

# Aurora on the Horizon for CML

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Chronic myelogenous leukemia (CML) is the model disease for targeted therapy. Imatinib has enjoyed great success in changing the natural history of CML. At this meeting, Kantarjian et al. (abstract #428) report long-term followup and outcomes for patients with late chronic phase CML treated with imatinib following interferon- $\alpha$ . With six-year followup, 93 percent of patients who achieved major cytogenetic response by 12 months remained in remission, resulting in marked improvement in survival with historical comparison. But, a small number of cells can adapt to single-target inhibition. Although more than 40 different mutations have been described, the T315I mutation in the "gatekeeper" position of the *BCR-ABL* gene product confers resistance to imatinib as well as the more potent second-generation tyrosine kinase inhibitors.

MK-0457 (VX-860) is a small molecule inhibitor of aurora kinases A, B, and C. MK-0457 also inhibits wild type and mutated *BCR-ABL*, including T315I. Aurora kinases A, B, and C are important regulators of mitosis and participate in cytokinesis and chromosome segregation.

Tomorrow, Dr. Giles (abstract #163) will present data from an encouraging phase I trial of MK-0457 in patients with refractory hematologic malignancies, including CML. Fifteen imatinib-refractory patients with CML have been treated — the majority with accelerated phase or blast crisis — 11 of whom had the T315I mutation. Remarkably, no non-hematologic, significant drug toxicities were observed and there were 1 major and 4 minor hematologic responses, including one complete, two partial, and one minimal cytogenetic response. This is the first compound to demonstrate activity in treating imatinib-resistant patients with the T315I *BCR-ABL* mutation. MK-0457 was very well tolerated and also had activity in relapsed and refractory patients with T315I positive ALL, giving hope for patients with refractory leukemia. "As an aurora, bcr-abl, Flt3, and JAK2 kinase inhibitor, MK-0457 is a very exciting agent with an unusually benign toxicity profile at effective doses" said Dr. Giles, the study's principal investigator. "A very interesting challenge will be how to isolate the contribution of aurora kinase inhibition to the clinical responses."

Resistance, either primary or secondary, to imatinib is not common. Primary resistance represents failure to respond to initial treatment with imatinib and occurs in the 2 percent of patients who do not achieve hematologic remission and the 8-13 percent who do not achieve major or complete cytogenetic remission with imatinib. Secondary resistance is characterized by an initial response that is subsequently lost. Patients may relapse with resistant chronic or accelerated phase or with blast crisis. Among patients with chronic phase, the rate of resistance is an estimated 3 percent per year. As the number of patients developing resistance to targeted agents increases, the development of new targeted agents, such as the aurora kinase inhibitors, will be an important addition to the formulary.