Potential Biomarkers in Metastatic Gastrointestinal Stromal Tumors

To the Editor: We read with great interest the article by Norden-Zfoni and colleagues in the May issue of Clinical Cancer Research. In this article, the investigators aimed to identify potential biomarkers in the blood of patients with metastatic gastrointestinal stromal tumors treated with sunitinib malate (Sutent, Pfizer, Inc.; ref. 1). One of these biomarkers was the number of circulating endothelial cells (CEC). CECs are thought to be derived from damaged vasculature and have been detected in increased numbers in disease conditions associated with vasculopathy varying from atherosclerosis to vasculitis (2).

The investigators enumerate CEC using the commonly applied flow cytometry–based assay developed by Bertolini and colleagues (3). At first glance, this is an attractive method given its easiness to perform, its minimal sample manipulation, and, most importantly, its apparent relationship with disease activity in cancer patients (4). It seems, however, that this method lacks appropriate validation and yields much higher CEC numbers compared with methods based on enrichment of CEC (2).

In an attempt to validate the flow cytometric approach of CEC enumeration (3), we found that the vast majority of cells meeting the criteria for CECs according to this method are actually large platelets rather than vascular-derived endothelial cells, as these cells have no nucleus, express platelet antigens, and show a clear platelet morphology on examination by electron microscopy (5). Consistent with their bone marrow origin, we could not detect any of such cells in patients with severe myelosuppression. In this context, it is interesting that Mancuso et al. reported a decrease in this cell population in mice after chemotherapy and also ascribed this to severe myelosuppression (4). We suggest that tumor-produced cytokines, such as interleukin-6 and thrombopoietin, which can mobilize platelets from the bone marrow, account for the apparent relationship between tumor activity and the cell population designated as CECs by Mancuso, Norden-Zfoni, and colleagues.

Disagreements on the exact phenotypes of CEC and their subsets, as well as on the proper techniques to enumerate these, severely hamper the research in this important field. Before implementation of a particular CEC assay, such an assay should be thoroughly validated, which requires isolation of the cell population of interest followed by further characterization using a wide range of different approaches to confirm that these cells are indeed CECs.

Michiel H. Strijbos
Jaco Kraan
Stefan Sleijfer
Jan W. Gratama
Department of Medical Oncology,
Erasmus Medical Center-Daniel den Hoed Cancer Center,
Rotterdam, the Netherlands

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