Tyrosine kinase inhibitors in hematologic malignancy: should we be concerned?

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After an outstanding symposium opening address by Dr. Kathleen Pritchard on the importance of addressing cardiovascular toxicity as a component of providing comprehensive cancer care, Dr. Michael Savona of Nashville's Vanderbilt-Ingram Cancer Center opened the meeting's first session, focused upon cardiovascular effects with tyrosine kinase inhibitors in CML with a discussion of the revolution in outcomes with Philadelphia Chromosome positive CML. New therapies have improved the 10-year survival likelihood from less than 10% prior to 1975 to more than 80% since 2001. Targeted therapies with several ABL1 protein kinase inhibitors have become the backbone of the current era of enhanced survival. Dr. Sebastian Szmit from the European Health Centre, Otwock, Poland provided a focused analysis of the incidence, presentation and treatment options of a unique complication profile of one of these agents dasatinib that includes pleural effusions and pulmonary hypertension. Dr. Michael Deininger from The Huntsman Cancer Institute at the University Utah, Salt Lake City closed the first session of the conference by outlining the array therapeutic advances and associated off target cardiovascular effects in treating Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia. The following is an integrated summary of key points from these three presentations.

The Philadelphia chromosome is an abnormality of chromosome 22 involving a translocation from chromosome 9 that produces a fusion gene known as BCR-Abl1 whose identification is a hallmark of CML. CML typically includes a chronic phase with < 10% blasts, an accelerated phase (AP) associated with increasing blasts in the marrow, splenomegaly and worsening cytopenias that is followed by a blast crisis (BC) where blood and bone marrow show a much higher blast % and evolution to acute leukemia which is resistant to therapy and associated with high 6-month mortality. Imatinib is the prototypic small molecule inhibitor of BCR-Abl tyrosine kinase that inhibits multiple protein kinases that lead to inhibition of CML cells in vitro and in clinical disease. Pivotal trials in the early 2000s led to reports in the same era of CHF in patients receiving imatinib.

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Imatinib, is the prototypic ABL1 kinase inhibitor with three other "next" generation agents, nilotinib, dasatinib and ponatinib also used in this disease [1–3]. The improvements in cancer outcomes with imatinib as compared to conventional combination chemotherapies were followed by the development of a second generation TKI of this class, nilotinib. Nilotinib, another Abl1 TK inhibitor, reduces the rate of patients entering accelerated phase or blast crisis (AP/BC) and improves rate of molecular response (MR) and complete cytogenetic response (CCyR) compared to imatinib. Higher rates of myocardial ischemic events, cerebrovascular events, peripheral arterial occlusive disease and more unfavorable changes in lipid profiles were seen with nilotinib. Nilotinib with benefits for patients not responding to imatinib has show an increase in the incidence of ischemic heart disease complications, cerebrovascular events and peripheral arterial disease that greatly exceeds the incidence seen with imatinib [4]. Similarly, dasatinib, an ABL1 kinase inhibitor in the Src/Abl class, also provides a higher incidence of molecular response than imatinib but with a three-fold increase in cardiac ischemia (3.9% vs. 1.2%) than with imatinib. Pleural effusions were reported with dasatinib in 35% of cases in one series that were more common in patients with cardiac history [5]. Pericardial effusions without tamponade were seen in some cases. Elevations in RV systolic pressure were associated with the effusions. Resolution of the effusions and reduction in RV pressure upon withdrawal of dasatinib but complete normalization of PA pressure was not the rule. Registry data has identified pulmonary hypertension as a more uncommon effect of dasatinib with 9 cases identified over 4 years [6]. Only one case occurred within the first year of therapy, the others were detected after 28 to 48 months of treatment. Risk factors for pre-capillary or post-capillary pulmonary hypertension are common in the population developing pulmonary hypertension with dasatinib, as is hypertension or BID dosing. Src kinase seems to be a molecular target of dasatinib but not imatinib or nilotinib with impact upon cell proliferation and vascular tone. By contrast, imatinib inhibition of PDGF is associated with reduction in pulmonary hypertension but carries its own side effects including edema, anemia and subdural hematoma [7]. Experiences with medical therapy for dasatinib mediated PH are as yet inconclusive but the most promising means of normalizing markedly elevated PA pressures seems to involve the addition of sildenafil after withdrawal of dasatinib [8, 9].

The lack of overall survival increase with dasatinib versus imatinib suggests that "the losses eat the gains" with dasatinib. Peripheral arterial disease is not increased with dasatinib. In contrast, studies of ponatinib, an ABL2 kinase inhibitor with different mechanism of action than the aforementioned agents provides salvage therapy for refractory patients but at the expense of an increased risk of higher grade hypertension and arterial thrombotic adverse events. Dr. Savona summarized by indicating that imatinib is effective in about 2/3 of these CML patients with roles for nilotinib, dasatinib and ponatinib but all three of these agents have distinctive cardiovascular toxicity profiles that impact outcomes and utility of these agents. The mechanisms by which these agents create cardiovascular events are poorly understood [10–12].

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References

1. Kantarjian HM, Giles FJ, Bhalla KN et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood 2011; 117(4): 1141-1145.
2. Saglio G, Kim DW, Issaragrisil S et al; ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362(24): 2251-2259.
3. Kantarjian H, Shah NP, Hochhaus A et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362(24): 2260-2270.
4. Valent P, Hadzijusufovic E, Schernthaner GH et al. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. Blood 2015; 125(6): 901-906.
5. Quintás-Cardama A, Kantarjian H, O'brien S et al. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007; 25(25): 3908-3914.
6. Montani D, Bergot E, Günther S et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012; 125(17): 2128-2137.
7. Hoeper MM, Barst RJ, Bourge RC et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013; 127(10): 1128-1138.
8. Shah NP, Wallis N, Farber HW et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol 2015; 90(11): 1060-1064.

9. Szmit S. Is dasatinib-related pulmonary hypertension a clinical concern? Future Oncol 2015; 11(18): 2491-2494.
10. Larson RA. Is there a best TKI for chronic phase CML? Blood 2015; 126(21): 2370-2375.
11. Moslehi JJ, Deininger M. Tyrosine Kinase Inhibitor-Associated Cardiovascular Toxicity in Chronic Myeloid Leukemia. J Clin Oncol 2015; 33(35): 4210-4218.
12. Kim TD, Rea D, Schwarz M et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 2013; 27(6): 1316-1321.