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Expression, prognostic and predictive impact of VEGF and bFGF in non-small cell lung cancer

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Contents

Abstract

Despite major advances in cancer therapeutics, the prognosis for lung cancer patients is still poor and the median survival for patients presenting with advanced non-small cell lung cancer (NSCLC) is only 8–10 months. Angiogenesis is an important biological process and a relatively early event during lung cancer pathogenesis. Anti-angiogenic agents are used in treating patients with NSCLC, and their molecular biomarkers are also being assessed to predict response. A better understanding of the biology of angiogenesis in NSCLC may reveal new targets for treating this malignancy. In this article, we review the expression and prognostic impact of the angiogenic growth factors, vascular endothelial growth factor and basic fibroblast growth factor, in NSCLC.

Keywords: Non-small cell lung cancer; VEGF; bFGF; Angiogenic markers; Expression; Prognostic impact; Review

1. Introduction

Despite major advances in cancer therapeutics, the survival rate for patients with lung cancer has not improved much even in the era of targeted therapy [1]. Lung cancer remains

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the leading cause of cancer death in the western world. The estimated number of new lung cancer cases in the United States was 219,440 cases in the year of 2009 and around 159,390 cases died from this disease [2]. Lung carcinoma is responsible for 1.3 million deaths worldwide annually [3]. Traditionally, the prognosis of lung cancer patients is generally poor and the median survival for patients presenting with advanced non-small cell lung cancer (NSCLC) treated with chemotherapy alone is about 10 months [4]. Thus, there is a need for better screening and treatment modalities for this disease. The dismal prognosis and the limited tumor response to conventional cytotoxic agents posed a challenge to the scientific community to come up with alternative targeted therapies heralding better clinical responses all with minimizing the adverse effects. Angiogenesis targeting agents were among the first to be recognized for potential benefit in NSCLC [5]. However when applied in different settings, monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and other classes of agents did not yield a consistent response among patients with NSCLC [6]. Hence emerges the role of biomarkers in tailoring therapeutic strategies to patient's biological makeup and optimizing clinical response. This paper revisits the role of anti-angiogenic agents in NSCLC and focuses mainly on the prognostic and predictive value of two major angiogenic markers vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

2. Angiogenesis: mechanisms and role in carcinogenesis

Angiogenesis is an important biological process not only under physiological conditions but also in a variety of disease conditions including cancer, diabetic retinopathy and rheumatoid arthritis [7]. For more than a decade, the role of vascular endothelial growth factor (VEGF) in the regulation of angiogenesis has been under investigation [8]. This process is important for the growth of new blood vessels during fetal development and tissue repair; however, uncontrolled angiogenesis promotes neoplastic diseases and other disorders. The successful implementation of this process depends upon the balance of growth promoting factors and growth inhibitory factors [9,10]. Tumor growth and metastasis are dependent on angiogenesis [11]. Angiogenesis depends on the balance between different molecules released by the host and tumor cells, and consists of a series of steps, including separation of endothelial cells from pericytes and the basement membrane, invasion and migration across basement membranes, and eventually resulting in extension into the tumor body [12,13]. Specific angiogenic molecules can initiate this process whereas specific inhibitory molecules can stop it [14].

There is evidence that angiogenesis is a relatively early event during lung cancer pathogenesis. Angiogenic squamous dysplasia which represents small lesions where capillary loops project into histologically abnormal bronchial epithelium, has been observed in preneoplastic lesions from individuals at high risk of developing lung cancer and was associated with high VEGF expression [15,16].

One of the most specific and crucial regulators of angiogenesis is VEGF [8,17]. The different processes of angiogenesis are controlled by a large number of other mediators including the vascular endothelial growth factors receptors (VEGFRs), the plasminogen activators (PAs), the matrix metallo-proteinases (MMPs) and their inhibitors (MMPIs), bFGF, the transforming growth factor-βs (TGF-β), and the platelet-derived growth factor (PDGF) [18] among many others.

3. Anti-angiogenic agents and potential molecular biomarkers in NSCLC

The growing understanding of angiogenesis has been useful in establishing a new family of biological agents targeting angiogenesis pathways. Monoclonal antibodies and receptor TKIs were designed and tested in clinical trials in attempt to improve the therapeutic effect of the conventional cytotoxic agents [19,20]. In the pivotal ECOG4599 trial, Bevacizumab a humanized monoclonal antibody targeting VEGF, demonstrated a significant survival benefit when added to paclitaxel and carboplatin compared to that combination alone [21]. In the AVAiL trial, a smaller clinical benefit was derived from adding bevacizumab to gemcitabine and cisplatin combination [22]. A closer look at the patient population shows that patients with squamous cell carcinoma were excluded based on safety data from a previous phase II trial [23]. Bevacizumab use was associated with major hemoptysis and fatal pulmonary hemorrhage in patients with squamous cell lung cancer. In the latter group, tumors have a predilection to be cavitating and centrally located. The friable nature renders them prone to erode into vicinous major pulmonary vessels and subsequently causing extensive pulmonary hemorrhage.

Further exploration of patients' susceptibility to bevacizumab requires the search for molecular markers associated with survival and response. On evaluation of sera of patients enrolled in ECOG4599 trial, higher plasma circulating levels of VEGF predicted better response to bevacizumab treatment, but this was not predictive of overall survival [24]. In the AVAiL trial a high baseline level of beta fibroblast growth factor (Beta FGF) and VEGF and other factors was associated with shorter overall survival [25,26].

In addition to bevacizumab, other agents have been implicated in phase II trials in NSCLC (Table 1).

One of the agents, Vandetanib, a VEGFR, EGFR and RET tyrosine kinase inhibitor showed improvement in progression free survival in three phase II trials in patients with advanced NSCLC [27–29]. Low baseline circulating VEGF predicted a therapeutic benefit in PFS in the above studies when using vandetanib [30]. In the ZODIAC trial, where patients were randomized in the second line setting to docetaxel with or without vandetanib, many biologic markers,

Table 1
Phase III clinical trials in NSCLC involving anti-angiogenic agents.

Agent	Class	Target	Study	Status
Sorafenib	Tyrosine Kinase Inhibitor	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-ß KRAS and Raf-1	1-A randomized controlled trial comparing safety and efficacy of carboplatin and paclitaxel ± sorafenib in chemo-naive patients with stage IIIB–IV non-small cell lung cancer (NSCLC)	Early terminated
			2-BRAF, KRAS and EGFR mutation detection in non-small cell lung cancer patients treated with sorafenib monotherapy	Not open yet
			3-A phase III, multi-center, placebo-controlled trial of sorafenib in patients with relapsed or refractory advanced predominantly non squamous non-small cell lung cancer (NSCLC) After 2 or 3 previous treatment regimens for advanced disease	Ongoing
			4-A phase III randomized, double-blind, placebo controlled trial comparing the efficacy of gemcitabine, cisplatin and sorafenib to gemcitabine, cisplatin and placebo in first-line treatment of patients with stage IIIb with effusion and stage iv non-small cell lung cancer (NSCLC)	Completed
BIBF 1120	Tyrosine kinase inhibitor	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/β, and FGFR	1-LUME lung 1 randomised double blind phase III trial of BIBF 1120 versus placebo in addition to standard therapy of docetaxel in patients with advanced NSCLC	Ongoing
			2-A randomized double-blind multicenter phase III trial of BIBF 1120 plus pemetrexed versus pemetrexed/placebo in advanced or recurrent non small cell lung cancer patients after failure of first line therapy	Ongoing
Cediranib (AZD2171)	Tyrosine kinase inhibitor	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/β,	1-A double blind randomized trial of cediranib versus placebo in patients receiving paclitaxel/carboplatin chemotherapy for the treatment of advanced or metastatic non-small cell lung cancer	Ongoing
			2-A phase II/III double blind randomized trial of AZD2171 versus placebo in patients receiving paclitaxel/carboplatin chemotherapy for the treatment of advanced or metastatic non-small cell lung cancer	Ongoing
Motesanib (AMG-706)	Tyrosine kinase inhibitor	VEGFR-1, VEGFR-2, PDGFR-a/β, and c-kit	A phase 3, multicenter, randomized, placebo-controlled, double-blind trial of AMG 706 in combination with paclitaxel and carboplatin for advanced non-small cell lung cancer	Ongoing
Pazopanib (GW786034)	Tyrosine kinase inhibitor	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/β, and c-kit	1-Double blind randomized phase iii study of maintenance pazopanib versus placebo in NSCLC patients non progressive after first line chemotherapy. MAPPING, an EORTC Lung Group Study.	Ongoing
			2-A randomized, double-blind, placebo-controlled phase II–III multi-centre study to evaluate the effect of adjuvant pazopanib (GW786034) versus placebo on post-surgical disease-free survival in patients with stage I non small cell lung cancer and tumor size equal or inferior to 5 cm	Ongoing
Ramucirumab (IMC-1121B)	Monoclonal antibody	VEGFR-2	A randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy	Ongoing
Vandetanib (ZD6474)	Tyrosine kinase inhibitor	VEGFR-2, VEGFR-3, EGFR, and RET	1-A phase III, randomized, double-blinded, multi-center, study to assess the efficacy of docetaxel (TAXOTERE™) in combination with ZD6474 (ZACTIMA™) versus docetaxel (TAXOTERE™) with placebo in subjects with locally advanced or metastatic NSCLC	Ongoing
			2-A phase III, randomized, double-blinded, parallel group, multi-centre study to assess the efficacy and safety of ZD6474 (ZACTIMA™) in combination with pemetrexed (Alimta®) versus pemetrexed alone in patients with locally advanced or metastatic NSCLC	Ongoing
			3-A phase III study to assess the efficacy of ZD6474 (ZACTIMA™) plus best supportive care versus best supportive care in patients with locally advanced or metastatic (Stage IIIB–IV) non-small cell lung cancer after therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)	Ongoing
			4-A phase III, international, randomised, double blind, parallel-group study to assess the efficacy of Zactima™ versus Tarceva® in patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy	Ongoing
Aflibercept (AVE0005)	Fusion protein	VEGF A, VEGFB and PIGF	A multinational, randomized, double-blind study comparing aflibercept versus placebo in patients treated with second-line docetaxel after failure of one platinum based therapy for locally advanced or metastatic non-small-cell lung cancer	Ongoing

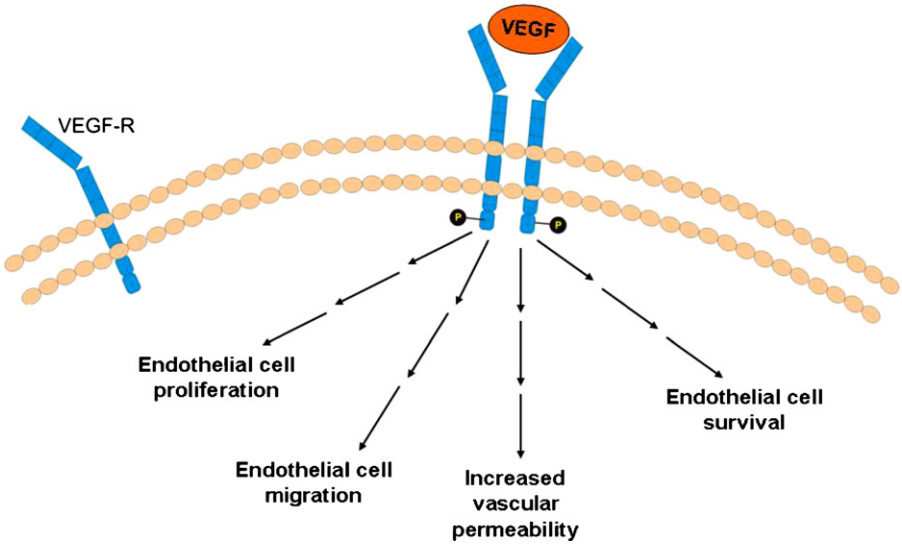

Fig. 1. VEGF binding to its receptor leads to receptor dimerization, activation of receptor tyrosine kinases by autophosphorylation. This leads to several biologic effects including the proliferation and migration of endothelial cells and increased vascular permeability.

including EGFR by both IHC and FISH, KRAS mutations, VEGF and VEGF-2 levels, failed to predict outcomes, possibly due to the low number of tissue samples submitted for correlative biomarker studies [25]. On the other hand, increases in VEGF and decreases in soluble VEGF receptor 2 (sVEGFR-2) have been found to be a class effect of vandetanib as reported in phase I and II studies of VEGFR TKIs [31,32]. The incongruity in the above findings can be attributed to the complexity of angiogenic pathways, lack of standardized detection techniques and poorly defined cutoff values [32]. In a study conducted on patients treated with pazopanib an antiangiogenic agent, plasma sVEGFR2 was associated with tumor shrinkage [33]. In the BATTLE trial, previously treated NSCLC patients, underwent core needle biopsies and were adaptively randomized to either of four biological therapies based on a panel of molecular biomarkers [34].

4. VEGF and VEGFR family

VEGF-A (also referred to as VEGF) was first identified by Senger et al. as a vascular permeability factor secreted by tumor cells [35]. It is the best characterized and most studied of the VEGF family members. It is a tumor-secreted cytokine with critical importance in both normal and tumor-associated angiogenesis [36]. The VEGF gene which is located on the short arm of chromosome 6 is composed of eight exons and is differentially spliced to yield four isoforms (VEGF121, VEGF165, VEGF189 and VEGF206) [37]. In addition, some less commonly expressed isoforms were identified (VEGF145 and VEGF183) [38].

The VEGF family comprises seven secreted glycoproteins that are designated VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placental growth factor (PlGF) and VEGF-F [39–41]. VEGF-A exerts its biologic effect through interaction with cell-surface receptors. These receptors are transmembrane tyrosine kinase receptors and include VEGF receptor-1 (VEGFR-1; Flt-1) and VEGFR-2 (kinase insert domain-containing receptor-KDR/Flk-1), selectively expressed on vascular endothelial cells, and the neuropilin receptors (NP-1 and NP-2), expressed on vascular endothelium and neurons [42]. Upon binding of VEGF-A to the extracellular domain of the receptor, a cascade of downstream proteins is activated after the dimerization and autophosphorylation of the intracellular receptor tyrosine kinases (Fig. 1). VEGF induces proliferation, sprouting and tube formation of endothelial cells [39]. VEGFR-2 appears to be the main receptor responsible for mediating the proangiogenic effects of VEGF-A [42,43].

VEGF-B binds to VEGFR-1 but not VEGFR-2 or VEGFR-3, and the activation of this receptor induces a poor mitogenic signal for endothelial cells suggesting that VEGF-B is an inefficient endothelial cell mitogen [44]. VEGF-B might have a role in inflammatory [45] and cardiac angiogenesis [46].

VEGF-C is a ligand for VEGFR-2 and VEGFR-3 [47]. During development, VEGF-C is expressed along with its receptor VEGFR-3 mainly in regions where lymphatic vessels develop [48]. VEGF-C is also chemotactic for macrophages, and its receptor VEGFR-3 is expressed by a fraction of peripheral blood monocytes and activated tissue macrophages [49]. VEGF-C induces selective lymphangiogenesis without accompanying angiogenesis [50], and it has been shown to have a positive role in lymphatic invasion, lymphatic metastasis and patient survival [51].

4.1. VEGF tumor expression in NSCLC

VEGF expression is regulated by very complex mixtures of cytokines, growth factors, hormones, and small molecules

Table 2
Studies showing a negative prognostic effect of VEGF tumor expression in patients with NSCLC.

Reference	Origin of patients	No. of patients[a]	% of positive VEGF immunostaining	HR (95% CI) and/or *p*-value	Comments
Ohta et al. [58]	Japan	122	VEGF-A/VEGF-C = 50%/10%	HR 1.50 (1.05–2.11) for VEGF-A; HR 1.34 (0.58–3.10) for VEGF-C	
Volm et al. [59]	Germany	109	59%	$p = 0.033$	In multivariate analysis VEGF expression was not an independent prognostic parameter[a]
Giatromanolaki et al. [62]	Greece	114 (of 120 cases)	68%	$p = 0.04$	In multivariate analysis VEGF expression was not an independent prognostic parameter[a]
Fontanini et al. [63]	Italy	104	44%	$p = 0.00001$	Significance determined by backward stepwise regression model
Imoto et al. [64]	Japan	91	53%	$p = 0.002$	In multivariate analysis VEGF expression was not an independent prognostic parameter[a]
Yuan et al. [67]	Taiwan	60	50%	$p = 0.0046$	
Nakashima et al. [68]	Japan	153	51% for VEGF-A; 41.8% for VEGF-C	$p = 0.010$ for VEGF-A	$p = 0.0025$ for VEGF-A in patients with adenocarcinomas; $p = 0.0143$ for VEGF-C in patients with squamous cell carcinomas
Huang et al. [69]	Japan	173	52.6% for VEGF-A; 42.2% for VEGF-C	$p < 0.01$ for VEGF-A; $p = 0.03$ for VEGF-C	
O'Byrne et al. [71]	UK	183	46.6%	$p = 0.02$	In multivariate analysis VEGF expression was not an independent prognostic parameter[a]
Han et al. [72]	USA	85	High VEGF expression 71%; low VEGF expression in 29%	$p = 0.018$	
Oshika et al. [74]	Japan	84	39.3–90.5%	$p = 0.01722$	Immunohistochemical examination confirmed VEGF protein expression in 33 cases; The VEGF189 isoform was expressed in 76 cases

VEGF: vascular endothelial growth factor; NSCLC: non-small cell lung cancer; HR: hazard ratio; CI: confidence interval
[a] Cases included in the survival analysis only.

including PDGF, bFGF, TGFs and epidermal growth factor [52]. In humans, VEGFs and their receptors are expressed in many solid tumors including breast [53], colon [54], ovary [55], cervix [56], and lung carcinoma [57,58]. The first report on VEGF expression in NSCLC was by Mattern et al. [57]. This group of investigators demonstrated a negative prognostic role of VEGF expression in lung cancer tumors [59,60]. Since then, numerous studies in early stage NSCLC have reported the overexpression of VEGF and its association with progression or poor survival [58,19,61–71]. In addition, other studies demonstrated an association with survival (either overall or progression-free) and a correlation between VEGF expression and microvessel density [72–76]. In contrast, some studies did not show any association between VEGF expression and survival [77,78]. Table 2 summarizes the main studies that showed a poor prognostic impact of VEGF expression in NSCLC. It is worth mentioning that most of the studies found a poor prognostic significance of VEGF expression in tumor cells; however, VEGF was not an independent prognostic parameter in multivariate analysis [59,60,64,71].

One meta-analysis studying the prognostic impact of VEGF expression in NSCLC was published by Delmotte et al. [79]. The authors performed a systematic review of the English and French literature with regard to both NSCLC and small cell lung cancer, and the inclusion criteria for articles demanded existing data on the expression of VEGF or its receptors as well as the association between expression and survival. Fifteen studies (1549 patients) were devoted to NSCLC. The meta-analysis showed that VEGF is an unfavorable prognostic factor in NSCLC (HR = 1.48; 95% confidence interval (CI) 1.27–1.72). Another recent meta-analysis included in the analysis 4499 patients with NSCLC from 38 studies that were categorized by patient ethnicity, histology, disease stage, VEGF isoform, and laboratory techniques used [80]. Combined hazard ratios suggested that VEGF over-expression regardless of its isoform indicated a poor prognosis for patients with NSCLC (HR = 1.46; 95% CI 1.38–1.54). However, VEGF-C overexpression did not significantly correlate with survival in these patients (HR = 1.22; 95% CI 0.96–1.47) [80].

In a relatively recent study, Nakashima et al. found that intratumoral expression of different classes of VEGF had unlike prognostic relevance in the different subgroups of NSCLC [68]. VEGF-C was a significant poor prognostic factor in patients with squamous cell carcinomas (relative risk = 3.946, $p = 0.0143$), while VEGF-A was a significant prognosticator for those with adenocarcinomas (relative risk = 3.816, $p = 0.0025$) [68]. Another study did not show any correlation between VEGF-A expression and prognosis in NSCLC [81]. On the other hand, the investigators found that VEGF-B and VEGF-D expression had a significant correlation with worse survival in patients with stage I and II NSCLC. The expression of VEGF-D was correlated significantly with better survival in patients with stage III and IV disease [81]. Very recently a study correlated the prognostic impact of angiogenic factors with tumor size. Donnem et al. [82] studied the prognostic impact of angiogenic factors and their association with tumor size in NSCLC. In multivariate analysis, high VEGFR-2 (HR = 1.87, 95% CI 1.02–3.45; $p = 0.043$), VEGFR-3 (HR = 2.18, 95% CI 1.28–3.71; $p = 0.004$) and the combination of high VEGF-A and high VEGFR-2 expression (low/low versus high/high; HR = 3.28, 95% CI 1.47–7.31; $p = 0.004$) were independent negative prognostic factors in T2a tumors [82].

Still other studies have been inconclusive or showed no correlation between tumor expression of VEGF and prognosis. In one of the studies, VEGF-A was highly expressed in resected tumors from NSCLC patients; however, this immunohistochemical expression did not have prognostic impact [83].

Presently, most studies support the clinical prognostic impact of VEGF expression in NSCLC tumors; in most of these studies, VEGF over-expression was associated with a poor prognosis.

4.2. Circulating VEGF in NSCLC

An increase in VEGF expression in some blood compartments (i.e. serum or plasma) has been found in solid and hematological malignancies of various origins and is associated with metastasis formation and poor prognosis [17,84]. Kondo et al. first recognized the potential of VEGF as a serum diagnostic marker for malignant disease [85]. They found that the VEGF levels in the sera from cancer patients were significantly higher than those from individuals with no sign of cancer [85]. Measuring the levels of circulating angiogenic factors can theoretically reflect the overall angiogenic activity of the tumor; in addition, it is more easily assessable than evaluating tumor expression of angiogenic factors which depends on the availability of adequate surgical or biopsy specimens. Compared to the immunohistochemical evaluation of angiogenic factors in tumor tissues, the assessment of these angiogenic factors in blood has theoretically several advantages: highly available, less expensive and less time-consuming, readily performed preoperatively, easily repeated serially, and less biased [86].

Published studies on circulating VEGF and its impact on survival in NSCLC are less frequent than those assessing tumor VEGF expression. Some studies revealed a significantly inverse association between circulating levels and survival [87–93]. Other studies did not find a significant correlation between circulating VEGF and survival [94–97].

Pre- and post-treatment serial assessments of circulating VEGF have been performed and the clinical significance of their changes was reported. Maniwa et al. found that the serum levels of VEGF increased after pulmonary surgery and led to rapid growth of dormant micrometastases early in the postoperative period [98]. In chemotherapy-treated lung cancer patients, researchers observed a significant decrease in circulating VEGF in responders, while non-responders showed increasing levels ($p = 0.006$) [99]. Very recently a

study investigated the role of plasma VEGF-A and VEGFR-2 as biomarkers in advanced NSCLC [93]. VEGF-A and sVEGFR-2 levels were higher in NSCLC patients than in controls. A patient subgroup characterized by a combination of high VEGF-A and low VEGFR-2 levels exhibited the worst patient prognoses in terms of time-to-progression and overall survival [93].

So the data on the prognostic implication of VEGF in blood of patients with NSCLC is heterogeneous and needs further investigation.

5. Basic fibroblast growth factor (bFGF)

The fibroblast growth factor (FGF) family represents a group of heparin-binding, multifunctional polypeptides which also are commonly found in malignant tumors [100]. b-FGF (also known as fibroblast growth factor 2-FGF2) is considered a potent stimulator of angiogenesis and binds with high affinity mainly to its receptor fibroblast growth factor receptor-1 (FGFR-1), a tyrosine kinase receptor [101]. bFGF also stimulates VEGF secretion [102] and the effects of VEGF and bFGF appear synergestic in vitro [103] and in vivo [104]. There are at least four isoforms of bFGF with different molecular masses (22, 22.5, 24 and 34 kDa) [105,106]. The bFGF gene is located on chromosome 4 [107].

bFGF may exert its effect on endothelial cells via a paracrine mode as a consequence to its release by tumor and stromal cells. It is also suggested that bFGF plays an autocrine role in endothelial cells [100,108]. A large body of research has implicated b-FGF as having a role in tumorigenesis. Early studies showed that elevated levels of b-FGF in urine samples were significantly correlated with the status and the extent of disease whether solid tumors or hematological malignancies [109]. bFGF also works synergistically with VEGF in inducing angiogenesis [104].

5.1. bFGF tumor expression in NSCLC

The majority of human NSCLC cell lines produce elevated levels of bFGF which in turn stimulate the growth of these tumor cells by intracrine mechanisms [110]. The tumor expression of bFGF in NSCLC was first reported by Takanami et al. [111]. Overall, 53–74% of the NSCLC cells express bFGF [111–113]. The prognostic impact of bFGF in NSCLC is still controversial. In tumor specimens of 206 patients with NSCLC, 70 of the tumors showed weak expression of bFGF, 109 moderate and 27 high expression of bFGF (evaluation was done according to the intensity of staining such that 0 = negative, 1 = weak, 2 = moderate, and 3 = high). However, the authors were unable to find any association between bFGF expression and survival [112]. Later, Shou et al. reported that bFGF expression significantly correlated to poor survival in 119 NSCLC patients [113]. However, in a study of 167 stage I–IV NSCLC adenocarcinomas, bFGF seemed an independent indicator of poor prognosis [111]. Also using frozen tissue and enzyme-linked immunosorbent assay technique, in a cohort of 71 resected NSCLC patients, Iwasaki et al. observed that bFGF had an independent negative impact on survival [114].

Data shows that the prognostic impact of bFGF expression in NSCLC is still controversial although the majority of tumor cells express bFGF.

5.2. Circulating bFGF in NSCLC

Elevated serum levels of bFGF in malignancy were demonstrated by enzyme immunoassay as early as 1991 [115]. Since that time, research has been active to investigate the clinical implications of circulating bFGF in cancer patients. In general, the clinical significance is more controversial for circulating bFGF than circulating VEGF in malignancies.

The first study investigating serum levels of bFGF in NSCLC was reported by Brattström et al. [116]. Since then other studies have investigated the clinical significance of circulating bFGF in NSCLC. Among 68 NSCLC patients with stage I–IV disease, Brattström et al. found that elevated bFGF at diagnosis was a statistically significant favorable prognostic factor for survival ($p = 0.048$) [116]. However, these results disagreed with the results from other studies. In a study by Ueno et al. in 60 NSCLC patients (31 adenocarcinomas and 29 squamous cell carcinomas), serum bFGF levels did not differ between the clinical stages of NSCLC and showed no correlation with survival [117]. It is worth mentioning here that these are small studies with a limited number of patients.

Other studies found that elevated bFGF levels correlated with poor survival in NSCLC [87,88,118]. Joensuu et al. evaluated the influence of serum bFGF on outcome in 138 NSCLC [118]. The median survival time of the patients with a high bFGF level was 5 months versus 11 months in those with a lower level ($p = 0.023$). Serum bFGF levels at diagnosis were associated with poor outcome. In the study by Brattström et al., 58 operable NSCLC patients were analyzed for the prognostic value of serum bFGF [87]. Univariate analysis found tumor burden, platelet counts, serum VEGF, and serum bFGF to be prognostic indicators for survival, while only serum bFGF remained significant in the multivariate analysis ($p = 0.014$) [87].

6. Conclusion and future prospects

The recognition that angiogenesis plays a critical role in a variety of pathologic conditions, including tumor growth, led to the discovery of several pro- and antiangiogenic factors. Angiogenesis has clearly shown to be a meaningful biological target in several tumor types. The potential application of different angiogenesis inhibitors is currently under intense clinical investigation.

The key mediator of angiogenesis is VEGF. The inhibition of angiogenesis continues to be an attractive target in the

treatment of patients with NSCLC. Based on randomized phase II and III trials, bevacizumab, a potent and specific anti-VEGF monoclonal antibody, is the only anti-angiogenic therapy approved to date for the treatment of patients with NSCLC [23,4]. Presently, there is a body of data supporting the clinical prognostic impact of angiogenic factor expression especially VEGF expression in NSCLC tumors. In most of the studies done, VEGF over-expression was associated with a poor prognosis in patients with NSCLC. This information could be of help in the designing of clinical trials mainly those including angiogenesis inhibitors.

The data on the prognostic implications of VEGF and bFGF in blood of these patients are more heterogeneous [119]. However, the evidence is still compelling and these circulating factors may in the future be used for evaluating treatment and monitoring response. Thus, further large-scale studies are still needed to define the role of these and other markers in NSCLC and to validate their performance. Such studies need to include different targeted agents or study multi-targeted drugs having anti-VEGF(R) or anti-FGR(R) activity. In the era of personalized medicine, there is growing interest in individualizing treatment approaches in lung cancer. Moreover the concept of reverse migration entails shifting frontline in the fight against cancer from therapy to prevention. In other words, identification of molecular biomarkers will have implications not only on guiding therapy but also for intercepting cancer in high risk patients [34,120]. With all of the above taken into account, a further preventive dimension will be added to the prognostic and predictive value of molecular biomarkers, hence raising the plea for a better definition of their use in NSCLC.

Conflict of interest statement

None declared.

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References

[1] Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al. EUROCARE Working Group. EUROCARE-3: survival of cancer patients diagnosed 1990–94—results and commentary. Ann Oncol 2003;14(Suppl. 5):v61–118.

[2] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–49.

[3] World Health Organization. World Health Statistics 2006. Geneva, Switzerland: World Health Organization; 2006. Available at: http://www.who.int/whosis/whostat2006/en/index.html.

[4] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.

[5] Wheatley-Price P, Shepherd FA. Targeting angiogenesis in the treatment of lung cancer. J Thorac Oncol 2008;3:1173–84.

[6] Burris 3rd HA. Shortcomings of current therapies for non-small-cell lung cancer: unmet medical needs. Oncogene 2009;28(Suppl. 1):S4–13.

[7] Risau W. Mechanisms of angiogenesis. Nature 1997;386:671–4.

[8] Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer 2002;2:795–803.

[9] Otrock ZK, Makarem JA, Shamseddine AI. Vascular endothelial growth factor family of ligands and receptors: review. Blood Cells Mol Dis 2007;38:258–68.

[10] Pandya NM, Dhalla NS, Santani DD. Angiogenesis—a new target for future therapy. Vascul Pharmacol 2006;44:265–74.

[11] Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990;82:4–6.

[12] Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. Nat Med 2000;6:389–95.

[13] Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353–64.

[14] Folkman J, Shing Y. Angiogenesis. J Biol Chem 1992;267:10931–4.

[15] Keith RL, Miller YE, Gemmill RM, Drabkin HA, Dempsey EC, Kennedy TC, et al. Angiogenic squamous dysplasia in bronchi of individuals at high risk for lung cancer. Clin Cancer Res 2000;6:1616–25.

[16] Fontanini G, Calcinai A, Boldrini L, Lucchi M, Mussi A, Angeletti CA, et al. Modulation of neoangiogenesis in bronchial preneoplastic lesions. Oncol Rep 1999;6:813–7.

[17] Poon RT, Fan ST, Wong J. Clinical implications of circulating angiogenic factors in cancer patients. J Clin Oncol 2001;19:1207–25.

[18] Otrock ZK, Mahfouz RA, Makarem JA, Shamseddine AI. Understanding the biology of angiogenesis: review of the most important molecular mechanisms. Blood Cells Mol Dis 2007;39:212–20.

[19] Mountzios G, Dimopoulos MA, Soria JC, Sanoudou D, Papadimitriou CA. Histopathologic and genetic alterations as predictors of response to treatment and survival in lung cancer: a review of published data. Crit Rev Oncol Hematol 2010;75:94–109.

[20] Custodio A, de Castro J. Strategies for maintenance therapy in advanced non-small cell lung cancer: current status, unanswered questions and future directions. Crit Rev Oncol Hematol 2011;(September) [Epub ahead of print].

[21] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355(24):2542–50.

[22] Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227–34.

[23] Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184–91.

[24] Dowlati A, Gray R, Sandler AB, Schiller JH, Johnson DH. Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab—an Eastern Cooperative Oncology Group Study. Clin Cancer Res 2008;14:1407–12.

[25] Quinton C, Ellis PM. An evidence-based approach to the use of predictive biomarkers in the treatment of non- small cell lung cancer (NSCLC). Cancers 2011;3:3506–24.
[26] Leighl N, Reck M, de Haas S, Evers S, Delmar P, Manegold C, et al. Analysis of biomarkers (bms) in the avail phase iii randomised study of first-line bevacizumab (bv) with cisplatin-gemcitabine (cg) in patients (pts) with non-small cell lung cancer (NSCLC). Eur J Cancer 2009;(Suppl. 7):558.
[27] Heymach JV, Paz-Ares L, De Braud F, Sebastian M, Stewart DJ, Eberhardt WE, et al. Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol 2008;26:5407–15.
[28] Heymach JV, Johnson BE, Prager D, Csada E, Roubec J, Pesek M, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. J Clin Oncol 2007;25:4270–7.
[29] Natale RB, Bodkin D, Govindan R, Sleckman BG, Rizvi NA, Capó A, et al. Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: results from a two-part, double-blind, randomized phase ii study. J Clin Oncol 2009;27:2523–9.
[30] Hanrahan EO, Ryan AJ, Mann H, Kennedy SJ, Langmuir P, Natale RB, et al. Baseline vascular endothelial growth factor concentration as a potential predictive marker of benefit from vandetanib in non-small cell lung cancer. Clin Cancer Res 2009;15:3600–9.
[31] Hanrahan EO, Lin HY, Kim ES, Yan S, Du DZ, McKee KS, et al. Distinct patterns of cytokine and angiogenic factor modulation and markers of benefit for vandetanib and/or chemotherapy in patients with non-small-cell lung cancer. J Clin Oncol 2010;28: 193–201.
[32] Longo R, Gasparini G. Challenges for patient selection with VEGF inhibitors. Cancer Chemother Pharmacol 2007;60:151–70.
[33] Nikolinakos PG, Altorki N, Yankelevitz D, Tran HT, Yan S, Rajagopalan D, et al. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor shrinkage in early-stage non-small cell lung cancer patients treated with pazopanib. Cancer Res 2010;70:2171–9.
[34] Gold KA, Kim ES, Lee JJ, Wistuba II, Farhangfar CJ, Hong WK. The BATTLE to personalize lung cancer prevention through reverse migration. Cancer Prev Res (Phila) 2011;4:962–72.
[35] Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 1983;219:983–5.
[36] Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Oncol 2005;23:1028–43.
[37] Tischer E, Mitchell R, Hartman T, Silva M, Gospodarowicz D, Fiddes JC, et al. The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing. J Biol Chem 1991;266:11947–54.
[38] Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999;13:9–22.
[39] Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669–76.
[40] Houck KA, Ferrara N, Winer J, Cachianes G, Li B, Leung DW. The vascular endothelial growth factor family: identification of a fourth molecular species and characterization of alternative splicing of RNA. Mol Endocrinol 1991;5:1806–14.
[41] Suto K, Yamazaki Y, Morita T, Mizuno H. Crystal structures of novel vascular endothelial growth factors (VEGF) from snake venoms: insight into selective VEGF binding to kinase insert domain-containing receptor but not to fms-like tyrosine kinase-1. J Biol Chem 2005;280:2126–31.
[42] Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002;20:4368–80.
[43] Cross MJ, Dixelius J, Matsumoto T, Claesson-Welsh L. VEGF-receptor signal transduction. Trends Biochem Sci 2003;28:488–94.
[44] Nash AD, Baca M, Wright C, Scotney PD. The biology of vascular endothelial growth factor-B (VEGF-B). Pulm Pharmacol Ther 2006;19:61–9.
[45] Mould AW, Tonks ID, Cahill MM, Cahill MM, Pettit AR, Thomas R, et al. Vegfb gene knockout mice display reduced pathology and synovial angiogenesis in both antigen-induced and collagen-induced models of arthritis. Arthritis Rheum 2003;48:2660–9.
[46] Bellomo D, Headrick JP, Silins GU, Paterson CA, Thomas PS, Gartside M, et al. Mice lacking the vascular endothelial growth factor-B gene (Vegfb) have smaller hearts, dysfunctional coronary vasculature, and impaired recovery from cardiac ischemia. Circ Res 2000;86:E29–35.
[47] Joukov V, Sorsa T, Kumar V, Jeltsch M, Claesson-Welsh L, Cao Y, et al. Proteolytic processing regulates receptor specificity and activity of VEGF-C. EMBO J 1997;16:3898–911.
[48] Karkkainen MJ, Haiko P, Sainio K, Partanen J, Taipale J, Petrova TV, et al. Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins. Nat Immunol 2004;5:74–80.
[49] Skobe M, Hamberg LM, Hawighorst T, Schirner M, Wolf GL, Alitalo K, et al. Concurrent induction of lymphangiogenesis, angiogenesis, and macrophage recruitment by vascular endothelial growth factor-C in melanoma. Am J Pathol 2001;159:893–903.
[50] Jeltsch M, Kaipainen A, Joukov V, Meng X, Lakso M, Rauvala H, et al. Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. Science 1997;276:1423–5.
[51] Fujimoto J, Toyoki H, Sato E, Sakaguchi H, Tamaya T. Clinical implication of expression of vascular endothelial growth factor-C in metastatic lymph nodes of uterine cervical cancers. Br J Cancer 2004;91:466–9.
[52] Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581–611.
[53] Brown LF, Berse B, Jackman RW, Tognazzi K, Guidi AJ, Dvorak HF, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer. Hum Pathol 1995;26:86–91.
[54] Brown LF, Berse B, Jackman RW, Tognazzi K, Manseau EJ, Senger DR, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. Cancer Res 1993;53:4727–35.
[55] Olson TA, Mohanraj D, Carson LF, Ramakrishnan S. Vascular permeability factor gene expression in normal and neoplastic human ovaries. Cancer Res 1994;54:276–80.
[56] Guidi AJ, Abu-Jawdeh G, Berse B, Jackman RW, Tognazzi K, Dvorak HF, et al. Vascular permeability factor (vascular endothelial growth factor) expression and angiogenesis in cervical neoplasia. J Natl Cancer Inst 1995;87:1237–45.
[57] Mattern J, Koomägi R, Volm M. Association of vascular endothelial growth factor expression with intratumoral microvessel density and tumour cell proliferation in human epidermoid lung carcinoma. Br J Cancer 1996;73:931–4.
[58] Ohta Y, Endo Y, Tanaka M, Shimizu J, Oda M, Hayashi Y, et al. Significance of vascular endothelial growth factor messenger RNA expression in primary lung cancer. Clin Cancer Res 1996;2: 1411–6.
[59] Volm M, Koomägi R, Mattern J. Prognostic value of vascular endothelial growth factor and its receptor Flt-1 in squamous cell lung cancer. Int J Cancer 1997;74:64–8.
[60] Mattern J, Koomägi R, Volm M. Coexpression of VEGF and bFGF in human epidermoid lung carcinoma is associated with increased vessel density. Anticancer Res 1997;17:2249–52.
[61] Ohta Y, Tanaka Y, Watanabe G, Minato H. Predicting recurrence following curative surgery in stage I non-small cell lung cancer patients using an angiogenesis-associated factor. J Exp Clin Cancer Res 2007;26:301–5.
[62] Giatromanolaki A, Koukourakis MI, Kakolyris S, Turley H, O'Byrne K, Scott PA, et al. Vascular endothelial growth factor, wild-type p53,

and angiogenesis in early operable non-small cell lung cancer. Clin Cancer Res 1998;4:3017–24.
[63] Fontanini G, Vignati S, Boldrini L, Chinè S, Silvestri V, Lucchi M, et al. Vascular endothelial growth factor is associated with neovascularization and influences progression of non-small cell lung carcinoma. Clin Cancer Res 1997;3:861–5.
[64] Imoto H, Osaki T, Taga S, Ohgami A, Ichiyoshi Y, Yasumoto K. Vascular endothelial growth factor expression in non-small-cell lung cancer: prognostic significance in squamous cell carcinoma. J Thorac Cardiovasc Surg 1998;115:1007–14.
[65] Yuan A, Yu CJ, Kuo SH, Chen WJ, Lin FY, Luh KT, et al. Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non-small-cell lung cancer. J Clin Oncol 2001;19:432–41.
[66] Yuan A, Yu CJ, Luh KT, Kuo SH, Lee YC, Yang PC. Aberrant p53 expression correlates with expression of vascular endothelial growth factor mRNA and interleukin-8 mRNA and neoangiogenesis in non-small-cell lung cancer. J Clin Oncol 2002;20:900–10.
[67] Yuan A, Yu CJ, Shun CT, Luh KT, Kuo SH, Lee YC, et al. Total cyclooxygenase-2 mRNA levels correlate with vascular endothelial growth factor mRNA levels, tumor angiogenesis and prognosis in non-small cell lung cancer patients. Int J Cancer 2005;115: 545–55.
[68] Nakashima T, Huang CL, Liu D, Kameyama K, Masuya D, Ueno M, et al. Expression of vascular endothelial growth factor-A and vascular endothelial growth factor-C as prognostic factors for non-small cell lung cancer. Med Sci Monit 2004;10:BR157–65.
[69] Huang C, Liu D, Masuya D, Nakashima T, Kameyama K, Ishikawa S, et al. Clinical application of biological markers for treatments of resectable non-small-cell lung cancers. Br J Cancer 2005;92:1231–9.
[70] Tanaka F, Ishikawa S, Yanagihara K, Miyahara R, Kawano Y, Li M, et al. Expression of angiopoietins and its clinical significance in non-small cell lung cancer. Cancer Res 2002;62:7124–9.
[71] O'Byrne KJ, Koukourakis MI, Giatromanolaki A, Cox G, Turley H, Steward WP, et al. Vascular endothelial growth factor, platelet-derived endothelial cell growth factor and angiogenesis in non-small-cell lung cancer. Br J Cancer 2000;82:1427–32.
[72] Han H, Silverman JF, Santucci TS, Macherey RS, d'Amato TA, Tung MY, et al. Vascular endothelial growth factor expression in stage I non-small cell lung cancer correlates with neoangiogenesis and a poor prognosis. Ann Surg Oncol 2001;8:72–9.
[73] Shibusa T, Shijubo N, Abe S. Tumor angiogenesis and vascular endothelial growth factor expression in stage I lung adenocarcinoma. Clin Cancer Res 1998;4:1483–7.
[74] Oshika Y, Nakamura M, Tokunaga T, Ozeki Y, Fukushima Y, Hatanaka H, et al. Expression of cell-associated isoform of vascular endothelial growth factor 189 and its prognostic relevance in non-small cell lung cancer. Int J Oncol 1998;12:541–4.
[75] Takahama M, Tsutsumi M, Tsujiuchi T, Kido A, Okajima E, Nezu K, et al. Frequent expression of the vascular endothelial growth factor in human non-small-cell lung cancers. Jpn J Clin Oncol 1998;28:176–81.
[76] Kadota K, Huang CL, Liu D, Ueno M, Kushida Y, Haba R, et al. The clinical significance of lymphangiogenesis and angiogenesis in non-small cell lung cancer patients. Eur J Cancer 2008;44:1057–67.
[77] Liao M, Wang H, Lin Z, Feng J, Zhu D. Vascular endothelial growth factor and other biological predictors related to the postoperative survival rate on non-small cell lung cancer. Lung Cancer 2001;33:125–32.
[78] Baillie R, Carlile J, Pendleton N, Schor AM. Prognostic value of vascularity and vascular endothelial growth factor expression in non-small cell lung cancer. J Clin Pathol 2001;54:116–20.
[79] Delmotte P, Martin B, Paesmans M, Berghmans T, Mascaux C, Meert AP, et al. VEGF and survival of patients with lung cancer: a systematic literature review and meta-analysis. Rev Mal Respir 2002;19:577–84 [article in French].
[80] Zhan P, Wang J, Lv XJ, Wang Q, Qiu LX, Lin XQ, et al. Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: a systematic review with meta-analysis. J Thorac Oncol 2009;4:1094–103.
[81] Carrillo de Santa Pau E, Arias FC, Caso Peláez E, Muñoz Molina GM, Sánchez Hernández I, Muguruza Trueba I, et al. Prognostic significance of the expression of vascular endothelial growth factors A, B, C, and D and their receptors R1, R2, and R3 in patients with nonsmall cell lung cancer. Cancer 2009;115:1701–12.
[82] Donnem T, Andersen S, Al-Saad S, Al-Shibli K, Busund LT, Bremnes RM. Prognostic impact of angiogenic markers in non-small-cell lung cancer is related to tumor size. Clin Lung Cancer 2011;12:106–15.
[83] Bonnesen B, Pappot H, Holmstav J, Skov BG. Vascular endothelial growth factor A and vascular endothelial growth factor receptor 2 expression in non-small cell lung cancer patients: relation to prognosis. Lung Cancer 2009;66:314–8.
[84] Pathak AP, Hochfeld WE, Goodman SL, Pepper MS. Circulating and imaging markers for angiogenesis. Angiogenesis 2008;11:321–35.
[85] Kondo S, Asano M, Matsuo K, Ohmori I, Suzuki H. Vascular endothelial growth factor/vascular permeability factor is detectable in the sera of tumor-bearing mice and cancer patients. Biochim Biophys Acta 1994;31(1221):211–4.
[86] Bremnes RM, Camps C, Sirera R. Angiogenesis in non-small cell lung cancer: the prognostic impact of neoangiogenesis and the cytokines VEGF and bFGF in tumours and blood. Lung Cancer 2006;51:143–58.
[87] Brattström D, Bergqvist M, Hesselius P, Larsson A, Lamberg K, Wernlund J, et al. Elevated preoperative serum levels of angiogenic cytokines correlate to larger primary tumours and poorer survival in non-small cell lung cancer patients. Lung Cancer 2002;37: 57–63.
[88] Brattström D, Bergqvist M, Hesselius P, Larsson A, Wagenius G, Brodin O. Serum VEGF and bFGF adds prognostic information in patients with normal platelet counts when sampled before, during and after treatment for locally advanced non-small cell lung cancer. Lung Cancer 2004;43:55–62.
[89] Laack E, Köhler A, Kugler C, Dierlamm T, Knuffmann C, Vohwinkel G, et al. Pretreatment serum levels of matrix metalloproteinase-9 and vascular endothelial growth factor in non-small-cell lung cancer. Ann Oncol 2002;13:1550–7.
[90] Laack E, Scheffler A, Burkholder I, Boeters I, Andritzky B, Schuch G, et al. Pretreatment vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) serum levels in patients with metastatic non-small cell lung cancer (NSCLC). Lung Cancer 2005;50:51–8.
[91] Kaya A, Ciledag A, Gulbay BE, Poyraz BM, Celik G, Sen E, et al. The prognostic significance of vascular endothelial growth factor levels in sera of non-small cell lung cancer patients. Respir Med 2004;98:632–6.
[92] Chakra M, Pujol JL, Lamy PJ, Bozonnat MC, Quantin X, Jacot W, et al. Circulating serum vascular endothelial growth factor is not a prognostic factor of non-small cell lung cancer. J Thorac Oncol 2008;3:1119–26.
[93] Jantus-Lewintre E, Sanmartín E, Sirera R, Blasco A, Sanchez JJ, Tarón M, et al. Combined VEGF-A and VEGFR-2 concentrations in plasma: diagnostic and prognostic implications in patients with advanced NSCLC. Lung Cancer 2011;74:326–31.
[94] Choi JH, Kim HC, Lim HY, Nam DK, Kim HS, Yi JW, et al. Vascular endothelial growth factor in the serum of patients with non-small cell lung cancer: correlation with platelet and leukocyte counts. Lung Cancer 2001;33:171–9.
[95] Suzuki M, Iizasa T, Ko E, Baba M, Saitoh Y, Shibuya K, et al. Serum endostatin correlates with progression and prognosis of non-small cell lung cancer. Lung Cancer 2002;35:29–34.
[96] Park SH, Lee SS. The relationship between serum VEGF concentration and prognosis of lung cancer. Korean J Intern Med 2003;18:207–11.

[97] Tas F, Duranyildiz D, Oguz H, Camlica H, Yasasever V, Topuz E. Serum vascular endothelial growth factor (VEGF) and bcl-2 levels in advanced stage non-small cell lung cancer. Cancer Invest 2006;24:576–80.
[98] Maniwa Y, Okada M, Ishii N, Kiyooka K. Vascular endothelial growth factor increased by pulmonary surgery accelerates the growth of micrometastases in metastatic lung cancer. Chest 1998;114:1668–75.
[99] Kido Y. Vascular endothelial growth factor (VEGF) serum concentration changes during chemotherapy in patients with lung cancer. Kurume Med J 2001;48:43–7.
[100] Klagsbrun M. Mediators of angiogenesis: the biological significance of basic fibroblast growth factor (bFGF)-heparin and heparan sulfate interactions. Semin Cancer Biol 1992;3:81–7.
[101] Presta M, Dell'Era P, Mitola S, Moroni E, Ronca R, Rusnati M. Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis. Cytokine Growth Factor Rev 2005;16:159–78.
[102] Tsai JC, Goldman CK, Gillespie GY. Vascular endothelial growth factor in human glioma cell lines: induced secretion by EGF, PDGF-BB, and bFGF. J Neurosurg 1995;82:864–73.
[103] Goto F, Goto K, Weindel K, Folkman J. Synergistic effects of vascular endothelial growth factor and basic fibroblast growth factor on the proliferation and cord formation of bovine capillary endothelial cells within collagen gels. Lab Invest 1993;69:508–17.
[104] Asahara T, Bauters C, Zheng LP, Takeshita S, Bunting S, Ferrara N, et al. Synergistic effect of vascular endothelial growth factor and basic fibroblast growth factor on angiogenesis in vivo. Circulation 1995;92:II365–71.
[105] Florkiewicz RZ, Sommer A. Human basic fibroblast growth factor gene encodes four polypeptides: three initiate translation from non-AUG codons. Proc Natl Acad Sci USA 1989;86:3978–81.
[106] Yu PJ, Ferrari G, Galloway AC, Mignatti P, Pintucci G. Basic fibroblast growth factor (FGF-2): the high molecular weight forms come of age. J Cell Biochem 2007;100:1100–8.
[107] Fukushima Y, Byers MG, Fiddes JC, Shows TB. The human basic fibroblast growth factor gene (FGFB) is assigned to chromosome 4q25. Cytogenet Cell Genet 1990;54:159–60.
[108] Gualandris A, Rusnati M, Belleri M, Nelli EE, Bastaki M, Molinari-Tosatti MP, et al. Basic fibroblast growth factor overexpression in endothelial cells: an autocrine mechanism for angiogenesis and angioproliferative diseases. Cell Growth Differ 1996;7:147–60.
[109] Nguyen M, Watanabe H, Budson AE, Richie JP, Hayes DF, Folkman J. Elevated levels of an angiogenic peptide, basic fibroblast growth factor, in the urine of patients with a wide spectrum of cancers. J Natl Cancer Inst 1994;86:356–61.
[110] Kuhn H, Köpff C, Konrad J, Riedel A, Gessner C, Wirtz H. Influence of basic fibroblast growth factor on the proliferation of non-small cell lung cancer cell lines. Lung Cancer 2004;44:167–74.
[111] Takanami I, Imamura T, Hashizume T, Kikuchi K, Yamamoto Y, Yamamoto T, et al. Immunohistochemical detection of basic fibroblast growth factor as a prognostic indicator in pulmonary adenocarcinoma. Jpn J Clin Oncol 1996;26:293–7.
[112] Volm M, Koomägi R, Mattern J, Stammler G. Prognostic value of basic fibroblast growth factor and its receptor (FGFR-1) in patients with non-small cell lung carcinomas. Eur J Cancer 1997;33:691–3.
[113] Shou Y, Hirano T, Gong Y, Kato Y, Yoshida K, Ohira T, et al. Influence of angiogenetic factors and matrix metalloproteinases upon tumour progression in non-small-cell lung cancer. Br J Cancer 2001;85:1706–12.
[114] Iwasaki A, Kuwahara M, Yoshinaga Y, Shirakusa T. Basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) levels, as prognostic indicators in NSCLC. Eur J Cardiothorac Surg 2004;25:443–8.
[115] Fujimoto K, Ichimori Y, Kakizoe T, Okajima E, Sakamoto H, Sugimura T, et al. Increased serum levels of basic fibroblast growth factor in patients with renal cell carcinoma. Biochem Biophys Res Commun 1991;180:386–92.
[116] Brattström D, Bergqvist M, Larsson A, Holmertz J, Hesselius P, Rosenberg L, et al. Basic fibroblast growth factor and vascular endothelial growth factor in sera from non-small cell lung cancer patients. Anticancer Res 1998;18:1123–7.
[117] Ueno K, Inoue Y, Kawaguchi T, Hosoe S, Kawahara M. Increased serum levels of basic fibroblast growth factor in lung cancer patients: relevance to response of therapy and prognosis. Lung Cancer 2001;31:213–9.
[118] Joensuu H, Anttonen A, Eriksson M, Mäkitaro R, Alfthan H, Kinnula V, et al. Soluble syndecan-1 and serum basic fibroblast growth factor are new prognostic factors in lung cancer. Cancer Res 2002;62:5210–7.
[119] Otrock ZK, Hatoum HA, Musallam KM, Awada AH, Shamseddine AI. Is VEGF a predictive biomarker to anti-angiogenic therapy? Crit Rev Oncol Hematol 2011;79:103–11.
[120] Blackburn EH. Cancer interception. Cancer Prev Res (Phila) 2011;4:787–92.

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