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Endothelial progenitor cells in patients with non-small cell lung cancer

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ABSTRACT

Introduction: Endothelial progenitor cells (EPCs) are known as putative cells in neovasculogenesis during pathological conditions, which are derived from bone marrow. This study was performed to systematically review the EPCs frequency in patients with non-small cell lung cancer (NSCLC) by evaluating the expression of CD133 and vascular endothelial growth factor (VEGF) markers.
Methods: We search the PubMed and Scopus databases for the following keywords; CD133 AND lung AND VEGF. Inclusion criteria were all the articles studied the expression of both CD133 and VEGF markers in patients with NSCLC. No language and date restrictions were imposed to the search strategy. All the articles that studied only one biomarker or those that investigated the markers expression and EPCs count in patients with other types of tumors except NSCLC were excluded from the study.
Result: Totally 51 articles obtained following the primary search of both databases. Only 7 of them had the eligibility to be included in this systematic review. Six articles were case- control and one was a cohort type of investigation. Flowcytometry and immunohistochemistry were the most applied methods for estimating the EPCs count and evaluating the expression of markers in circulating peripheral blood and tumors tissue. The expression of EPCs markers was increased in patients with NSCLC compared to healthy control individuals; however, the frequency of EPCs was low in peripheral blood of patients.
Conclusion: Although it is not clear that circulating EPC numbers are associated with lung cancer patients angiogenesis, EPCs and VEGF levels are elevated in patients with operable NSCLC. The ideal method for evaluating circulating endothelia cells (CECs) or EPCs levels in vivo is still a matter of debate and because of the low number of EPCs in peripheral blood, their detection is technically challenging.

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Introduction

Endothelial progenitor cells (EPCs) are immature progenitor bone marrow cells with the ability of migration to peripheral circulation and differentiation into mature endothelial cells, which contribute in newly formed vessels process. CD34, vascular endothelial growth factor (VEGF), and CD133 are among cell surface biomarkers, which can be applied for the identification of progenitor cells (1). Circulating endothelia cells (CECs) are mature endothelial cells in peripheral circulation. In normal condition and healthy individuals, very low amounts of circulating vessel wall–derived ECs are present; however, during disease conditions the number of CECs will be increased not only for

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the regeneration of the vascular endothelium, but also in cancerous conditions the increased number of these bone marrow derived endothelial cells will lead to neovascularization and tumor growth (2). The low amount of EPCs in healthy individuals correlates with the low number of CECs. The presence of angiogenic growth factors such as VEGF is essential for neovasculature during cancerous conditions.

CD133

The surface antigen AC133 (CD133) was firstly identified following producing monoclonal antibody to $CD34^+$ hematopoietic stem cells isolated from fetal liver, bone marrow and cord blood (3). A subset of the pluripotent $CD34^+$ human hematopoietic stem cells that express cell surface marker CD133 (AC133) are indicator of cells destined for endothelial cell differentiation and angiogenesis (4). CD133 is known as a surface antigen, which can be expressed on cell surface of cancer stem cells (CSC) in various solid tumors. In patients with glioblastomas, and colon or prostate cancers, the presence of CSCs has been shown to be associated with poor prognosis (5-8).

It has been proposed that highly purified endothelial cells, which are superior to fibroblasts in supporting hematopoiesis, are highly proliferative and can be activated by inflammatory cytokines; these highly purified endothelial cells are derived from bone marrow CD133(+) progenitor cells (9). Mature endothelial progenitor cells of the peripheral circulation express VEGF and CD34 markers, but not CD133 that is a 120 kDa glycosylated polypeptide; this marker will be lost during the differentiation process (10).

VEGF

Vascular endothelial growth factor (VEGF), as vascular permeability factor (VPF) and an endothelial cell-specific mitogen can be produced by tumor cells, macrophages, platelets, keratinocytes, and renal mesangial cells (11-13). Despite the roll of VEGF in neovascularization and pathological angiogenesis through stimulating endothelial cells proliferation and migration, this factor participates in various normal physiological processes including bone formation, hematopoiesis, wound healing, physiological angiogenesis, and developmental process (14). The importance of VEGF as a target for preventing angiogenesis and neovascularization has been investigated during examining various strategies for treating cancers(15,16). It is now accepted that VEGF is among principal factors that stimulate and activate EPCs proliferation and migration from the bone marrow and can be proposed as a prognostic factor for patients with non-small cell lung cancer (NSCLC). So molecular targeted therapies and inhibition of these influential cytokines on angiogenesis are the promising treatment methods (17).

NSCLC

Non-small cell lung cancer (NSCLC) accounts for almost 85% of lung cancer, so it can be regarded as the leading cause of cancer-related deaths, which is associated with unpredictable clinical outcomes and is even fatal despite various surgical treatment and chemotherapy strategies (18). It has been proposed that tumor development and metastasis in patients with NSCLC is associated with tumor angiogenesis through bone marrow-derived circulating EPCs mobilization by tumor- or ischemic-induced signals, which leads to vasculogenesis (10). According to recent findings, tumor vascular system is the result of vasculogenesis, which is in turn the consequence of recruitment and differentiation of the bone marrow derived EPCs to mature endothelial cells and developing new vessels (19,20).

Despite the close association between EPCs and tumor neovascularization, pathogenesis of NSCLC, and the precise effect of EPCs in patients with lung cancer is not revealed. In this systematic review, we aimed to study the EPCs counts and expression rate of cell surface markers in patients with NSCLC.

Material and Methods

PubMed and Scopus were both searched at August 2015 with the following search terms: CD133 AND lung AND VEGF. Inclusion criteria were all the articles that studied the expression of both CD133 and VEGF markers on EPCs of the patients with NSCLC. No language and date restrictions were imposed on our search strategy. Exclusion criteria were articles that specifically studied the expression of only one of the EPCs marker, or investigated markers expression in patient with other types of tumors. Quality of the included studies was checked based of the Newcastle Ottawa checklist and reported in Table 1.

Results

Totally 51 articles were identified in the PubMed and Scopus based on the mentioned search strategy. From those, 17 articles were the same in both databases. Experimental articles and those that were not relevant with the scope of this study were omitted following reviewing the title and abstract of the obtained articles. None-English language articles were covered only by PubMed. Only 9 articles were extracted for studying the full text; however, 2 of them did not have enough data to be included. Eventually, 7 articles were included in our system-

atic review as the most relevant articles to the purpose of this systematic review. Data regarding the selection of articles from the PubMed and Scopus are provided in Figure 1.

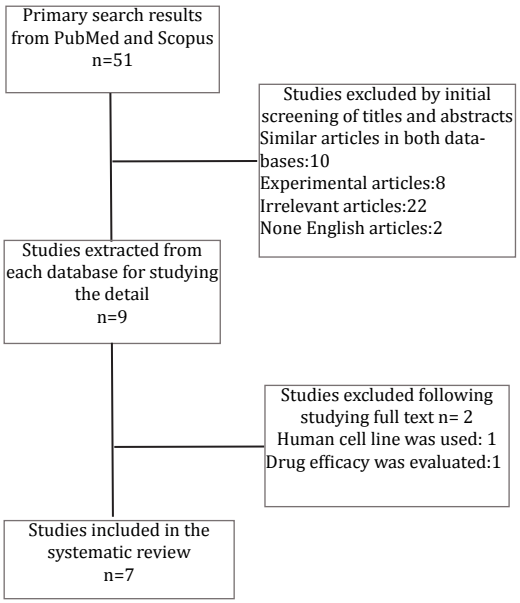

Figure 1. Flowchart of the included articles.

Table 1. Quality control of the articles included in this systematic review.

Author Reference	Is the case definition adequate? Consecutive series of cases? Community controls?	Comparability of cases and controls on the basis of the design or analysis	Same method of ascertainment for cases and controls/ same non-Response rate for both group
Pircher A (21)	Y	Y	Y/Y
Dome B (22)	Y	Y	Y/Y
Hilbe W (23)	Y	Y	Y/Y
Salnikov AV (24)	Y	Y	
Nowak K (25)	Y	Y	Y/Y
Zhou (26)	Y	Y	Y/Y
Morita R (27)	Y	Y	Y/Y

Y: Yes

Detail information extracted from the included articles is presented in Table 2.

Flowcytometry technique was used in 4 out of 7 included studies for estimating the frequency of EPCs labeled with CD133, and VEGF receptor-2 (VEGFR2) antibodies in peripheral blood of patients with NSCLC (21-24).

Flowcytometry was followed by quantitative real-time RT-PCR only in one study (21).

Flowcytometry was followed by fluorescence-activated cell sorting (FACS) technique in one of the included studies (23,24).

Sandwich ELISA and immunohistochemistry techniques have also been used for evaluating the serum level of VEGF in 2 and 3 of the 7 included studies, respectively (22-26).

Three studies estimated the cutoff value for evaluating positive expression of the markers in their sample size (21,24,26).

Only one study applied immunofluorescent labeling of microvessels on tumor sections in addition to other methods (21).

Immunocytological staining of singular circulating endothelial progenitor cells (CEPs) (MCA method) using monoclonal antibody against CD133 was firstly tested in the study of Pircher, et al on patients with NSCLC (24). This technique is proposed to be highly sensitive for identification of small cell populations and even single positive cells with the CD133 expression.

Discussion

According to the studies, there is still no method as the gold standard for detection of EPCs in clinical investigations. The clinical involvement of these circulating endothelial precursors in neovasculogenesis in NSCLC patients is not clear.

However, based on experimental studies, bone marrow-derived EPCs contribute to tumor angiogenesis and VEGF is responsible for their recruit-

Table 2. Extracted information from the included studies regarding the EPCs frequency in NSCLC patients.

Author Year Reference	Patients	Stufy	Method	Results
Pircher A 2008 (21)	N: NSCLC:10 Control: 10 Mean age: 61.4 years (range 45-73 years) 5 males: 5 females	Case- control	FCM FACS ELISA IHC MCA	MCA method: CD133+ in patients (Median %, range %) preoperative 1.25 (0.75-1.59) postoperative 0.81 (0.38-1.30) Control : all CD133- Cases above the cutoff value(0.97): N% Preoperative: 80 Postoperative:50 All control< cutoff FACS method CD34+/CD133+/KDR+ (Median %, range %) Preoperative 0.3 (0.1-2.1) Postoperative 0.55 (0.1-0.9) Cases above the cutoff value (0.38): N% Preoperative: 50 Postoperative:80 All control< cutoff Immunohistochemistry: Increased numbers of CD133+ cells: 7/10 cases ELISA: serum VEGF levels NSCLC cases: (median ; range) pg/ml Preoperative: (418 ; 63-811) Postoperative: (1109 ;230-2193) Cases above the cutoff value (351 pg/ml): N% Preoperative: 60 Postoperative:90
Dome B 2006 (22)	N: 53 NSCLC 14 healthy controls 28 male and 25 Female median age of 58 years (range, 45-67)	Case-control	IFA FCM RTPCR	Pretreatment CEPC low*: 36/53 CEPC high*:17/53 Mean number of posttreatment EPCs/mL of blood (mean ± SE)
Hilbe W 2004 (23)	N: 63 NSCLC tumor specimen Mean age: 62 (range, 37–79) years Gr1: Tumor tissues of NSCLS cases (N=63) Gr2: Tumor free tissues of NSCLC cases (N=66) Gr3:Control (N:11)	Case-control	IHC	CD133+ cells: (Median %, range %) Gr1: (0.2%, 0–50%) Gr2: (0%, 0–1%) Gr3: (0%, 0–1%) Cases above the cutoff value (0.7%): number(%) Gr1: 43(68%) Gr2: 0(0%) Gr3: 0(0%) VEGF+ cells: (Median %, range %) Gr1: (2%, 0–20%) Gr2: (2.50%, 0–20%) Gr3: (2%, 0.2–20%) Cases above the cutoff value: number(%) Gr1: 30(48%) (cutoff 2.5%) 5(8%) (cutoff 12.3%) Gr2: 32(48%) (cutoff 2.5%) 4(6%) (cutoff 12.3%) Gr3: 4(36%) (cutoff 2.5%) 1(9%) (cutoff 12.3%)

Author Year Reference	Patients	Stufy	Method	Results
Salnikov AV 2010 (24)	N:88 NSCLC Age: CD133+: 56±8 CD133-: 61±9 Male:79 Female:9	Cohort	IHC	CD133+ : 56 CD133- : 32 VEGF+ : 51 VEGF- : 28 CD133-/VEGF- : 9 CD133+/VEGF+-: 31 CD133-/VEGF+: 20 CD133+/VEGF-: 19
Nowak K 2010 (25)	N: NSCLC: 32 Control: 15 Age: NSCLC gr UICC I-IIB (63- 9 yrs) UICC III-IV (60-11 yrs) SCLC gr (68-10 years)	Case- control	FCM FACS ELISA	CD34+/CD133+: 0.35± 0.19% Control: 0.13± 0.04% Mean serum VEGF concentration Median; range Control: 23; 20-35 NSCLC: UICC stage IA-IIB: 389; 273-735 UICC stage IIIA—IV: 633; 364-1168
Zhou 2015 (26)	N: NSCLC: 305 Control: 80 Age: 26 to 82 years old, median age of 59.8 years. Male: 233 Female: 72	Case-control	IHC	CD133 and VEGF protein expression in cases: 48.9% and 45.6% In control: 10.0% and 0%,
Morita R 2011 (27)	N: NSCLC: 31 Control: 20 Male: 22 Female: 9 Median age of 66 years (range, 59–77).	Case-control	FCM ELISA	CEPCs: (Mean) NSCLC: 1,240 ± 779.3 Control: 644.5 ± 397.2 Serum VEGF-A NSCLC: 714.8 ± 555.3 Control: 415.1 ± 271.7

*Cutoff value between low and high pretreatment EPC levels was defined as 1,000 EPCs/mL of peripheral blood
FACS: Fluorescence-activated cell sorting, IHC: Immunohistochemistry, FCM: Flowcytometry, IFA: Immunofluorscent staining, Gr: group, N:number, NSCLC: none small cell lung cancer, CEPCs: circulating endothelial progenitor cells, VEGF: vascular endothelial growth factor, ELISA: The enzyme-linked immunosorbent assay.

ment from bone marrow (19,25). It has been suggested that bone-marrow-derived EPCs circulate in the blood and contribute in the formation of new blood vessels (27).

Because mature endothelial cells do not express CD133, co-expression of VEGFR-2 and CD133 on CD34(+) cells leads to a phenotypically and functionally unique population of CEPs that are engaged in neoangiogenesis (28). Early EPCs can be detected by a triple positivity of CD34/VEGFR2/CD133; however, during differentiation, CD133 would not be expressed anymore. Based on in vitro findings, CD133+ cell population are such as progenitor and stem cells not only with hematopoietic characteristic but also with the capacity to differentiate into ECs (29).

The study of Hilbe et al, applied immunohistochemistry on tumor tissues of patients with NSCLC and revealed increased number of CD133 positive EPCs, their relation with VEGF receptor2 (VEGFR2) expression, and contribution to capillary forming units in invading tumor formations, for the first time (26). They reported increased number of EPCs with CD133 expression and capillary forming structures in 43 out of 63 patients with NCSLC; CD133 expression showed marginal correlation with VEGFR2 expression. According to their report, CD133 positive EPCs are involved in vasculogenesis of solid tumors (NSCLC), and can regulate tumor growth in humans. This positive correlation between CD133 expression and VEGFR2 was also confirmed in another study from China (30).

Dome, B. in 2006 was the first article that based on flowcytometry technique evaluated the circulating EPCs in peripheral blood of patients with NSCLC; however, they did not reveal the exact data regarding the levels of CD133+VEGF+ cells in patients pre and post treatment. They only proposed the increased level of VEGFR2 mRNA in NSCLC patients compared with healthy controls and the level of this marker was significantly higher in patients with progressive disease than patients who achieved a tumor-free status (21). In that article, no significant relation was also found between the CD133 expression and tumor malignancy level, which might be due to the continuously decreasing expression of this marker on the cell surface

of circulating EPCs and no expression on EPCs differentiated into more mature endothelial cells in the endothelial tube (21). Based on their findings, small intratumoral capillaries, and endothelium of larger vessels or capillary walls were the sites that EPCs could be detected with higher frequency, respectively.

In another study in 2008, EPCs as well as VEGF levels were evaluated in the both circulation and tumor specimens of patients with NSCLC during the therapy of primarily curable NSCLC patients before and after surgical treatment (24). They showed that early EPCs counts will be increased in peripheral circulation. In this study, immunocytological staining of singular CEPs was also tested for the first time using monoclonal antibody against CD133, which revealed significant increase of CD133+ cells in the peripheral circulation of the NSCLC patients compared with control individuals. The FACS analysis also confirmed the elevated levels of CD133+/VEGF+ in NSCLC patients. Increased numbers of CD133+ cells in patients compared with controls was also indicated through immunohistochemistry (24).

It is eventually proposed by the mentioned studies that EPCs expression will be elevated in peripheral blood and tumor tissues compared to controls (21,24). These studies also revealed increased level of VEGF in NSCLC patients pre and post operatively; however, there was no significant relationship between the increase of the CD133 and VEGF levels in these patients (21,24).

This poor relationship between CEPs and VEGF levels has been previously reported by investigating on patients with breast cancer; they proposed that this poor relationship might be due to the contribution of various types of cytokines on recruitment of EPCs (31).

In 2010, immunohistochemistry of tissues samples of patients with NSCLC showed no association between CD133 and VEGF, VEGFR-1 expression. According to this study, there is even inverse relationship between CD133 expression and microvessel density in NSCLC tumors (26).

Although positive relationship had been reported between CD133+ EPCs and angiogenesis in NSCLC, in the study of Salnicove et al slight decrease was detected in microvessel density of tissues of CD133+ NSCLC patients compared to CD133- cases, and no correlation was found between CD133 positivity with expression of angiogenic factor VEGF (26).

In another study, the level of EPCs and their relationship with serum VEGF concentration was also investigated and suggested positive correlation between VEGF levels with CEPs numbers in NSCLC patients. They eventually, not only proposed an augmented mobilization of CEPCs, but also showed the elevated serum concentrations of VEGF in patients with NSCLC compared with healthy individuals (23).

According to these reports, circulating EPCs in peripheral blood are elevated in NSCLC patients and can be considered as a possible biomarker of angiogenesis. Morita et al confirmed the mentioned finding regarding the increased level of EPCs in NSCLC patients; they also proposed that serum VEGF-A is the most important factor among released angiogenesis cytokines, which is significantly increased in NSCLC patients compared with healthy individuals. VEGF will be produced from tumors following hypoxic stimulation, consequently serum VEGF-A will be increased in lung cancer patients (22). According to Morita et al, despite significant increase in the numbers of circulating EPCs in peripheral blood and levels of VEGF-A in serum, no correlation was observed between the number of EPCs and VEGF-A level in NSCLC patients. This might be due to binding of VEGF-A to VEGFR-2 (KDR/Flt1) on the surface of vascular endothelial cells and participating in many reactions that result in tumor angiogenesis (22).

Conclusion

The detection of EPCs in the peripheral blood is technically challenging because of their low number, and the ideal method for evaluating CECs or EPCs levels in vivo is still a matter of debate. EPCs and VEGF levels are elevated in patients with operable NSCLC; however, the relationship between circulating EPC numbers and angiogenesis in patients with lung cancer is not clear. Although EPCs may as an important endogenous stimulus of tumor vasculogenesis, incorporation of EPCs has been found to be a rare phenomenon in NSCLC tissue. Further studies are needed to accurately reveal this relation.

Conflict of Interest

The authors declare no conflict of interest.

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