Second Generation Tyrosine Kinase Inhibitor Effective In First Line CML Therapy

October 22, 2012

VA Morris

Chronic myeloid leukemia (CML) is a cancer characterized by the overgrowth of the myeloid lineage of white blood cells, mainly granulocytes and their progenitors, in the bone marrow and blood. CML was the first cancer identified as driven by a single chromosomal translocation known as the Philadelphia chromosome, joining coding regions of the *ABL1* gene from chromosome 9 to the break point cluster (*BCR*) gene from chromosome 22, generating the BCR-ABL fusion protein. BCR-ABL functions as an oncogene; the fused ABL tyrosine kinase constitutively activates a number of pathways that control cell growth and survival. In the 1990s, CML became the first cancer treated by targeted drug therapy by blocking ABL activity with a tyrosine kinase inhibitor (TKI), imatinib.

While effective in most CML patients, some patients are refractory or develop mutations that prevent imatinib from working. Second generation TKIs, nilotinib and dasatinib, were originally developed and approved to treat patients who failed imatinib therapy, but because of promising initial clinical trial reports, both drugs were FDA approved for treatment of newly diagnosed patients in 2010. While imatinib binds to ABL in the ATP-binding domain and stabilizes the inactive conformation, dasatinib binds and stabilizes the active confirmation of ABL to inhibit ATP binding and kinase activity. Dasatinib is 325-fold more potent than imatinib in inhibiting BCR-ABL activity due to an enhanced binding affinity. Furthermore, dasatinib is active against a number of imatinib-resistant BCR-ABL mutations, except for the T315I mutation that blocks effectiveness of all TKIs. Early stage CML, called chronic phase (CP-CML), is readily treatable by TKIs, while disease progression to the more acute blast crisis CML is less sensitive to TKI treatment.

Previous pharmaceutical-sponsored randomized trials suggested that dasatinib and nilotinib gave better short-term responses in newly diagnosed CP-CML patients. Lead author Dr. Jerald Radich, Clinical Research Division director Dr. Fred Applebaum, and Dr. Ken Kopecky from the SWOG Statistical Center contributed to the recent report of a multicenter clinical trial (NCT00070499) comparing first-line CP-CML therapy with imatinib (400 mg/kg dose) versus dasatinib (100 mg/kg dose). Initiated in 2006, the trial enrolled 253 patients who were randomized to either drug treatment. The therapeutic molecular response, as measured by sensitive PCR assays for BCR-ABL mRNA transcripts, was significantly better for dasatinib versus imatinib in the short term; at one year a 1,000-fold reduction in BCR-ABL was achieved for 59% of patients treated with dasatinib versus

44% of imatinib-treated patients (P=0.059), and a 10,000-fold decrease in 27% versus 21% of patients, respectively (P=0.32). Furthermore, dasatinib treatment yielded an increased proportion of patients with complete cytogenetic response versus imatinib (84% versus 69%, P=0.04), as determined by the absence of BCR-ABL translocations in at least 20 bone marrow cells. However, overall survival, progression-free survival, and relapse-free survival were not statistically different for the two drug treatments. Importantly, dasatinib treated patients had more grade 3-4 toxicities than imatinib (58% versus 35%, P=0.0001), with mostly hematologic toxicities such as thrombocytopenia and pleural effusions with dasatinib, and fluid retention and nausea for imatinib.

The results of this trial were comparable to other first-line CP-CML clinical trials, which show a significantly better molecular response to the second generation TKIs dasatinib or nilotinib versus imatinib. Importantly, benefits of this improved short-term molecular response to patient survival have not been shown. Overall, the study confirms the effective use of dasatinib in first-line therapy for CML as FDA-approved in 2010, however, the report emphasizes that the clinician must consider potential increased toxic side effects, as imatinib has a longer record for safety, as well as a reduced cost as imatinib moves off patent to become a generic drug. Importantly, no TKI approved for CML is a curative treatment, so the treatment goal is to drive CML into remission and prevent disease progression by lifelong treatment with TKIs.

Radich JP, Kopecky KJ, Appelbaum FR, Kamel-Reid S, Stock W, Malnassy G, Paietta E, Wadleigh M, Larson RA, Emanuel P, Tallman M, Lipton J, Turner AR, Druker BJ. 2012. A randomized trial of dasatinib 100 mg vs imatinib 400 mg in newly diagnosed chronic phase chromic myeloid leukemia. Blood. Epub ahead of print, doi: 10.1182/blood-2012-02-410688.

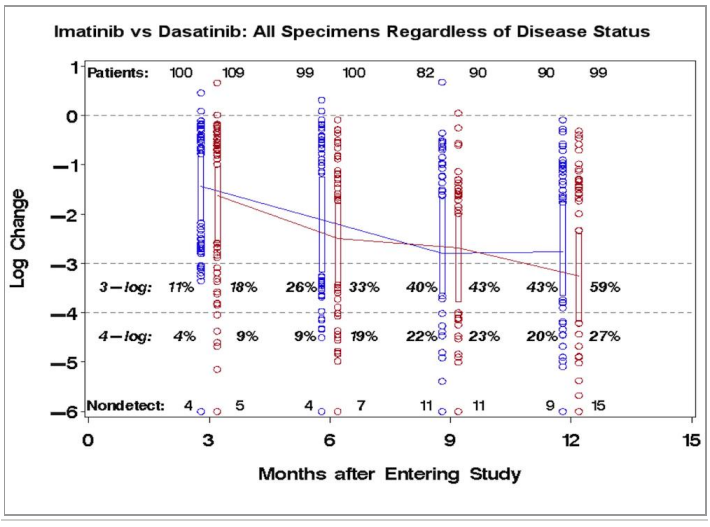

Image courtesy of JR Radich

Molecular response measured by detecting BCR-ABL transcript by quantitative reverse transcriptase-PCR is displayed for imatinib (blue) and dasatinib (red) treatment of CP-CML and time on study. Changes are displayed relative to a group-specific median baseline value on a log10 scale, with no change, 3-log and 4-log decrease from baseline show with horizontal dashed lines. The median reduction in BCR-ABL expression was 2.8 log for the