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Nilotinib treatment-associated accelerated atherosclerosis: when is the risk justified?

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Atherosclerosis is the leading cause of death and morbidity in developed countries and is the culprit behind coronary artery disease (CAD), cerebral vascular disease (CVD) and peripheral artery occlusive disease (PAOD). Atherosclerosis leads to segmental narrowing and occlusion of arteries, and current opinion favors a complex pathogenetic process that involves the endothelium, platelets, monocytes/macrophages, neutrophils, dendritic cells, T and B lymphocytes, lipids, inflammation and chemokines/cytokines.

Two papers in *Leukemia* recently reported the prevalence of PAOD in tyrosine kinase inhibitor (TKI)-treated patients with chronic myeloid leukemia (CML)[1,2] Conflict of interest statements declared 'editorial assistance' from Novartis pharmaceuticals (manufacturer of nilotinib and imatinib) for one of the reports[2] My comments will focus on the other report by Kim *et al.*,[1] who prospectively screened 129 CML patients for pathological PAOD, using ankle-brachial index (ABI). Pathological PAOD (defined by <0.9 ABI) was documented in 6.3% of patients receiving imatinib as first-line therapy, 26% receiving nilotinib as first-line therapy and 35.7% receiving nilotinib as second-line therapy ($P<0.05$). Clinically overt PAOD was seen in five patients, all of whom were exposed to nilotinib therapy. The detrimental effect of nilotinib was evident despite a shorter duration of treatment (median 30 vs 102 months for imatinib). Cardiovascular risk factors were similar between the two groups.

In the second part of their study, Kim *et al.*[1] reviewed 27 cases of TKI treatment-associated overt PAOD accrued from several collaborating centers and discovered that all but one of these patients were exposed to nilotinib therapy, including 20 patients who were receiving nilotinib as first- or second-line treatment of CP-CML. These events were severe enough to require percutaneous transluminal angioplasty in 33.3% of the cases, stent implantation in 22.2%, amputation in 22.2% and surgery in 18.5%.

The observations from Kim *et al.*[1] are consistent with those of earlier[3,4] and more recent[5,6] reports associating nilotinib with accelerated atherosclerosis. Aichberger *et al.*[3] reported a 33% incidence of PAOD, myocardial infarction, spinal infarction or subdural hematoma, among 24 CML patients treated with nilotinib. Tefferi *et al.*[4] described two patients who experienced sudden death or severe PAOD/CAD; continued nilotinib treatment in the latter patient was associated with rapid progression of intra- and extracranial atherosclerosis leading to stroke.[6] Most recently, Levato *et al.*[5] reported their single-institution experience with 82 CML patients treated with imatinib ($n=55$) or nilotinib ($n=27$); four (14.8%) nilotinib-treated patients developed severe PAOD or other vascular disease. In contrast, none of the 55 imatinib-treated patients developed PAOD and only one experienced myocardial infarction, despite a longer median duration of treatment with imatinib (79.5 months) vs nilotinib (21.5 months).

Taken together, the above observations strongly implicate nilotinib therapy as being proatherogenic. Regardless of what the underlying mechanisms for this might be, the question is whether or not it is necessary or appropriate to subject newly diagnosed patients with CP-CML to this risk, considering the remarkable efficacy and safety of imatinib therapy. The 6-year follow-up of 553 imatinib-treated patients in the first international randomized study (the IRIS study) showed an overall complete cytogenetic remission (CCyR) rate of 83% and overall (OS) and progression-free (PFS) survival of 88 and 93%, respectively. PFS was higher ($>95\%$) in patients achieving CCyR or partial (PCyR) cytogenetic remission (corresponding to BCR–ABL1 transcripts of $<10\%$) at 6 months.[7] Disease progression after the first 3 years of treatment was unusual. The majority of the patients assigned to the imatinib arm of the IRIS study have remained on the drug long-term.

The observations from the IRIS study were similar to those of many other studies, including a single-institution study of 204 CP-CML patients receiving imatinib as first-line therapy; 5-year follow-up with full event accounting revealed CCyR of 82.7%, major molecular response (MMR) of 50.1%, OS of 83.2%, PFS of 82.7% and imatinib discontinuation rate of 25%.[8] As was the case in the IRIS study, CCyR was crucial for improved survival but achieving MMR over and above CCyR conferred no further advantage. In yet another large-scale study of imatinib therapy in newly diagnosed CP-CML, survival was similar in CCyR patients with ($<0.01\%$ BCR-ABL1 transcripts) or without (0.1 to $<1\%$ BCR-ABL1 transcripts) MMR.[9]

The importance of close monitoring of response to imatinib therapy and the possibility of early identification of suboptimal responders with inferior long-term outcome has been addressed by multiple studies and highlighted in a recent report of 1303 patients with CP-CML receiving frontline imatinib therapy.[10] In the particular study, BCR–ABL1 transcripts at 3 months decreased to $\leqslant 1\%$ in 31% of the patients, to >1–10% in 41% and remained $>10\%$ in 28%; the corresponding 5-year OS were 97, 94 and 87% ($P<0.05$).[10] Similarly, 5-year OS was 95% in patients with at least PCyR (73% of the patients) vs 87% otherwise.[10] At 6 months, BCR–ABL1 transcripts remained $>1\%$ (that is, no CCyR) in 37% of the patients, and 5-year OS was 89% in this group of patients vs 97% for the 63% of patients achieving $\leqslant 1\%$ transcript level (that is, CCyR).[10]

For patients who do not tolerate imatinib or show resistance to it, several second generation TKIs (SG-TKI) have been developed and some have recently been approved for clinical use (nilotinib, dasatinib, bosutinib and ponatinib). These drugs are usually more potent than imatinib and are able to effectively substitute for it in case of drug intolerance and also offer an alternative to allogeneic stem cell transplant in case of drug resistance. The question is

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whether or not their benefit-to-risk balance favors their use as first-line therapy. Randomized studies have compared imatinib with nilotinib,[11] dasatinib[12,13] or bosutinib.[14] None of these studies showed a significant survival difference, although SG-TKIs enabled faster attainment of CCyR, deeper molecular remissions and fewer disease progressions. More importantly, none of the aforementioned studies compared their new drug with 'imatinib use according to current practice', which includes close monitoring and switching to SG-TKI at the earliest sign of suboptimal response.

The adverse effect profile of imatinib (for example, periorbital edema, muscle cramps and joint pain) has not changed over the years whereas those of SG-TKIs are more concerning, especially in terms of long-term morbidity: for example, accelerated atherosclerosis with nilotinib,[1] pleural and pericardial effusions with dasatinib,[12] diarrhea/vomiting and elevated liver function tests with bosutinib[14] and clinically overt pancreatitis with ponatinib.[15] Therefore, in the absence of evidence for survival advantage, it is hard to justify the risk of treatment with SG-TKIs, in the context of frontline therapy for CP-CML. It makes more sense to start with imatinib and switch to SG-TKI, in case of drug intolerance or suboptimal response. Such a treatment strategy effectively identifies a subset of CP-CML patients with $>95\%$ chance of long-term PFS and allows early introduction of SG-TKIs in those who need them;[10] the latter should exclude patients with poor treatment adherence. Incidentally, I am not fully convinced that all imatinib-treated patients with $>10\%$ BCR–ABL1 transcript level at 3 months or $>1\%$ at 6 months require switching to SG-TKI. I am more comfortable with a drug switch in the presence of less than complete hematological remission at 3 months or $>10\%$ BCR–ABL1 transcript level at 6 months. As for second-line therapy, I would encourage full disclosure, to patients, of adverse effects associated with each one of the currently available SG-TKIs, including the above-elaborated risk of nilotinib-associated accelerated atherosclerosis.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Acute erythroid leukemia (AEL) can be separated into distinct prognostic subsets based on cytogenetic and molecular genetic characteristics

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Acute erythroid leukemia (AEL) ($=$AML FAB M6) comprises $<5\%$ of adult acute myeloid leukemia (AML), but becomes more frequent with higher age.[1] AEL patients were described to have more frequently poor risk cytogenetics and worse survival than other AML subtypes.[2] The cytogenetic risk group was suggested to be prognostically relevant for AEL patients, but the diagnosis of AEL was no independent prognostic parameter when the cytogenetic risk group or the history of the disease were considered.[3] AEL was described to differ from overall AML, for

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