Biomarkers in Gastrointestinal Stromal Tumor: Should We Equate Blood-Based Pharmacodynamics with Tumor Biology and Clinical Outcomes?

□□ *Commentary on Norden-Zfoni et al., p. 2643*

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The article by Norden-Zfoni et al. (1) provides evidence that administration of sunitinib, a multitargeted kinase inhibitor, to patients with advanced gastrointestinal stromal tumor (GIST) correlates with alterations of cellular and plasma biomarkers. The objective of this study was 2-fold: (*a*) to identify blood-based biomarkers to measure the biological effects of targeted therapy and (*b*) to identify those patients who will benefit from treatment.

Doxorubicin-treated and imatinib-resistant GIST patients experience a median overall survival as brief as 9 months (2) and a median progression-free survival of 2.3 months with ineffective therapy (3). Therefore, rational, surrogate, blood-based biomarkers could revolutionize therapeutic decision making by discontinuing ineffective therapy and its accompanying side effects earlier and allowing patients more rapid access to alternative therapeutic approaches.

Identification of useful valid biomarkers is a difficult task and the biomarker must be subjected to rigorous evaluation, particularly with reference to causation (4). For instance, serum biomarkers, such as prostate-specific antigen, are commonly used in clinical practice to assess antitumor efficacy and often accepted as an end point of response in clinical trials, yet this remains controversial (5). Characteristics of the ideal biomarker have been described and should include biological rationale, clinical relevance, adequate sensitivity and specificity, assay reliability, practicality, and ease of use (6). Moreover, biomarkers have been described as testable end points indicative of relevant biological aspects of cancer (7). However, caution should be exercised because serum biomarkers may reproducibly show biological effects that correlate with drug administration but may not reflect changes in tumor cell biology. In the current study, the authors have used blood-based assays that seem to be practical as well as relatively easy to use and have undertaken the arduous task to study the biological rationale and clinical relevance of this assay in patients with advanced GIST treated with sunitinib.

This study showed that administration of sunitinib resulted in an increase in serum vascular endothelial growth factor (VEGF) and circulating endothelial cells with concomitant decreases in soluble VEGF receptor and monocytes. Strikingly, the alterations in VEGF, soluble VEGF receptor, monocytes, and circulating endothelial cells that occurred on therapy normalized while patients were off therapy. A natural extension of this pharmacodynamic observation is understanding the precise events that are occurring within the tumor and whether those are at all related to serum biomarker alterations. A similar assessment of these markers in both tumor and serum may shed light on the relationship between blood-based and tumor microenvironmental changes in response to therapy. Moreover, a study correlating tumor specimens and blood may validate these markers as end points relevant to cancer rather than systemic effects of therapeutic intervention.

The authors showed a thoughtful identification of a major VEGF-binding population in monocytes. But how are monocytes relevant to GIST? What is their role or mechanism in this malignancy? What do changes in blood counts of monocytes in response to therapy mean? Recent reports have implicated $CD14^+$ monocytes in recruitment and possible tumor vasculature assimilation (8). Therefore, changes in $CD14^+$ may be relevant to posttherapeutic vasculogenic rebound via endothelial progenitor recruitment shown previously (9, 10). The results herein display interesting biology, and surely, this field requires more study as the authors conclude.

The designation of endothelial progenitors by cellular markers remains a topic of controversy. The continuum of differentiation from an endothelial stem cell to a mature endothelial cell begins with cells expressing "primitive" markers for which are lost, giving rise to "mature" markers. A complex customized expression profile may exist as cells go from the bone marrow niche to peripheral blood to the tumor microenvironment, as multiple cytokines influence progenitor recruitment and homing. The authors clearly define their circulating endothelial cell population as $CD45^-$, $CD133^-$, $CD31^+$, and $CD146^+$. Their definition for circulating endothelial progenitor cells is similar but positive for the primitive CD133 marker. Therefore, the authors have designated a progenitor population that expresses a mature marker (CD31) but also a primitive marker (CD133), which may account for their low or no circulating endothelial progenitor cell counts. More commonly, circulating endothelial progenitor cells are designated as VEGF receptor-2 and CD133 positive (11, 12). Using VEGF receptor-2 and CD133 positivity to define circulating endothelial progenitor cells rather than their definition may be valid and make available important studies of endothelial progenitors in response to sunitinib in the treatment of GIST.

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Interestingly, the authors showed that increases in circulating endothelial cells and decreases in monocytes correlated with a progression-free survival greater than 6 months. However, prudence should be taken when assuming that a progression-free survival greater than 6 months is due to drug effect, particularly when dealing with a disease that is represented by a broad spectrum of tumor growth rates and risk of malignancy as evidenced by the variations in tumor size and mitotic rate on histopathologic evaluation. For instance, in the study by Nilsson et al., patients whose primary GISTs had a low mitotic rate were found to have a median survival of more than 16 years, whereas patients whose tumors had a high mitotic rate experienced a median overall survival of 3.4 years. Therefore, perhaps the changes in circulating endothelial cell and monocytes may be a phenomenon that occurs in tumors with a slow rate of growth (i.e., less than 20% increase in the sum of the unidimensional diameters in 6 months) rather than a therapeutic effect on GIST.

Surprisingly, there is no mention nor control for other known factors that may affect progression-free survival, such as Kit mutation status (13), tumor size and mitotic rate (14), gastric primary site (14), Bcl-2 expression (15), or Kit intensity (16), in patients from this study. *Kit* mutation site is a robust marker of progression-free and overall survival. Patients with Kit exon 11 mutation have a superior progression-free and overall survival on imatinib therapy compared with those patients whose tumors have exon 9 mutation or wild-type Kit (13). It is our current clinical practice to perform mutation analysis of the *kit* gene in all new patients because this provides prognostic and therapeutic guidelines. Perhaps the pharmacodynamic effects of sunitinib occur only in patients whose tumors have exon 9 mutation for which a superior 6-month progression-free survival may be realized compared with patients whose tumors have exon 11 mutation.

As the authors explain, the mechanisms underlying changes in serum markers remain unknown. Thus, it remains a critical point that validation of serum biomarkers is required. Validations require correlations with clinical outcome and also correlations to changes in the tumor microenvironment. Without this rigorous methodology, the validity of serum biomarkers will remain shrouded in assumption and uncertainty, posing difficult predictions for clinical benefit and patient care.

The authors should be applauded for their work herein, initiating the characterization of peripheral blood components as a means of assessing clinical benefit and biological response to sunitinib therapy of GIST. Unfortunately, the understanding of clinical and biological observations in GIST is still in its infancy. So, while achieving their objectives for this study, future studies should include better control of important confounders with tissue validation. With this type of validation, serum markers such as these may one day make a significant impact on patient care.

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