Anti-angiogenic agents in the treatment of non-small cell lung cancer

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The role and process of angiogenesis in the development of a neoplasm

The development and growth of a neoplasm requires an appropriate supply of oxygen, nutrition, growth factors, hormones, and proteolytic enzymes [1]. The neoplasm cannot increase its dimensions to more than 2-3 mm³ without the formation of new blood vessels (angiogenesis). Blood vessels that develop as a result of pathological angiogenesis are abnormal; they do not form hierarchical networks, their diameter is variable, they are kinked, dilated, and they form sac-like structures. They are also characterized by increased permeability [3-6]. The abnormal distribution of chemical therapeutics is intensified by the uneven distribution of blood vessels within the tumor, the pressure exerted by proliferating tumor cells, and the turbulent and chaotic blood flow through the pathological vessels [7].

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As with most solid tumors, numerous clinical studies have confirmed that, in lung cancer, a high density of small vessels in the tumor is an unfavorable prognostic factor and correlates with metastasis formation [8-12].

The process of angiogenesis, both physiological and pathological, is initiated at the moment when the balance between anti-angiogenic and pro-angiogenic factors shifts towards the latter. In the case of a tumor, the phenotype of the tumor cells is then changed to an invasive one.

**The mechanism of angiogenesis in lung cancer**

The best understood mechanism of angiogenesis is the sprouting of new blood vessels in the direction of neoplastic cells, consisting in the proliferation and migration of endothelial cells from previously existing vessels and the formation of tubular vascular structures. The key factor in this process is vascular endothelial growth factor (VEGF). VEGF-A induces the distention of existing blood vessels and increases their permeability. Plasma proteins, particularly fibrinogen, undergo extravasation and accumulate in the extracellular space, while metalloproteinases are activated, and the concentration of the plasminogen activator influences the angiogenic process by regulating the survival of endothelial cells [13-15]. Platelet-derived growth factor (PDGF) causes pericytes to accumulate in the vicinity of the newly formed vessels.

**Factors regulating the process of angiogenesis**

A disturbance in the balance between the activity of factors which stimulate and inhibit angiogenesis in favor of the pro-angiogenic factors initiates the process of forming new vessels. The primary and best understood pro-angiogenic factor is vascular endothelial growth factor (VEGF-A). Its glycoprotein family also includes VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PIGF). VEGF-A was initially defined by Dvorak et al. as vascular permeability factor (VPF) [16]. Out of the 4 isoforms of the VEGF-A gene, VEGF<sub>165</sub> is dominant. VEGF-A plays a key role both in physiological angiogenic processes (during wound healing, ovulation, menstruation, and pregnancy) and in pathological processes (such as diabetic retinopathy, macular degeneration, and psoriasis) [17, 18]. Hypoxia is the primary factor stimulating VEGF synthesis through the activation of hypoxia-inducible factor-1α (HIF1α). The most important property of VEGF is the increase of vascular permeability, even up to 50,000 stronger than that resulting from histamine action, in the vascular bed of the skin, peritoneum, mesentery, and diaphragm, among others. This can lead to the occurrence of pleural or peritoneal effusion, while inhibiting the function of VEGF reduces the occurrence of these conditions, as confirmed by conducted studies [19, 20]. VEGF also causes vascular distention by releasing nitric oxide and prostaglandins from endothelial cells. This results in a transient acceleration of heart action and a reduction in arterial pressure and cardiac output. The effect of inhibiting VEGF activity may also be responsible for the adverse reactions to anti-angiogenic therapies observed in clinical studies, such as headaches or arterial hypertension [17].

**Platelet-derived growth factor**

The family of platelet-derived growth factors (PDGF) influences the angiogenic process by regulating the survival of endothelial cells and by recruiting pericytes, smooth muscle cells, and tumor-associated fibroblasts producing VEGF [22-24]. High concentrations of immunohistochemically labeled PDGF result in worse prognoses in lung cancer patients [25].

**Bevacizumab**

Bevacizumab is a recombinant humanized monoclonal antibody (93% human and 7% murine), the action of which consists in binding with free vascular endothelial growth factor (all VEGF-A isoforms), thus inhibiting the combination of VEGF and receptors of Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of the endothelium. It is the first anti-angiogenic agent which was proven by clinical studies to exert a favorable influence on patient survival time in combination with chemotherapy. A phase II trial assessing the efficacy and safety of bevacizumab dosed at 7.5 or 15 mg/kg in combination with chemotherapy (carboplatin and paclitaxel) demonstrated the prolongation of time to progression (7.4 months vs. 4.2 months, \( p = 0.023 \)) and the prolongation of overall survival (17.7 months vs. 14.9 months, \( p = 0.63 \)) achieved with the dose of 15 mg/kg, which turned out to be more successful. Six out of 66 patients treated with bevacizumab suffered from massive hemoptysis; 4 of them died due to a lethal lung hemorrhage from centrally located tumors located in the vicinity of large vessels with the presence of cavitation. Additionally, it has been established that the diagnosis of squamous carcinoma is a risk factor for bleeding. Consequently, multicenter, randomized clinical phase III trials were conducted in order to assess the efficacy and safety of bevacizumab in combination with chemotherapy as a first-line therapy for patients with non-small-cell non-squamous lung cancer. In order to reduce the risk of bleeding, the exclusion criteria included, among others, a histological diagnosis of squamous carcinoma, metastasis within the central nervous system, anticoagulant treatment, and massive hemoptysis.
sis in the patient’s medical history. Study E4599 included 878 patients with recurrent or advanced non-squamous non-small-cell lung carcinoma. The patients received chemotherapy (carboplatin AUC 6 with paclitaxel 200 mg/m²) every 3 weeks with bevacizumab dosed at 15 mg/kg or with placebo. Longer overall survival (12.5 months vs. 10.2 months, \( p = 0.0075 \)), longer progression-free survival (PFS: 6.4 vs. 4.5 months, \( p < 0.0001 \)), and an increased treatment response rate (35% vs. 15%) were observed in the study arm with bevacizumab. Fifteen deaths were noted in the bevacizumab group, including 5 due to pulmonary hemorrhage. The same study demonstrated that an initially low concentration of intercellular adhesion molecules (ICAM) was associated with an increase in response rate (RR: 32% vs. 14%) [26].

The second phase III trial was the randomized AVAIL study assessing the efficacy and safety of bevacizumab dosed at 7.5 and 15 mg/kg in combination with cisplatin/gemcitabine. The trial confirmed bevacizumab’s benefits in terms of progression-free survival (similar efficacy and safety of both doses); it failed, however, to demonstrate improvements in terms of overall survival [2, 3, 7, 8].

One of the most common adverse reactions to bevacizumab is the development of arterial hypertension (1/3 of patients; stages 3 and 4 of arterial hypertension were observed in 18% of patients treated with bevacizumab) [27]. Hypertension most likely develops as a result of the inhibition of nitric oxide production caused by the blockage of VEGF action leading to increased vascular tension. Other hypotheses underscore the reduced density of capillaries and the development of embolic microangiopathy in the renal vessels, leading to disturbances in the regulation of the renin-angiotensin system [2, 3, 28]. Nonetheless, researchers emphasize the positive predictive value of the occurrence of arterial hypertension during treatment with bevacizumab [29].

Other adverse reactions observed in clinical studies include gastro-intestinal perforations, fistulas, wound-healing impairment, proteinuria, and vascular complications such as arterial and venous thromboembolisms, bleeding (including hemoptysis), as well as congestive heart failure and myocardial infarction.

Although bevacizumab is the only registered agent in the treatment of non-small-cell lung cancer, it is not widely used in therapy.

**Small-molecule anti-angiogenic tyrosine kinase inhibitors**

Sorafenib is an oral multikinase inhibitor. Its action is aimed at inhibiting tumor growth (by inhibiting Raf, c-kit, Flt-3) and impeding the development of new vessels (by acting on VEGFR-2, VEGFR-3, and PDGFR-β). Its most commonly observed adverse effects are diarrhea (> 25%), palmoplantar erythrodysesthesia (hand-foot syndrome), fatigue, and nausea [30]. After 2 months of treatment, study E2501 demonstrated that a significantly larger number of patients responded favorably to the treatment (SD/PR/CR) in comparison to the placebo group (47% vs. 19%); PFS was 3.6 vs. 2.0 months, OS was 11.9 vs. 9.0 months. The randomized phase III ESCAPE trial, encompassing 926 patients with advanced non-small-cell lung carcinoma, compared the efficacy of carboplatin/paclitaxel chemotherapy and chemotherapy combined with sorafenib in the first line of treatment. No statistically significant differences were confirmed in terms of RR, PFS, or OS between the two groups, which resulted in the early termination of the trial [31].

Sunitinib is a small-molecule multikinase inhibitor. Its action consists in the inhibition of tumor cell proliferation, new vessel formation, kinase activity of VEGFR-1, -2, and -3, as well as of PDGFR-α and -β, tyrosine kinase similar to Fms-3 (Flt3), c-kit, and tyrosine kinase of the receptor encoded by the RET proto-oncogene [32, 33]. Its most common adverse effects are fatigue, pain, myalgia, nausea, vomiting, dyspnea, stomatitis, and gastritis. Another important adverse effect is skin discoloration, probably related to the yellow color of the active ingredient; hair may become discolored as well.

Pazopanib blocks the kinase activity of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and c-kit (34). It has been demonstrated that, after pazopanib treatment, the serum levels of VEGFR-2 and PlGF are significantly reduced and, additionally, correlate with the degree of neoplastic tumor reduction [35].

Vandetanib is an oral angiogenesis inhibitor acting on VEGFR-2, VEGFR-3, and the EGFR/HER1 receptor as well as an inhibitor of tumor growth acting on RET. Numerous clinical studies have reported higher objective treatment response rates in groups treated with vandetanib in comparison to groups with chemotherapy alone. A phase III clinical study (ZODIAC) assessed the combination of vandetanib and docetaxel in the second-line treatment of patients suffering from advanced non-small-cell lung carcinoma. The addition of vandetanib prolonged progression-free survival (PFS 4.0 vs. 3.2 months); however, no prolongation of overall survival was observed [36]. The most frequent adverse effects of this therapy included rash, diarrhea, and asymptomatic prolongation of the QTc interval. Another phase III clinical study (ZEIST) demonstrated that, in patients with advanced non-small-cell lung carcinoma, after the failure of previous chemotherapy, vandetanib and erlotinib exhibit similar efficacy in terms of PFS and OS, but vandetanib treatment is associated with substantially increased toxicity [37].

**Nintedanib**

Nintedanib (BIBF 1120) is an oral triokinase inhibitor, assessed in clinical studies, which inhibits the activity of vascular endothelial growth factor receptor 1-3 (VEGFR 1-3), fibroblast growth factor receptor 1-3 (FGFR 1-3), and platelet-derived growth factor α and β (PDGFR α and β). Nintedanib acts on three types of cells: endothelial cells (VEGFR 1-3, FGFR 1-3), smooth muscle cells (FGFR 1-3, PDGFR α and β), and pericytes (PDGFR α and β). It has been suggested that the signaling pathways associated with FGFR and PDGFR...
are responsible for the development of potential mechanisms of the loss of control over neoplastic cells via signaling pathways associated with VEGFR, which are blocked by anti-angiogenic agents and, thus, constitute an alternative mechanism of neoplasm progression. Therefore, blocking three tyrosine kinases responsible for the angiogenic process appears to be a promising starting point for new targeted therapies [38, 39].

Considering the period over which it acts on target cells and some of its pharmacokinetic parameters, BIBF 1120 differs from other angiogenesis inhibitors. After exposing cell cultures to BIBF 1120 in a concentration of 50 mmol/l for 1 hour, the inhibition of receptor phosphorylation was maintained for at least 32 hours, indicating long-lasting anti-angiogenic action [40].

A multicenter, randomized, double-blinded, and placebo-controlled phase III clinical study (LUME-Lung 1) assessed the efficacy and safety of using nintedanib after failure of the first line of treatment for locally advanced or metastatic non-small cell lung carcinoma (IIIb/IV according to the TNM classification). The study excluded patients with centrally located tumors, tumor necrosis or cavitation, and neoplastic large vessel invasion, as well as patients whose medical history indicated hemorrhagic or thrombotic events within the past 6 months or hemoptysis within the past 3 months. The study encompassed 1314 patients from Europe, Asia, and South Africa. One of the study groups received docetaxel dosed at 75 mg/m² on the 1st day and nintedanib dosed at 200 mg twice per day on days 2-21 (n = 655), while the other group received docetaxel in the same dose and placebo (n = 659). The primary endpoint of the examination was progression-free survival; its prolongation was demonstrated in the patients receiving nintedanib independently of the histological subtype of the neoplasm (PFS: 3.4 months [95% CI: 2.9-3.9] vs. 2.7 months [95% CI: 2.6-2.8], p = 0.0019). It is worth noting that the study provided the earliest proof for the efficacy of using an anti-angiogenic agent in the 2nd line of treatment with regard to prolonging overall survival; however, this pertained only to adenocarcinoma patients (OS: 12.6 months [95% CI: 10.6-15.1] vs. 10.3 months [95% CI: 8.6-12.2], p = 0.0359). The most common adverse effects of administering nintedanib as compared with placebo were nausea (24% vs. 18%), emesis (17% vs. 9%), diarrhea (42% vs. 22%), and increased liver enzyme activity (29% vs. 8%). All side effects were transient and abated when symptomatic treatment was employed or the dose was reduced [63]. The primary adverse events requiring the lowering of the nintedanib dose were gastrointestinal ailments and increased liver enzyme concentration. No increase in the frequency of adverse events characteristic of anti-angiogenic therapies, such as arterial hypertension, bleeding, or gastrointestinal tract perforation, was noted in the subgroup receiving nintedanib. More precise analyses indicated that adenocarcinoma patients in whom the disease progresses within a period shorter than 9 months from the beginning of 1st line chemotherapy achieve greater benefits in terms of overall survival from the use of docetaxel in combination with nintedanib than from treatment with docetaxel alone (OS: 9.8 months [95% CI: 6.1-15.5] vs. 6.3 months [95% CI: 5.0-8.1], p = 0.0246). These data may suggest that fast disease progression is a positive predictive factor in the case of nintedanib administration [41]. It has also been demonstrated that patients with neoplasms of greater mass before the start of therapy achieve more substantial benefits from treatment with docetaxel in combination with nintedanib [42].

**Radiological evaluation of anti-angiogenic treatment response – diagnostic pitfalls**

In patients treated with angiogenesis inhibitors in combination with chemotherapy, standard radiological evaluation according to the RECIST 1.1 criteria based on computed tomography with contrast does not enable the precise assessment of treatment response. Morphological changes are observed within the tumors, including the formation of cavities (cavitation), bleeding, bleeding into the tumor, necrosis, or changes in the density of the tumor's pattern. It is assumed that cavitation occurs in neoplastic tumors due to the development of central necrosis associated with the inhibition of angiogenesis; their frequency in patients undergoing anti-angiogenic treatment is estimated at 19-24% [43, 45]. Nishino et al. demonstrated in their study that in 79% of patients undergoing anti-angiogenic treatment, the cavities are subsequently filled in, which is defined as a reduction of any dimension of an air-filled cavity (from the smallest reduction visible to the complete disappearance of the cavity) resulting from the growth of the solid tumor component within the cavitary area. The filling in of cavities is considered to be a morphological change, which corresponds to disease progression, but is not reflected in the evaluation of treatment response based on the RECIST 1.1 criteria [44, 45]. Crabb et al. [46] retrospectively evaluated the response to anti-angiogenic treatment of 33 patients, using the RECIST criteria and an alternative method, in which the largest dimension of the cavity was subtracted from the largest dimension of the target change, which correlated much more significantly with the change in tumor volume. The use of the abovementioned method, alternative to RECIST 1.1, resulted in a different treatment response, different time to best response, and time to disease progression, but this only pertained to a decided minority of patients [44].

Yoo Na Kim et al. evaluated anti-angiogenic treatment response with the use of dual-energy computed tomography (DECT), employing the criteria developed by Choi et al. and comparing the results with an evaluation conducted according to the RECIST criteria. The researchers noted that the appearance of bleeding within the tumor as a morphological change constituting a form of treatment response may imitate an increase in tumor dimensions and lead to an erroneous diagnosis of progressive disease (PD) instead of stable disease (SD) or partial response (PR) [47-49]. The Choi criteria, which were initially introduced for the monitoring of the efficacy of treating gastrointestinal stromal
tumors with imatinib, are based on the evaluation of tumor density, defined as the CT attenuation coefficient measured in Hounsfield units (HU) (Table I) [49, 50].

Hence, evaluating treatment efficacy based only on CT images and according to the RECIST 1.1 criteria, which define treatment response based only on the changes in tumor size, may be inaccurate.

Conclusions

Anti-angiogenic treatment based on tumor biology is one of the more recently developed therapeutic options. Bevacizumab is the first anti-angiogenic agent for which prolongation of overall survival has been demonstrated in non-small-cell lung carcinoma patients in the first line of treatment. During clinical studies, the observed adverse effects necessitated the exclusion of patients with tumor cavitation or necrosis, patients with neoplastic invasion of large vessels or centrally located tumors, patients with the histological diagnosis of squamous carcinoma, and patients whose medical history indicated hemorrhagic or thrombotic events. The only anti-angiogenic agent demonstrated to improve overall survival in non-small-cell lung carcinoma patients in the 2nd line of treatment is nintedanib (LUME-Lung 1 study); this pertains, however, only to patients with the histopathological diagnosis of adenocarcinoma. The search for biomarkers constituting predictive factors for anti-angiogenic treatment response is ongoing. It has been demonstrated that the development of arterial hypertension during therapy is a factor associated with better response to treatment with bevacizumab, while, in the case of nintedanib treatment for pulmonary adenocarcinoma patients, a better response is achieved in patients who did not respond to the first line of treatment, or in whom the disease progressed shortly after the end of therapy. As a result of treatment, morphological changes occur within the tumor, including the formation of cavities/necrosis or bleeding into the tumor. Bleeding within the tumor may imitate an increase in tumor dimensions and lead to an erroneous diagnosis of PD. Similarly, the diagnosis may be incorrect if, within the cavity resulting from the anti-angiogenic treatment, the solid tumor component from the cavity grows, while the tumor itself does not change its dimensions.

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