Vascular Endothelial Growth Factor Concentration as a Predictive Marker: Ready for Primetime?

To the Editors: The article by Hanrahan et al. in the May issue of *Clinical Cancer Research* (1) describes the clinical utility of baseline vascular endothelial growth factor (VEGF) to identify subjects who may benefit from treatment with vandetanib (a VEGF receptor/epidermal growth factor receptor/RET inhibitor; ref. 1). However, important issues, such as preanalytic, analytic, and postanalytic interpretation for VEGF concentrations, need to be addressed before a VEGF cutoff can be "applied to clinical practice" as the authors conclude.

First, an important preanalytic issue is the choice of sample type (e.g., matrix). Hanrahan and colleagues indicate that sample type (serum versus EDTA plasma) is a major factor in the concentrations observed, which cannot be easily extrapolated when considering reference intervals and cutoffs. For example, despite using the matrix-specific cutoffs in their study groups (e.g., study groups 3, 6, and 7), only the low VEGF group in study groups 3 and 6 (both with EDTA plasma) had significant lower hazard ratios ($P < 0.05$). This was not observed in study group 7, which had serum as the source (1). This finding may be due to different combinations of agents, but the matrix effect must also be taken into account as a possible reason for the lack of association. In fact, the differences in VEGF concentrations in serum versus EDTA plasma are not an isolated finding in that many more cytokines (e.g., epidermal growth factor) display matrix-specific concentrations (2).

Second, the analytic performance of the VEGF assay was not reported; only the limit of detection and analytic range were stated. Without knowledge of the precision across the analytic range, it cannot be assumed that adequate performance was obtained at the different cutoffs used in the study.

Third, the cutoffs chosen are likely inappropriate. The population where the cutoffs are derived is not characterized (e.g., sex, age, and biochemical indices not provided) and the sample size is too small ($n = 37$; ref. 1). Minimaly, 120 healthy individuals are required to establish a reference interval, and more if subgrouping is required (3). This type of reference interval study has previously been done for VEGF in EDTA plasma ($n = 304$ children; $n = 540$ adults), which showed that VEGF concentrations are age dependent, with positive associations existing with platelet count, alanine aminotransferase, and oral contraceptive use (4). Unfortunately, Hanrahan et al. (1) did not include these important covariates in their models.

We believe that future prospective studies assessing VEGF measurement should incorporate these important preanalytic, analytic, and postanalytic issues.

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