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Dear Pharmacogenomic Tests for Cancer Treatment Technology Assessment Panel,

The American Society of Hematology (ASH) appreciates the opportunity to comment on the January 27, 2010 draft of the Agency for Healthcare Research & Quality (AHRQ) technology assessment: "Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, KRAS for anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia".

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases such as leukemia, lymphoma, sickle cell disease, anemia and hemophilia. ASH will specifically provide comment on the section of BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia (CML). ASH solicited input on the technology assessment from hematology experts throughout the organization and is uniquely qualified to assess the appropriateness of this testing.

Specific Response to QuestionsDoes BCR-ABL1 mutation testing predict response to TKI therapy?

Yes. There is enough evidence, both in vitro and in vivo that different mutations have different sensitivity to different inhibitors and that the in vitro sensitivity correlates well with the clinical response of patients. Several laboratories have published on the in vitro sensitivity of different mutants to tyrosine kinase inhibitors.^{1,2} These studies have shown that some mutations, such as V299L and F317L are not very sensitive to dasatinib (or imatinib), but are sensitive to nilotinib. In contrast, mutations such as F359V and Y253F/H are more sensitive to dasatinib than to nilotinib. In addition, none of the available agents has shown any efficacy against T315I. More important, this information has been shown to correlate strongly with clinical outcome of patients treated with these agents. In a study of 281 patients with mutation analysis prior to treatment with nilotinib, 40% of patients with no mutation or with mutations sensitive to nilotinib in vitro (ie, IC50 ≤150 nM) achieved a complete cytogenetic remission, while none of the patients with less sensitive mutations (ie, IC50 >150 nM) achieved this response.³ Similarly, among 1043 patients treated with dasatinib after imatinib failure, 402 (39%) had mutations. Those with the most sensitive mutations (ie, IC50 ≤3 nM) or with no mutations had a higher rate of complete cytogenetic response (53% and 56%, respectively) than those with the least sensitive mutations (ie, IC50 >3nM; complete cytogenetic response 32%).⁴ The significance of the mutation is also reflected in terms of the event-free survival probability (EFS). For patients in chronic phase, the 2-year EFS probability for patients with no mutation was 63%, and 78% for those with mutations sensitive in vitro to dasatinib or nilotinib, compared to 22% and 0% for those with mutations with intermediate or low sensitivity to these agents, respectively.⁵

Similar differences can be seen in overall survival (96-100% at 2 years with no mutation or sensitive mutations, vs 70-75% for those with mutations of intermediate or low sensitivity).⁵ In view of the recognized value of mutations analysis in predicting for response, this assay is recommended by a panel of international experts sponsored by the European LeukemiaNet in all patients after failure or suboptimal response to imatinib, and before changing therapy.⁶

What patient- and disease-relevant factors affect the test results, their interpretation or their predictive response to therapy?

The most important factor is the response to prior therapy. Some studies have suggested that mutations can be found in patients while still in complete cytogenetic remission, and these patients have an inferior outcome than those that do not have mutations.⁷ However, the value of a change of therapy based on such a finding is uncertain. In contrast, the value of the in vitro sensitivity of the mutation found is well documented (see response to previous question). Thus, in clinical practice, the development of failure of suboptimal response to imatinib mandates the search for mutations. Similarly, any patient who will change therapy to a new tyrosine kinase inhibitor or other treatment option should have a mutation analysis.

How does the gene testing impact the therapeutic choice?

As mentioned earlier, patients with mutations of intermediate or low sensitivity to a certain tyrosine kinase inhibitor should be offered the alternative agent. For example, a patient with F317L should be treated with nilotinib and not dasatinib, and a patient with F359V should be treated with dasatinib, not nilotinib. A patient with T315I should be considered for stem cell transplant. There are new agents specifically targeting this patient population (patients with T315I) as these patients currently have no treatment options available.⁸

What are the benefits and harms or adverse effects for patients when managed with gene testing?

The obvious benefit is the possible selection of an agent that may offer the best probability of response. There are no known adverse events other than those implicated with the venipuncture. However, the test is usually obtained at the time other routine monitoring tests are obtained.

Overall Summary


In summary, there is compelling evidence that kinase domain mutations predict response to TKI therapy. There are a large number of mutations associated with imatinib resistance and a smaller number of specific mutations that are associated with lack of response and/or resistance to nilotinib and dasatinib. These are in addition to T315I. The most important reason for mutation testing in patients who have developed resistance to (or failed) imatinib therapy is to determine optimal second-line management. The T315I mutation indicates that neither dasatinib nor nilotinib will be effective. When the rest of the imatinib resistant mutations are pooled together it is hard to show that they have an impact on response and progression to dasatinib or nilotinib, but this is because of the

dilutional effect of many mutations with little or no impact on response overwhelming the negative impact of a small number with a major impact.

There are three mutations in addition to T315I that respond poorly to nilotinib and these three mutations are detected in about 14% of all imatinib resistant patients. The evidence emerging is that these three mutations will respond well (or as well as patients with no mutation) to dasatinib. Likewise with dasatinib, the F317L and V299L mutations are clearly resistant to dasatinib and likely to be fully sensitive to nilotinib based on in vitro data. **Overall, around 20-25% of patients with imatinib resistance have a mutation profile that should influence the choice of second-line therapy.**

Please contact ASH Senior Manager of Policy & Practice Carol Schwartz at (202) 292 - 0258 or cschwartz@hematology.org for additional discussion on this document or other relevant AHRQ endeavors. Attached are several references that were instrumental in development of this summary.

Sincerely,

A handwritten signature in black ink that reads "Lawrence A. Solberg, Jr." The signature is written in a cursive, flowing style.

Lawrence A Solberg, MD, PhD
Chair
ASH Committee on Practice

References for Specific Questions

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