High VEGFR-3–positive Circulating Lymphatic/Vascular Endothelial Progenitor Cell Level Is Associated with Poor Prognosis in Human Small Cell Lung Cancer

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Abstract

Purpose: The newly identified bone marrow–derived cell population, called lymphatic/vascular endothelial progenitor cells (LVEPC), has been shown to contribute to lymph capillary growth in experimental tumor systems. The clinical significance of these cells has not yet been investigated in a human malignancy. Our aim was to study whether peripheral blood circulating LVEPCs participate in the progression of human small cell lung cancer (SCLC).

Experimental Design: A total of 88 patients with limited-stage SCLC and 32 tumor-free control subjects were included. Peripheral blood circulating LVEPC labeled with CD34 and vascular endothelial growth factor receptor-3 (VEGFR3) antibodies and the serum levels of the key lymphangiogenic molecule VEGF-C were measured by flow cytometry and ELISA, respectively.

Results: CD34-positive/VEGFR3-positive LVEPC levels were significantly increased in patients (versus controls; \( P < 0.01 \)), and there was also a significant relationship between LVEPC counts and lymph node metastasis (\( P < 0.01 \)). High pretreatment circulating LVEPC numbers correlated with poor overall survival (\( P < 0.01 \)). Although we observed significantly elevated VEGF-C concentrations in patients (versus controls; \( P < 0.01 \)), there was no significant correlation between VEGF-C and LVEPC levels. Moreover, no significant differences in peripheral blood VEGF-C levels were seen between patients subgrouped by clinicopathologic variables including tumor and lymph node stages and survival.

Conclusions: Peripheral blood levels of bone marrow–derived LVEPCs are significantly increased in patients with SCLC and correlate with lymphatic involvement and prognosis. This is the first study that shows evidence of increased numbers of circulating LVEPC in patients with a malignant tumor.

Small cell lung cancer (SCLC) is an aggressive pulmonary malignancy that constitutes approximately 13% of lung cancers (1). Despite its sensitivity to chemotherapy and radiotherapy, SCLC is rarely curable with these treatment strategies (2). Consequently, new biological targets are needed to develop more effective therapies. Among the potential targets are hemangiogenesis and lymphangiogenesis, which are thought to be fundamental to the progression of different solid tumors (3, 4). However, because no specific markers for lymphatic endothelium were available until recently, our knowledge of the lymphatic system of malignant tumors lags far behind that of the vascular system (5), and the role of lymphangiogenesis in the growth and dissemination of SCLC remains unexplored. Nevertheless, based on recent observations, lymphangiogenesis seems to be a critical mechanism for the progression in a variety of human cancers (6). As part of the lymphangiogenic machinery, the newly identified bone marrow–derived cell population, called lymphatic/vascular endothelial progenitor cells (LVEPC; ref. 7), has been shown to contribute to \( \text{de novo} \) lymphangiogenesis in human renal transplants (8), and more importantly, in experimental tumor systems (9). It is still unclear, however, whether LVEPC participate in SCLC-induced...
Translational Relevance

According to recent results, lymphatic vessels in tumors do not necessarily derive from capillary sprouting; instead, similar to the mechanism of vasculogenesis, they can also arise through “lymphvasculogenesis,” a process by which bone marrow-derived lymphatic/vascular endothelial progenitor cells (LVEPC) are recruited and differentiate in situ into mature endothelial cells to form new lymphatic capillaries. The current study shows for the first time that small cell lung cancer patients have peripheral blood circulating CD34-positive/VEGFR3-positive LVEPC numbers significantly higher than those in tumor-free control subjects. Moreover, this is the first study that shows the clinical significance of these cells in a human cancer.

lymph vessel growth. Nevertheless, because an analogous cell population [vascular endothelial growth factor receptor 2 (VEGFR2)-positive hemangiogenic endothelial progenitor cells (EPC)] has been shown recently to have clinical significance in the hemangiogenic process of a wide range of human malignancies (10–14), including non-SCLC (15, 16), we hypothesized that LVEPC could be involved in the progression of human SCLC. Hence, using peripheral blood samples obtained from SCLC patients, we assessed the numbers of circulating LVEPCs by flow cytometry and investigated whether these numbers might be related to the levels of the key lymphangiogenic molecule VEGF-C and/or to the risk of lymph node metastasis and to patient survival.

Materials and Methods

Clinical data. To measure the number of circulating LVEPC, peripheral blood samples were collected in EDTA tubes through 21G needles from 88 patients with limited-disease SCLC before therapy. According to the consensus report of the International Association for the Study of Lung Cancer, limited disease was defined as disease that is limited to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and/or contralateral mediastinal and/or ipsilateral and/or contralateral supraclavicular nodes (17). However, patients with limited disease with the presence of malignant pericardial effusion, and/or pleural effusions were not included in the current study. SCLC patients were free of additional malignant or inflammatory diseases, and/or chronic obstructive lung disease, and/or pulmonary fibrosis, wounds or ulcers, and cardiovascular risk states including diabetes mellitus, chronic renal failure, untreated hypertension, and rheumatoid arthritis that, as described in the case of the analogous bone marrow–derived cell population (VEGFR2-positive hemangiogenic EPC; ref. 28), might influence the number of LVEPC. Moreover, because Fadini et al. have found the depletion of VEGFR2-positive hemangiogenic progenitors in the peripheral blood of patients with chronic lung disease and long-lasting hypoxia recently (18), SCLC patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease; ref. 19) stage III-IV (severe or very severe) and exacerbating stage I-II chronic obstructive pulmonary disease (COPD) were also excluded from the study. There were 54 male and 34 female patients with a median age of 63 y (range, 44-77 y; Table 1). Patients underwent staging work-ups consisting of physical examination, complete blood counts, spirometry tests, comprehensive chemistry panels, chest radiographs, computed tomography scans of the chest and abdomen, bone scintigraphy, and magnetic resonance image or computed tomography scans of the brain. All limited-stage SCLC patients received chemotherapy (cisplatin and etoposide) plus thoracic irradiation. In case of disease progression, patients with chemosensitive tumors (progression >3 mo after the last cycle of first-line therapy) were retreated with the cisplatin and etoposide regimen. Patients who progressed during or within 3 mo after first-line therapy received a cyclophosphamide, epirubicin, and vincristine combination as a second-line treatment. Survival was defined as the time between the date of diagnosis and the date of death. The actual median follow-up was 15 mo (range, 4-27 mo). Potential median follow-up calculated by the “reverse Kaplan-Meier” analysis (20) was 26 mo (range, 25-27 mo). By the end of the study 77 patients (87%) had died of their SCLC. The control group included 32 individuals matched for age, gender, smoking status, and spirometry test result (Table 1). Informed consent was obtained from all patients and control volunteers, and the study was done with the approval of the ethics committees of the host institutions and in accordance with the ethical standards prescribed by the Helsinki Declaration of the World Medical Association.

Enumeration of LVEPC by flow cytometry from the peripheral blood of SCLC patients. To quantify the content of circulating LVEPC by flow cytometric analysis, following erythrocyte lysis, the remaining peripheral blood mononuclear cell fraction was resuspended in 90 μL of a fluorescence-activated cell-sorting buffer containing PBS and 0.1% bovine albumin and incubated for 30 min at 4°C with phycoerythrin-Cy5-conjugated antihuman CD34 (BD Biosciences) and phycoerythrin-conjugated antihuman VEGF3 (R&D Systems). Fluorochrom-conjugated isotype controls were used for each staining procedure. After appropriate gating, the number of CD34-positive/VEGFR3-positive double-positive cells were quantified and expressed as the number of cells per milliliter of blood using the CyFlow SL flow cytometer and the FlowMax software (both from Partec).

Measuring the levels of VEGF-C in the peripheral blood of controls and patients with SCLC. For VEGF-C measurements, serum samples from all patients and controls were prepared and stored at -80°C until further analysis. Levels of VEGF-C were quantified with the use of a commercial ELISA kit (R&D Systems) according to the manufacturer’s instructions. Results were compared with standard curves, and the lower detection limit was 4 pg/mL. Measurements were done in duplicate.

Statistical analysis. Continuous variables were compared with Student’s t test if the sample distribution was normal or with Mann-Whitney U test if the sample distribution was asymmetrical. Categorical data were compared using Fisher’s exact probability and χ² tests. Correlations of LVEPC and VEGF-C levels were determined using Spearman’s rank correlation test. Overall survival analyses were done using the Kaplan-Meier method. Overall survival intervals were determined as the time period from initial diagnosis to the time of death. The comparison between survival functions for different strata was assessed with the log-rank statistic. Multivariate analysis of prognostic factors was done using Cox’s regression model. Differences were considered significant when P < 0.05. All statistical analyses were done using Statistica 7.0 (StatSoft Inc.) software program.

Results

Characterization and levels of LVEPC in peripheral blood samples of SCLC patients. Endothelial progenitor cells (both blood and lymphatic) are thought to derive from CD34-positive hematopoietic progenitor cells (7, 21, 22). Whereas hemangiogenic progenitors can be identified by the expression of the cell surface markers CD34, CD133, and VEGFR2 (3), LVEPC are characterized by the expression of CD34, CD133, and VEGFR3 (7). However, because both types of endothelial progenitor cells rapidly lose their CD133 expression after the migration into the circulation from the bone marrow and
CD133-positive LVEPC correspond to a subfraction of the total CD34-positive LVEPC population, we determined the numbers of CD34-positive/VEGFR3-positive double-positive LVEPC in the peripheral blood of 32 control subjects and 88 SCLC patients by flow cytometry (Fig. 1A). In the control group, the median value of CD34-positive/VEGFR3-positive circulating LVEPC was 455/mL (interquartile range, 370-530/mL) of peripheral blood (n = 32; Fig. 1B). In patients with SCLC, this level was significantly higher, with a median value of 1,625 (interquartile range, 600-2,750/mL; n = 88; P < 0.01; Fig. 1B).

Correlations between LVEPC levels and clinicopathologic parameters. LVEPC numbers were also evaluated according to the clinicopathologic factors of our patients. There was a statistically significant relationship between LVEPC levels and lymph node involvement (P < 0.01; Table 2). However, no significant associations with age, smoking history, gender, or tumor (T) stage were detected (Table 2).

LVEPC levels as prognostic markers in patients with SCLC. Because lymphatic involvement of SCLCs was associated with increased LVEPC counts, we next used Kaplan-Meier analysis to calculate the overall survival rates for patients with low and high peripheral blood LVEPC levels (Fig. 2). We found that patients whose peripheral blood samples were categorized by low pretreatment CD34-positive/VEGFR3-positive LVEPC levels (based on median value, <1,625/mL of peripheral blood) had significantly longer survival times than those with high levels of circulating LVEPC (median survival time was 20 versus 11.5 months; P < 0.01; Fig. 2). The median overall survival for all patients was 14 months. Multivariate analysis (including standard prognostic variables, such as age, gender, and tumor and lymph node stage) also indicated that pretreatment circulating LVEPC levels predicted outcome independent of other variables (P < 0.01; Table 3). In accordance with the latest International Association for the Study of Lung Cancer analysis of clinical staging for SCLC (23), a further independent prognostic factor related to poor survival was N2,3 disease (versus N0,1 stage; P = 0.014; Table 3).

Peripheral blood levels of VEGF-C in SCLC patients. Although VEGF-C serum levels of patients were significantly elevated as compared with those of control subjects (4931 ± 881 versus 3992 ± 462 pg/mL, respectively; P < 0.01; Table 1), we were unable to detect a significant relationship between the concentrations of the key lymphangiogenic molecule, VEGF-C, and circulating CD34-positive/VEGFR3-positive LVEPC counts (P = 0.74; data not shown). Moreover, when VEGF-C levels were evaluated according to the clinicopathologic factors of our patients, no significant associations with age, smoking history, gender, or tumor stage were detected (Table 2).

Table 1. Characteristics and VEGF-C levels of patient and control groups

<table>
<thead>
<tr>
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<th>Patients (n = 88)</th>
<th>Controls (n = 32)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>54/34 (61.4% vs. 38.6%)</td>
<td>19/13 (59.4% vs. 40.6%)</td>
<td>0.5*</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63 (range, 44-77)</td>
<td>61 (range, 48-70)</td>
<td>0.62</td>
</tr>
<tr>
<td>Smoking status (current or ex-smoker/non-smoker)</td>
<td>75/13 (85.2% vs. 14.8%)</td>
<td>26/6 (81.2% vs. 18.8%)</td>
<td>0.39*</td>
</tr>
<tr>
<td>Lung function, spirometry (normal/mild or moderate COPD)</td>
<td>74/14 (84% vs. 16%)</td>
<td>27/5 (84.4% vs. 15.6%)</td>
<td>0.61*</td>
</tr>
<tr>
<td>VEGF-C (pg/mL)</td>
<td>4,931 ± 881</td>
<td>3,992 ± 462</td>
<td>&lt;0.01</td>
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</table>

Fischer’s exact test.
Mann-Whitney test.
According to the GOLD (Global Initiative for Chronic Obstructive Lung Diseases) classification of COPD severity (ref. 19).
Mean ± SD.
Student’s t-test.
Significant difference between patient and control groups.

Fig. 1. Quantitative evaluation of circulating LVEPC by flow cytometric analysis (A to B). A, representative flow cytometric analysis for determining the number of CD34-positive/VEGFR3-positive LVEPC (Q1, CD34-negative/VEGFR3-positive; Q2, CD34-positive/VEGFR3-positive; Q3, CD34-negative/VEGFR3-negative; Q4, CD34-positive/VEGFR3-negative cells). B, box plots showing median (central dots), 25%-75% quartile ranges (boxes), and minimum/maximum levels (whiskers) of circulating CD34-positive/VEGFR3-positive LVEPC levels in control subjects (n = 32) and patients with SCLC (n = 88).
gender, or more interestingly, with lymph node status, tumor stage, or survival were detected (data not shown).

Discussion

This study presents the novel finding that patients with SCLC have peripheral blood circulating CD34-positive/VEGFR3-positive LVEPC numbers significantly higher than those in tumor-free control subjects, and that the levels of these cells correlated to lymphatic progression and to clinical behavior. Although increased levels of bone marrow–derived circulating VEGFR2-positive hemangiogenic EPC have been reported in various malignant diseases (10–16), to the best of our knowledge, this is the first study that shows evidence of high numbers of circulating lymphatic/vascular EPC in the peripheral blood of patients with a malignancy.

There is a growing body of evidence that tumor blood vessel growth not only depends on cells formerly residing within the vascular walls (i.e. endothelial sprouting) but also is considerably supported by vasculogenesis, the mechanism by which a subset of bone marrow–derived cells, EPC, enhance ongoing vascularization by providing a circulating cell population that home to the blood capillary walls and incorporate into the endothelial tube (3, 14). It is also well established now that lymphangiogenesis (i.e. in situ lymph vessel sprouting), facilitated by VEGFR3 signaling, contributes to tumor progression (24, 25). However, more recent evidence suggests that tumor lymphatics do not necessarily derive from endothelial sprouting; instead, similar to the mechanism of vasculogenesis, tumor lymph vessels can also arise through “lymphvasculogenesis,” a process by which bone marrow–derived LVEPC are recruited and differentiate in situ into mature endothelial cells to form new lymphatic capillaries (9). These VEGFR3-positive LVEPC are functionally a unique population of progenitor cells expressing CD34 but not CD105, CD11b, CD14, or VEGFR1 (7). Because they have been shown to have an in vitro capacity to differentiate into lymphatic and/or vascular endothelial cells (7), LVEPC could contribute to both lymph and blood capillary growth of human SCLCs. The data from this current study do not allow us to measure the vasculogenic activity of LVEPC or determine the

Table 2. Correlation of clinicopathologic features and circulating LVEPC numbers in 88 SCLC patients

<table>
<thead>
<tr>
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<th>CD34+/VEGFR3+ LVEPC</th>
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<tr>
<td></td>
<td>Low* (%)</td>
<td>High* (%)</td>
<td></td>
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<tr>
<td>Age (y)*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>63&lt;</td>
<td>22 (50%)</td>
<td>21 (47.7%)</td>
<td></td>
</tr>
<tr>
<td>63&gt;</td>
<td>22 (50%)</td>
<td>23 (52.3%)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>6 (13.7%)</td>
<td>7 (15.9%)</td>
<td></td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>38 (86.3%)</td>
<td>37 (84.1%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (56.8%)</td>
<td>29 (65.9%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (43.2%)</td>
<td>15 (34.1%)</td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N0-1</td>
<td>21 (47.3%)</td>
<td>3 (6.8%)</td>
<td></td>
</tr>
<tr>
<td>N2-3</td>
<td>23 (52.7%)</td>
<td>41 (93.2%)</td>
<td></td>
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<tr>
<td>T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>6 (13.6%)</td>
<td>2 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>T2-T4</td>
<td>38 (86.4%)</td>
<td>42 (95.5%)</td>
<td></td>
</tr>
<tr>
<td>VEGF-C level †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>22 (50%)</td>
<td>22 (50%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22 (50%)</td>
<td>22 (50%)</td>
<td></td>
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<tr>
<td>Chemotherapy regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>37 (84.1%)</td>
<td>31 (70.5%)</td>
<td></td>
</tr>
<tr>
<td>EP+CEV</td>
<td>7 (15.9%)</td>
<td>13 (29.5%)</td>
<td></td>
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Abbreviations: EP, cisplatin and etoposide; CEV, cyclophosphamide, epirubicin and vincristine.
* Cut-off value is median value.
† Cut-off value is mean value. Data shown in parentheses are column percentages.

Fig. 2. Kaplan-Meier curves for the overall survival of the patient population with SCLC, according to peripheral blood circulating CD34-positive/VEGFR3-positive LVEPC numbers as determined with flow cytometry. Cutoff value between low and high pretreatment CD34-positive/VEGFR3-positive LVEPC levels was 1,625 LVEPC/mL of peripheral blood.
ratio of LVEPC contributions between vasculogenesis and lymphvasculogenesis. However, given the observation that LVEPC numbers were related to the extent of lymph node metastases, one can hypothesize a potential role for these cells in the lymphangiogenic machinery, or at least the possibility that the driving force behind the lymphatic progression of SCLC and the mobilization of LVEPC from the bone marrow is similar.

Based on the above theory, one can assume that our observation on increased LVEPC numbers is the result of elevated levels of the VEGFR3 ligand VEGF-C. Recent studies in experimental animal models have shown direct evidence that this key lymphangiogenic cytokine plays a critical role in cancer progression by inducing lymphangiogenesis and enhancing metastatic spread via the lymphatics, and that these effects can be suppressed by blocking VEGFR3 signaling (reviewed in ref. 26). In a human non-SCLC xenograft model, for example, tumors overexpressing VEGF-C had higher lymph vessel densities than control tumors, and inhibition of VEGFR3 signaling suppressed tumor lymphangiogenesis and metastasis to regional lymph nodes (27). Thus, we assayed the peripheral blood levels of VEGF-C and found that although its concentrations were significantly higher in SCLC patients than in control subjects, no statistically significant relationship existed between VEGF-C levels and numbers of circulating LVEPCs. However, although the possibility of VEGF-C–induced LVEPC release from the bone marrow in SCLC is not supported by the current results, chances are that as in other (for example cardiovascular, malignant, or inflammatory) disorders in which the interaction of several inflammatory and noninflammatory cytokines controls vasculogenic EPC (reviewed in refs. 28, 29), the dynamic balance of multiple growth factors is also likely to determine the number and function of LVEPC in cancer.

In addition to the observation of significantly higher pretreatment circulating LVEPC counts in SCLC patients as compared with control subjects, this prospective study presents the novel finding that a single flow cytometric measurement of CD34-positive/VEGFR3-positive LVEPC is a useful tool to predict outcomes in patients with SCLC. During the follow-up period of 25 months, a significantly higher incidence of death from SCLC was observed in patients with high pretreatment LVEPC levels as compared with patients with low LVEPC levels, suggesting that the pretreatment levels of LVEPC, detectable by flow cytometry in the peripheral blood, correlate with the clinical behavior of human SCLC.

Besides the previous experimental findings mentioned above, several studies in various human cancers have suggested that VEGF-C expression, as assessed by immunohistochemistry in tumor tissue and/or by ELISA in peripheral blood samples, correlates with lymph node metastasis and/or patient survival (5, 30–35). Hence, we also evaluated the potential of measuring peripheral blood levels of VEGF-C as a tool for determining lymph node metastasis and/or prognosis in SCLC. However, although we showed elevated VEGF-C concentrations in SCLC patients over tumor-free controls, we failed to detect an association between VEGF-C levels and patients’ survival, and analysis of the cancer patient cohort showed no differences between clinicopathologic subgroups. In particular, no difference in VEGF-C levels was seen between patients with N0,1 and with N2,3 stages. This accords with the results obtained in the only previous study on peripheral blood VEGF-C measurements in SCLC (36). In contrast, peripheral blood VEGF-C levels predicted lymph node status in a variety of tumor types including esophageal (37), gastric (38), and papillary thyroid (39) cancers, and in malignant melanoma (40) and non–small cell lung carcinoma (41). In addition to studies further investigating the regulation of LVEPC numbers/function in malignant disease, there is also a need, therefore, to better clarify and understand the biological and clinical significance of VEGF-C in SCLC.

In conclusion, in SCLC, as well as in most types of malignant tumors, lymphatic metastasis is associated with poor survival and is one of the factors associated with poor prognosis. Whether lymphatic spread is a mechanism for poor prognosis or a marker for aggressive biological behavior remains to be decided. The current study shows, for the first time, that the circulating numbers of bone marrow–derived LVEPC are significantly increased in SCLC patients and that these numbers correlate with the extent of tumor spread to regional lymph nodes and with patients’ survival. Although our data suggest a participation of LVEPC in lymphatic tumor progression in SCLC patients, it is not clear yet whether LVEPC play a role only in the lymphatic spread of the tumor, or whether they also facilitate primary tumor growth and the development of blood-borne metastases via the enhancement of blood capillarization. Moreover, it has yet to be determined if LVEPC can be used as a surrogate marker to monitor the efficacy of standard or future anti(lymph)angiogenic therapies.

### Table 3. Multivariate analysis of various prognostic factors in patients with SCLC

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>RR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age in y (&lt;63 versus ≥63)</td>
<td>1.213 (0.747-1.969)</td>
<td>0.434</td>
</tr>
<tr>
<td>Gender (female versus male)</td>
<td>1.081 (0.655-1.782)</td>
<td>0.761</td>
</tr>
<tr>
<td>T stage (T1 versus T2-4)</td>
<td>2.024 (0.725-5.65)</td>
<td>0.178</td>
</tr>
<tr>
<td>N stage (N0 versus N2-3)</td>
<td>2.634 (1.215-5.711)</td>
<td>0.014</td>
</tr>
<tr>
<td>CD34+/VEGFR3+ LVEPC level (low versus high)*</td>
<td>5.379 (2.659-10.882)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VEGF-C serum level (low versus high)†</td>
<td>1.221 (0.76-1.961)</td>
<td>0.408</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; 95% CI, 95% confidence interval.

* Cutoff value is median value.

† Cutoff value is mean value.
in SCLC. Further research is also needed on whether LVEPCs can be targeted to treat patients with SCLC, or alternatively—as they are endowed with the capacity to home to the tumor lymphatic network—can be manipulated to deliver toxins or lymph vessel--targeting agents. Finally, because the above results are most likely not specific for SCLCs, they may lead to a number of novel approaches in the diagnosis and treatment of other malignant diseases as well.

References


Disclosure of Potential Conflicts of Interest

The authors declare that they have no competing financial interest concerning this manuscript.

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