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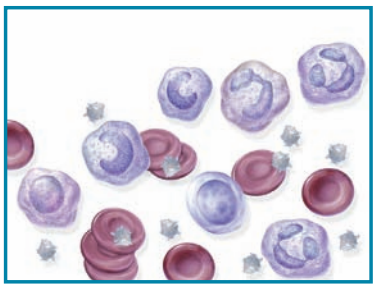

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PERIODICALS

CML: Sensitive Detection of Resistant Mutations May Help Predict Subsequent Therapy

BCR-ABL1 MutationCML

BY MARK FUERST

Sensitive detection of resistant mutations after imatinib resistance via a mass spectrometry assay may be a new way to predict the outcome of subsequent therapy with a second-line tyrosine kinase inhibitor (TKI) for chronic myeloid leukemia (CML) patients, according to the results of a study in the November 10 issue of the *Journal of Clinical Oncology (29;32:4250-4259)*.

Using a sensitive multiplexed mass spectrometry assay to detect BCR-ABL1 mutations, Australian researchers were the first to clearly demonstrate that low-level BCR-ABL1 mutations detected after imatinib failure in CML patients are clinically relevant.

"We found that a significant number of CML patients who have failed therapy with imatinib have low-level nilotinib — and/or dasatinib—resistant mutations that are detectable only using an assay that is more sensitive than conventional direct sequencing," lead author Wendy Parker, PhD, Research Officer in the Leukaemia Unit of the Department of Molecular Pathology at the University of Adelaide, said in an interview.

She and her co-researchers assessed the mutation status of 220 patients treated with nilotinib or dasatinib after they became resistant to imatinib. Mutations were detected by sequencing in 128 patients before commencing nilotinib or dasatinib therapy to switchover from imatinib. In 64 patients, 132 additional low-level mutations were detected by mass spectrometry alone. Fifty of the

WENDY PARKER, PHD: "Our study showed that low-level BCR-ABL1 kinase domain mutations—i.e., those present below the detection level of conventional direct sequencing—detected after imatinib failure are clinically relevant…. Mutation analysis is essential to facilitate selection of appropriate therapy for CML patients who have developed resistance to imatinib. Sensitive mutation analysis before treatment with second-generation TKIs enables detection of clinically relevant mutations in more patients than using conventional direct sequencing, and therefore aids informed decision making for a greater number of patients."

132 mutations were resistant to nilotinib and/or dasatinib.

Nilotinib- and/or dasatinib-resistant mutations were detected before starting nilotinib or dasatinib therapy after imatinib failure in 9% more patients using the sensitive mass spectrometry assay compared with conventional direct sequencing (32% vs 23%).

"Detection of low-level mutations that confer clinical resistance to nilotinib and/or dasatinib is highly predictive of their rapid clonal expansion under the selective pressure of nilotinib or dasatinib therapy and is associated with therapy failure," Dr. Parker said. "In patients who received the second generation TKI that retains sensitivity to the low-level mutation detected, the mutation rarely expanded."

> "Detection of low-level mutations after imatinib resistance offers critical information to guide subsequent therapy selection. If an inappropriate kinase inhibitor is selected, there is a high risk of treatment failure with clonal expansion of the resistant mutant."

When patients received the inhibitor for which the mutation confers resistance, 84% of the low-level resistant mutations rapidly became dominant clones detectable by sequencing, including 11 of 12 T315I mutations. Subsequent complete cytogenetic response rates were lower for patients with resistant mutations at switchover detected by sequencing (0%) or mass spectrometry alone (16%) compared with patients with other mutations or no mutations (41% and 49%, respectively).

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→CML

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The failure-free survival rates among the 100 patients with chronic phase CML when resistant mutations were detected at switchover by sequencing or mass spectrometry alone were 0% and 0% compared with 51% and 45% for patients with other mutations or no mutations.

Below the Detection Limit

The sensitive mutation assay may be used to detect nilotinib- and/or dasatinib-resistant BCR-ABL1 kinase domain mutations that are present below the detection limit of conventional direct sequencing, she said. "Therefore, mutations that would aid informed decision making as to the most appropriate TKI therapy after imatinib failure may be detected in a greater number of patients than using conventional direct sequencing.

"If a nilotinib-resistant mutation (Y253H, E255K, E255V, F359V, F359C) was detected using the multiplex mass spectrometry assay, dasatinib would be preferred. If a dasatinib-resistant mutation (V299L, T315A, F317L, F317I, F317C, F317V) was detected using the multiplex mass spectrometry assay, nilotinib would be preferred."

If an inappropriate kinase inhibitor is selected, there is a high risk of treatment failure with clonal expansion of the resistant mutant, she added.

Patients with a T315I mutation, which confers resistance to both nilotinib and dasatinib, or multiple mutations resistant to both nilotinib and dasatinib, may benefit from stem cell transplantation or experimental therapy such as ponatinib, rather than nilotinib or dasatinib. If nilotinib- or dasatinib-resistant mutations are not detectable, factors such as tolerance and disease phase should be considered when making therapeutic decisions, she said.

Now in Three International Trials

Dr. Parker said that currently, the mass spectrometry assay is being used to analyze samples of patients in three international clinical trials.

"The assay is also available upon request to clinicians in Australia. We are continuing to assess the clinical

significance of sensitive mutation analysis in various clinical settings," she said.

Take-Home Message

The study's message, said Dr. Parker, is that "low-level BCR-ABL1 kinase domain mutations—i.e., present below the detection level of conventional direct sequencing—detected after imatinib failure are clinically relevant.

"Mutation analysis is essential to facilitate selection of appropriate therapy for CML patients who have developed resistance to imatinib. Sensitive mutation analysis before treatment with second-generation TKIs enables detection of clinically relevant mutations in more patients than using conventional direct sequencing, and therefore aids informed decision making for a greater number of patients."

MICHAEL J. MAURO, MD: "With better detection and prediction of mutations with this type of assay, we can move more efficiently to newer generations of selective drugs and better understand the performance of later- generation kinase inhibitors in a *proactive* rather than entirely *reactive* manner."

For a Molecular Test to Be Useful…

Asked for his opinion for this article, Michael Mauro, MD, Associate Professor of Hematology at the Knight Cancer Institute, Center for Hematologic Malignancies, at Oregon Health & Science University, said that for a molecular test to be useful it has to be accessible in multiple locations, reproducible, and validated. "If a mass spectrometry assay could become a standard diagnostic marker we could clarify the question of low-level mutations."

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Dr. Mauro noted that specifically at the time of switch-over from imatinib to another drug, "we need to better define the population at risk, who at the moment still may not get enough treatment. We haven't been able to make perfect sense of their mutations nor predict which mutations may arrive later in the course of the disease."

In current molecular analysis, a predictable number of patients show mutational resistance, he continued. "These are not the only patients who would be served by a mass spectrometry assay. If this test were widely available, it would increase the number of mutations identified and help to see mutations at a lower level, not only the mutations we see now but 'forecasting' those that may emerge later. It would help us tailor the choice of post-imatinib treatment with greater confidence and data."

At the moment, oncologists are left referencing in vitro sensitivity of mutations in Bcr-Abl if a patient does not respond to imatinib, he said.

"Ideally, we would need more clinical trial data of patients with different mutations on different therapies to best define which drug works best for which mutations. With better detection and prediction of mutations with this type of assay, we can move more efficiently to newer generations of selective drugs and better understand the performance of later generation kinase inhibitors in a *proactive* rather than entirely *reactive* manner."

He said that in the future, he foresees better ways to help choose optimal treatment for CML patients. "We will continue to look for early cytogenetic response because that matters and inquire early regarding any resistance to imatinib or to one of the second-generation TKIs. Our growing repertoire of knowledge and therapies will tell us what to do next.

"With identification of mutations present or predicted to emerge that we recognize we can shuttle patients to the best drug to subvert those mutations — for example, use ponatinib if a patient has evidence or risk of an emerging T315I mutation."