Quantification of Circulating Vascular Endothelial Growth Factor Receptor-3–Positive Lymphatic/ Vascular Endothelial Progenitor Cells

To the Editor: We read with interest the article by Bogos et al. (1), which showed that circulating lymphatic/vascular endothelial progenitor cells (LVEPC) are significantly increased in small cell lung cancer (SCLC) patients and correlate with clinical behavior. We wish to comment on several unconvincing issues regarding the methodology and patient characteristics presented in the study.

Circulating LVEPC are an extremely rare cell population in peripheral blood that may contribute to lymphangiogenesis and/or angiogenesis and may be phenotypically identified by combining markers CD34, CD133, and vascular endothelial growth factor receptor 3 (VEGFR3). Unfortunately, the quantification of LVEPC reported by Bogos et al. is confusing. Here, authors recovered a mononuclear cell fraction after erythrocyte lysis (instead of the expected whole leucocyte fraction) to measure LVEPC as $CD34^+VEGFR3^+$ events using a two-color fluorescence-activated cell sorting method in which neither the blood volume nor the number of events accumulated for fluorescence-activated cell sorting analysis was specified. Bogos et al. show what they consider to be a typical analysis (Fig. 1A) in which LVEPC represented 95% of total $CD34^+$ cells, but where morphologic characteristics, isotypic controls, and the gating strategy are cruelly lacking. Moreover, Salven et al. (2) initially reported LVEPC levels in healthy adults of 0.2 ± 0.1% of $CD34^+$ cells, representing approximately 5 LVEPC/mL of blood (based on a mean value of 2,500 $CD34^+$ cells/mL). Here, authors report a median value of 1,625 LVEPC/mL in SCLC patients, which is not only inconsistent with those values reported by Salven et al. but also appears highly improbable in light of the fact that LVEPC, like $VEGFR2^+$ circulating endothelial progenitor cells, represent a tiny fraction of circulating $CD34^+$ cells (3, 4).

Moreover, the prognostic value of LVEPC levels in the SCLC patient group analyzed in this study is very questionable. First, multivariate analysis included neither performance status (a major prognostic factor) nor achievement of a complete response (5). Also, no information on the sequence of radiotherapy and chemotherapy was provided although the time to thoracic radiotherapy has been recently highlighted as a potential factor of treatment efficacy. Finally, the overall survival reported may have been affected by the absence of prophylactic cranial irradiation, which is a standard treatment in responding patients.

Finally, Bogos et al. proposed that LVEPC could be surrogate markers to monitor the efficacy of antiangiogenic therapies in SCLC. Although it is likely that circulating endothelial progenitor cells and LVEPC will become biomarkers in cancer, the authors have omitted that there is currently limited data supporting the clinical interest of such agents in SCLC.

Francoise Farace
Melissa Taylor
Laboratory of Translational Research and UPRES 3535 "Pharmacology and New Treatments in Cancer," University Paris-Sud, Gustave Roussy Institute, Villejuif, France

Jochen Rössler
Department of Pediatric Haematology/Oncology, Ludwig Heilmeyer Comprehensive Cancer Center (CCCF), Freiburg, Germany

Yohann Loriot
Benjamin Besse
Department of Medicine, Gustave Roussy Institute, Villejuif, France

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Published OnlineFirst 10/27/09.

doi:10.1158/1078-0432.CCR-09-1372