Targeting the Achilles' Heel of Tyrosine Kinase Inhibition in CML

By Paul Cheng, MD, PhD, and
Richard Schwab, MD

With the initial discovery of the Philadelphia chromosome in 1960 and protein tyrosine phosphorylation in 1979, no other malignancy has better typified successful use of tyrosine kinase inhibitors (TKI) than chronic myelogenous leukemia (CML). The underlying molecular defect involves a chromosomal translocation t(9,22) which results in the production of a fusion protein with the breakpoint cluster region (BCR) protein replacing a key regulatory domain of Abl kinase. This results in dysregulated Abl, leading to aberrant signaling and cancer. In 2001, the FDA rapidly approved imatinib (Gleevec®), a promiscuous Abl TKI, which binds in the ATP-binding pocket of Abl when it is in the closed conformation, thus inhibiting kinase activity. In fact, the IRIS investigators have published results this week showing durability of response to imatinib, with an overall survival of 89 percent at five years. Imatinib has validated the approach of kinase inhibition in cancer therapy and revolutionized treatment of CML.

However, a minority of patients with CML develop distinct patterns of resistance to imatinib. These resistant clones have mutations in the Abl kinase domain, some at T315I, but there are other locations as well. Neither of the two new Abl inhibitors developed for use in imatinib-resistant CML — dasatinib (Sprycel®, already FDA-approved) or nilotinib (Tasigna®, on FDA fast-track) inhibit the T315I mutant. These findings have put the spotlight on assessing the Abl kinase domain in patients with CML treated with targeted therapies.

The importance of finding new drugs to prevent the development of or to overcome T315I-resistant disease cannot be overstated. In addition to aurora kinase inhibition as described in a previous *ASH News Daily* article, this morning's oral presentations will also detail the work of two separate groups that address the question of whether sequential or combination therapy with two tyrosine kinase inhibitors is preferable. Dr. Elias Jabbour from M.D. Anderson Cancer Center will present data that sequential therapy only gives rise to 4 percent T315I mutations, which is not significantly increased from baseline. On the other hand, Dr. Neil Shah from the University of California, San Francisco, will discuss alternative data suggesting that sequential therapy leads to the development of compound resistance such as M244L/L364I/T315A that was more potently oncogenic than non-mutated BCR-ABL.

Other approaches to overcoming resistance will also be described in today's oral presentations. One approach is to use farnesyltransferase inhibitors (FTIs). Dr. Mhairi Copland from the University of Glasgow will present data that the FTI BMS-214662 inhibited proliferation of T315I and nonmutated BCR-ABL in a Ba/F3 cell culture systems. A second approach, inhibition of the canonical Wnt/ β-catenin pathway, also may provide a new avenue of therapy. Previously it was shown that β-catenin undergoes nuclear-localization in CML granulocyte-macrophage progenitors (GMP) in blast crisis. Dr. Edward Kavalerchik from the Jaimeson Laboratory at the University of California, San Diego, presented data yesterday showing that MC-001, a novel Wnt inhibitor derived from a marine sponge, can block *in vitro* replating capacity of CML GMPs. Current studies involve *in vivo* evaluation of GMPs transplanted into immunodeficient mice in a bioluminescence imaging model.

Hematologists interested in CML faced a daunting but exciting annual meeting this year. Numerous pharmacologic interventions, clinical studies of kinase mutations, and revealing data on CML stem cells were presented. It is hard to believe that the Philadelphia chromosome was discovered less than 50 years ago. It appears that neither hematologists nor CML patients will need to wait another 50 years for major changes in the treatment, and possibly even the cure, of CML.