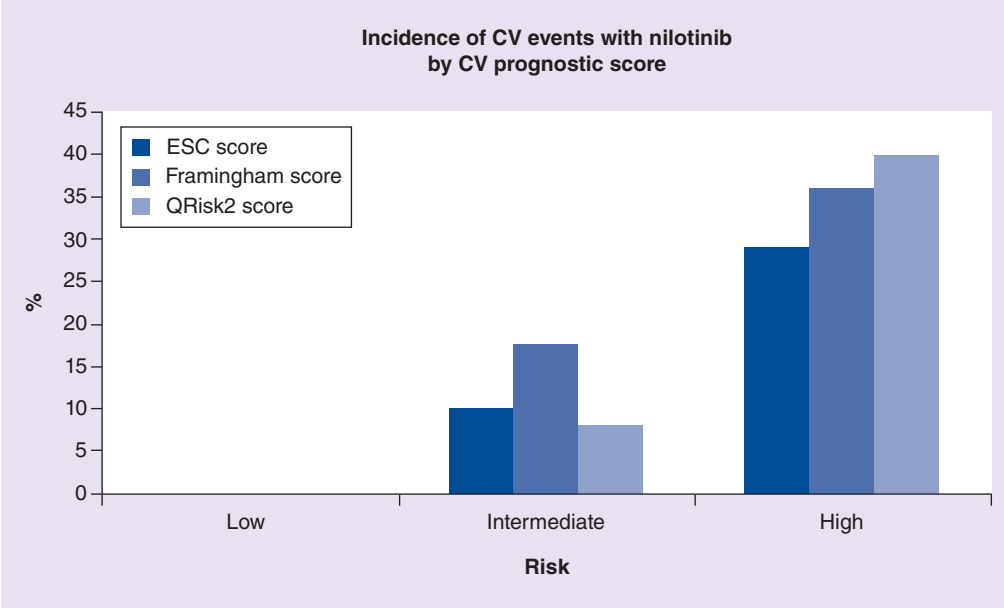

Figure 1. Bar graph showing incidence of vascular adverse events of 82 chronic myeloid leukemia patients being treated with nilotinib (400–600 mg twice a day) as divided into low, intermediate and high risk for cardiovascular events by Framingham, European Society of Cardiology SCORE and QRisk2 risk assessment. The cumulative incidence of atherosclerotic events at 48 months was 8.5% in this cohort.
CV: Cardiovascular; ESC: European Society of Cardiology.
Data taken from [20].

they have shown significant clinical benefit in patients who have limited therapeutic options due to imatinib resistance. It is imperative that cardiovascular-protective strategies are developed to identify and intervene on high-risk patients so they can safely continue their treatment that can potentially prolong their survival and ensure remission. Screening for vascular disease and toxicity in patients before and while undergoing treatment with these newer TKIs is a necessary additional step in evaluating for short- and long-term development of PAOD. Until further studies that are powered for and include vascular events as a safety endpoint are conducted, this would seem to be the most prudent step. TKIs can potentially provide a mechanistic – and accelerated – glimpse into the development of atherosclerotic disease that may yield insights into how specific kinase targets can play a role in the regulation of vascular cell growth, repair and plaque formation. These intriguing observations warrant further investigation both at the basic science and clinical level, which will hopefully further close our knowledge gaps about the overlap of hematologic and cardiovascular disease.

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