



**Statement of The American Society of Hematology To
The Medicare Evidence Development & Coverage Advisory Committee
Regarding the Pharmacogenomic Testing in the Diagnosis and Treatment of Cancer
January 27, 2010**

The American Society of Hematology (ASH) appreciates the opportunity to comment on the appropriateness of BCR-ABL for chronic myeloid leukemia (CML) patients who are candidates for imatinib. ASH believes that, based on evidence, this testing is not only justified, but necessary and it extends to monitoring during therapy. 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 and is uniquely qualified to assess the appropriateness of this testing.

CML is characterized by a balanced translocation between chromosomes 9 and 22, t(9;22) (q34, q11.2) known as the Philadelphia chromosome (Ph).¹ The reciprocal translocation between chromosomes 9 and 22 results in chimeric gene, BCR-ABL, that translates into a fusion protein with increased tyrosine kinase activity.^{2,3} The breakpoint in chromosome 9 is fairly constant, upstream of exon 2, while the breakpoint in chromosome 22 may occur in different regions of the BCR gene. Depending on the breakpoint in the BCR gene, the fusion protein can vary in molecular weight from 185 (190) kilodaltons (kDa) to 230 kDa. Most frequently patients with CML express a protein of 210 kD, p210.^{BCR-ABL} Regardless of their molecular weight, the unregulated constitutive tyrosine kinase activity of these proteins activates a number of intracellular signaling pathways that affect cell proliferation, differentiation, and apoptosis rendering the cell independent of cytokine regulation.^{2,4}

The introduction of tyrosine kinase inhibitors (TKI) has radically altered the outcome of patients with CML. Imatinib is a potent, orally administered inhibitor of ABL and BCR-ABL and other kinases such as PDGF-R and c-Kit. The efficacy of imatinib in CP CML was first established in a randomized study in patients with CML in CP, where it was compared to the combination of IFN- α and cytarabine. After 7 years of follow-up, the rate of complete cytogenetic responses was 82%⁵ and these responses have been durable, with an event-free survival of 81% at 7 years of follow-up, and overall survival of 86% (94% considering only CML-related deaths). Although this study did not confirm a survival advantage compared to interferon-treated patients because of an early crossover of most patients, comparison with historical groups treated with interferon demonstrated the expected survival advantage based on the high rate of CCyR.⁶

Approximately 30% of patients treated with imatinib will eventually demonstrate resistance or intolerance to imatinib. The most common mechanism of resistance to imatinib is the development of mutations of the kinase domain of ABL.⁷ For patients with resistance or intolerance to imatinib, second generation tyrosine kinase inhibitors have been developed that have demonstrated significant clinical efficacy. Dasatinib is a potent BCR-ABL inhibitor that also inhibits other kinases, including the Src family of kinases (SFK), PDGFR β and c-KIT.⁸ In vitro, dasatinib inhibits most BCR-ABL kinase domain mutants against which it has been tested, with the exception of T315I.^{9,10} Nilotinib is derived from the crystal structure of imatinib, with approximately 30-fold increased potency against unmutated BCR-ABL, and increased selectivity against this kinase.¹¹ Nilotinib also has activity against nearly all BCR-ABL mutants against which it has been tested, except T315I.¹¹ Approximately 50% of patients who have experienced failure to imatinib achieved a CCyR after treatment with one of these second generation inhibitors.^{12,13}

With the availability of more specific and effective therapy, a central part of the proper management of patients with CML has been the proper diagnosis and follow-up of patients with cytogenetic and molecular testing. Current recommendations from international experts in the field emphasize the importance of these elements.¹⁴ The evidence for these recommendations can be summarized as follows:

Diagnosis

The presence of BCR-ABL is required for the diagnosis of CML. Patients with CML features that do not have either the Ph chromosome or the BCR-ABL rearrangement are classified as atypical CML, which is considered a completely different entity. However, other than the name, atypical CML shares very little with Ph-positive, BCR-ABL-positive CML. The Ph chromosome is found in approximately 95% of patients with CML. Approximately 5% of patients with typical morphologic CML lack the Ph chromosome but demonstrate the BCR-ABL rearrangement.¹⁵ Thus, all patients with CML have a BCR-ABL rearrangement. Imatinib, dasatinib and nilotinib are highly selective agents that work specifically against ABL, BCR-ABL and few other kinases. Patients with atypical CML have minimal or no benefit from the use of imatinib¹⁶, making this treatment inadequate for such patients. Thus, it is mandatory to investigate the presence of the Ph-chromosome for all patients with clinical features suggestive of CML. For those with no evidence of the Ph-chromosome by routine karyotype, documentation of the BCR-ABL rearrangement is required to justify treatment with TKI.

The assessment of BCR-ABL by PCR at the time of diagnosis is also important for all patients as it allows the identification of the specific transcript (e13a2, e14a2, e1a2, etc) present, or whether the patient may carry one of the less common fusion transcripts that are not amplified by standard primers. This is important to avoid confusion after therapy when a patient may have undetectable transcripts, and to allow differentiation between a favorable response to therapy versus a transcript that cannot be amplified by the standard assay.¹⁷

Monitoring during therapy

As therapy for patients with CML has improved, the focus has changed from achievement of a hematologic response (primary objective in the era of hydroxyurea and busulfan), to achievement of a cytogenetic response (primary objective in the interferon era), to achievement of a molecular response (primary goal in the TKI era). With TKI, the majority of patients (over 80%) achieve a complete cytogenetic response. A significant proportion of patients can also achieve a major molecular response. This level of response is associated with improved long-term outcome. The results from the IRIS study suggest that among patients with CML treated with imatinib as initial therapy, patients who achieve a complete cytogenetic response but not a major molecular response by 18 months of therapy have a significantly inferior long-term outcome than those that achieve a complete cytogenetic response and a major molecular response (7-year event-free survival probability 86% versus 95%; $p=0.01$).¹⁸ The probability of achieving a major molecular response may in turn be predicted by the level of molecular response at earlier time points. Patients with BCR-ABL levels of <1% in the international scale by 3 months have a 94% probability of eventually achieving a major molecular response, compared to 62% and 35% from those with transcript levels of 1-10% and >10%, respectively at 3 months.¹⁹ Lower transcript levels at early time-points are also associated with a decreased probability of eventually losing a response and progressing.²⁰ Similar results have been reported with the use of second generation TKI after

imatinib failure. Among patients treated with dasatinib who were resistant or intolerant to imatinib, 35% had achieved a major molecular response at 12 months. Those with a major molecular response had a significantly longer duration of complete cytogenetic response.²¹

Recently it has become evident that achievement of a complete molecular response (ie, undetectable transcript levels) may be particularly beneficial. Among patients who achieve a complete cytogenetic response and major molecular response, those who achieve undetectable BCR-ABL levels have a significantly lower probability of relapse compared to those with major but not complete molecular response.²² The benefit is particularly evident for patients who have sustained complete molecular response after imatinib therapy. Patients with a complete molecular response that has been documented at least twice consecutively over a period of at least 6 months have a superior event-free and transformation-free survival compared to those with sustained major molecular response (but not complete).²³ Achievement of a complete molecular response may be particularly relevant towards the goal of eventual discontinuation of therapy. In one study, patients that have had a sustained complete molecular response for at least 2 years were offered treatment discontinuation. Approximately half of these patients had a sustained response despite discontinuation of therapy.²⁴ Although this is not considered standard practice at the moment, the results emphasize the importance of the achievement of a complete molecular response and thus of adequate continued monitoring of patients.

Proper monitoring during therapy includes a cytogenetic analysis and PCR at the time of diagnosis. Cytogenetic analysis should be repeated every 3 to 6 months until achievement of complete cytogenetic response, and every 1-2 years after that if a sustained complete cytogenetic and major molecular response has been achieved. Molecular monitoring should be performed every 3 months until achievement of major molecular response, and every 3-6 months after that.¹⁴

Development of resistance

Despite the great success achieved with imatinib, a significant number of patients are resistant to imatinib. Continued monitoring of patients is essential in detecting development of resistance to therapy. Several studies have demonstrated that an increase in transcript levels by PCR is associated with loss of response.^{22,25-28} This is important information as it may be used to revisit therapy with a reassessment of compliance, dose optimization, and investigation of other features that may prompt a change in therapy. In fact, a doubling in transcript levels has been associated with the appearance of mutations in the kinase domain.²⁹ Thus, continued monitoring is an important element of adequate treatment, not only to assess the success of therapy, but also for early detection of failure.

Among patients with resistance to imatinib, the most common mechanism of resistance to imatinib is the development of kinase domain mutations. More than 90 different mutations have been identified with different levels of resistance to imatinib and other TKI.³⁰ Detection of resistance is important, not only as documentation of resistance to imatinib, but also as it may help determine the ideal treatment approach. Different mutations have different levels of sensitivity to imatinib and other TKI in vitro.^{31,32} The sensitivity in vitro has been found to be highly predictive of the response to subsequent therapy with second generation TKI.³³⁻³⁵ Thus, for example, patients with a mutation F317L may be better served by offering nilotinib, whereas those with an F359V mutant would be better served by using

dasatinib. In addition, the T315I mutation is not sensitive in vitro to any of the available agents, and patients with a T315I mutation indeed have no response to any available TKI. These patients should be offered a stem cell transplant when eligible. Therefore, a mutation analysis should be performed in all patients who develop clinical evidence of resistance to a TKI and before changing therapy to a different TKI.¹⁴

Conclusion

In summary, CML is a model disease where a common molecular abnormality has led to very effective targeted therapy. Excellent results can be achieved with TKI for patients with CML. Optimal use of these agents, and optimization of patients' outcome is dependent on the adequate diagnosis and monitoring of patients. ASH is highly confident that there is sufficient evidence to determine that pharmacogenomic testing for BCR-ABL for chronic myeloid leukemia (CML) patients who are candidates for imatinib improves health outcomes and that these results are generalizable to the Medicare beneficiary population and the community based setting. It is ASH's opinion, that the proper use of this testing as suggested by the European Leukemia Net¹⁴ optimizes the patient care and outcome.

Please feel free to contact Carol Schwartz, Senior Manager of Policy & Practice at (202)292-0298 or cschwartz@hematology.org for additional discussion on this issue.

Review by: Jorge Cortes, MD, MD Anderson Cancer Center

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