

Dual Drugs in Tandem: A Comparative Study of Gefitinib and Bevacizumab in the Treatment of Non-Small Cell Lung Cancer

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Abstract. The field of lung cancer research includes non-small-cell lung cancer (NSCLC), which has been a common subject of medical research in recent years. As an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), Gefitinib blocks the activity of EGFR. Thereby inhibiting the proliferation of cancer cells. Another drug, Bevacizumab, takes a different way by cutting off the blood that is supplied to cancer cells. Whether used alone or in combination, these two drugs have significantly advanced the field of NSCLC treatment and offered new hope for patients.

Keywords: non-small-cell lung cancer, Gefitinib, Bevacizumab, epidermal growth factor receptor, vascular endothelial growth factor.

1. Introduction

Non-small-cell lung cancer (NSCLC) is one of the main types of lung cancer, and its treatment has been the focus of medical attention [1]. Targeted therapy has become the main therapy for NSCLC, and the two most classic targeted drugs for non-small cell lung cancer are gefitinib and bevacizumab.

As a member of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI), Gefitinib specifically inhibits the activity of EGFR. It blocks the proliferation signal transduction of tumor cells, thereby achieving the treatment of NSCLC patients with EGFR gene mutation [2].

Bevacizumab is an anti-tumor angiogenic drug, which indirectly blocks the nutrient supply of tumors by inhibiting the formation of tumor neovascularization, thus inhibiting tumor growth [3].

Since the mechanism of action of Gefitinib and Bevacizumab in treating NSCLC differs, this article aims to explore the comparison and combination of the two drugs.

2. Overview of non-small-cell lung cancer

2.1. Introduction and Symptoms

The lungs are important organs of the human body and essential for extracting oxygen from the air and efficiently transferring it to the blood, while releasing carbon dioxide from the blood to the atmosphere, facilitating gas exchange. In the internal structures of mammals, and most other vertebrates, two lungs are present. The two lungs are not randomly distributed, but are located in specific locations on the body -that is, near the sides of the spine, and the two lungs are located on the left and right sides of the heart.

More specifically, when we look at a standing mammal, such as a human or a dog, from the front, the heart is usually located slightly to the left of the center of the thorax. The lungs, on the other hand, spread out like wings, covering each side of the heart and close to the spine.

The lungs are located in the chest cavity, one on each side of the mediastinum. The lung can be divided into parenchyma and stroma. Pulmonary parenchyma refers to the bronchioles, alveolar ducts, and alveolar sacs in the lungs at all levels, which are the main parts of the lungs for gas exchange. Pulmonary interstitium includes the structures of blood vessels, lymphatics, and nerves in the lungs, which play an important role in maintaining the normal function of the lungs.

Lung cancer is malignant tumors occurring in the bronchus or lungs that tumors originate from epithelial cells. Therefore, lung cancer is an epithelial cancer. The type of lung cancer can be roughly divided into two parts by the sizes of cells and morphologic evaluation: one is NSCLC, and another is Small-cell lung cancer (SCLC). The main type of lung cancer is NSCLC. The types of NSCLC are composed of squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, as well as several other less prevalent and less common types. SCLC, also known as "oat-cell carcinoma", is named because of its unique flat cell morphology and poor cytoplasm. This type of cancer often exhibits more aggressive and more extensive metastatic behavior compared to NSCLC.

Early NSCLC has no obvious symptoms until the disease has progressed to a certain extent. Terminal symptoms include chronic coughing, bleeding, hoarseness, shortness of breath, chest pain, weight loss, and loss of appetite.

2.2. Impacts and number of mortalities

Lung cancer, accounting for 1.8 million diagnoses and claiming 1.6 million lives annually, stands as one of the most prevalent cancers globally and the primary cause of cancer-related mortality worldwide [1, 4]. Most of the lung tumors are NSCLC. The incidence is currently decreasing in some countries due to smoking regulations, but unfortunately, it is increasing in other regions, especially in Asia [1].

2.3. Significance in China and other countries in the world

In China, lung cancer is in the first place among malignant tumors in terms of incidence and mortality in both men and women. In 2022, there were 1,060,600 new cases of lung cancer, accounting for 22.0% of all malignant tumors, and 733,300 deaths, accounting for 28.5% of all malignant tumor deaths [5]. Lung cancer has surpassed breast cancer to become the most common cancer among women. The male-to-female ratio of the mortality rate for lung cancer (2.66) is higher than that of the incidence rate (1.69) [5]. Men with lung cancer have a poorer survival rate compared to women. Lung cancer constitutes a significant and pressing public health concern, accounting for a staggering number of fatalities globally. Therefore, it is significant to take measures to tackle the disease comprehensively.

2.4. Drugs used to treat the disease

Among the myriads of therapeutic options available for the treatment of NSCLC, two drugs stand out as the most prevalent and widely employed: Gefitinib and Bevacizumab.

3. Gefitinib

3.1. The Structure of Drug

Gefitinib, scientifically known as 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline, is a synthetic anilinoquinazoline compound. Belonging to the promising 4-anilinoquinazoline class, Gefitinib stands as a member of EGFR-TKIs [6]. This class of inhibitors works by targeting EGFR activity to disrupt the signaling pathways associated with tumor growth and proliferation.

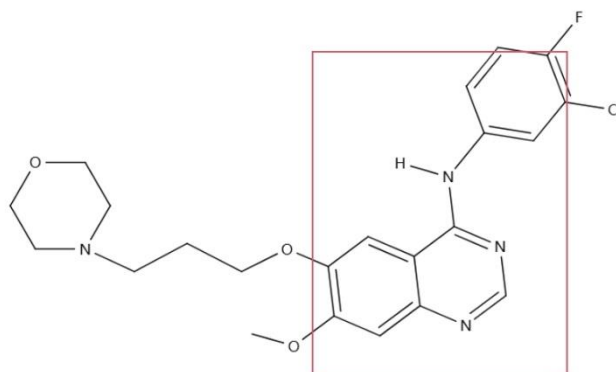


Figure 1. The chemical structure of Gefitinib. The red box is anilinoquinazoline, which binds to the active part of EGFR.

3.2. Description of Drug Targets and how their function is affected by drugs

The development of NSCLC is mainly driven by genetic mutations. This means that during the pathogenesis of NSCLC, certain genes within cells are mutated, and these mutations lead to abnormalities in cell growth and division, which in turn promote tumor formation and progression. These genetic mutations may be inherited or may have occurred due to environmental factors during the life course of the individual. One of the important driver mutations has been detected in EGFR.

EGFR is a transmembrane tyrosine kinase receptor. Epithelial cancers are typically characterized by overexpression of EGFR. This overexpression acts as a catalyst to initiate a cascade of molecular events that begin with the autophosphorylation of tyrosine residues. This autophosphorylation acts as a key switch to turn on EGFR intrinsic protein tyrosine kinase activity, thereby releasing a complex array of cellular responses. By activating tyrosine kinase activity, EGFR stimulates downstream signaling cascades that regulate gene expression, metabolism, and ultimately the transformation of normal cells into tumor entities. Overexpression of EGFR is therefore a critical step in the onset of epithelial cancer, making it a prime target for therapeutic intervention [2, 7]. When EGFR is activated by its ligand, it triggers a complex series of signal transduction cascades. These signaling cascades are important for both normal cell function and pathological changes. *In vivo* and *in vitro* studies have shown that EGFR can induce cell transformation. In addition, it has profound effects on tumor progression, including the control of cancer cell migration, cell survival, angiogenesis, and other key aspects. This multifaceted influence reflects its critical role in regulating the complex landscape of tumorigenesis and progression.

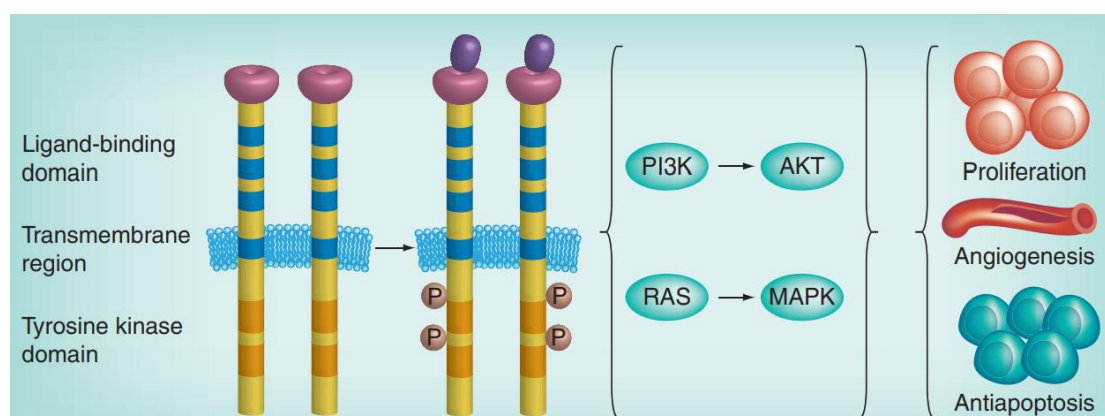


Figure 2. EGFR and its signaling pathway. An EGFR monomer consists of an extracellular region with two ligand-binding subdomains. It mainly coordinates cell proliferation and survival mechanisms through the key PI3K-AKT-mTOR and RAS-RAF-MEK-MAPK signaling pathway. Reproduced from [2]. Copyright 2011, Informa UK Limited.

As shown in Figure 2, EGFR is a transmembrane receptor protein consisting of a monomeric structure and an extracellular domain, including two structurally distinct ligand-binding subdomains. The EGFR structure is complex and specific, allowing it to recognize and bind to specific growth factors.

The PI3K/AKT/mTOR signaling cascade is a common intracellular mechanism that regulates cell cycle processes and various cellular functions[2]. It regulates cell metabolism, growth, and proliferation by promoting protein synthesis and inhibiting cell apoptosis.

At the same time, the Ras-Raf-MEK-ERK signaling pathway acts as a complex protein delivery system responsible for delivering signals from surface receptors to DNA in the nucleus, thus coordinating the necessary cellular responses and processes. It responds to growth stimulation mainly by regulating gene expression and cell differentiation.

Both pathways are part of a complex network of signals within cells. Through these two signaling pathways, EGFR induces cell transformation and influences several key processes in tumor progression. Thus, in modern times, EGFR and their signaling pathways have emerged as key targets for the treatment of NSCLC and other EGFR-driven cancers.

Gefitinib is the first EGFR-TKI approved for NSCLC. Gefitinib has demonstrated significant antitumor activity, both as a standalone agent and in conjunction with diverse chemotherapy drugs [8]. It is used to treat NSCLC by inhibiting EGFR activation through its auto-phosphorylation. By blocking those signals which are above mentioned, it keeps the cancer cells from multiplying and spreading, which can help in fighting lung cancer.

As an EGFR-TK inhibitor, Gefitinib lowers the proliferation rate of tumor cells. It exhibited a profound effect by comprehensively inhibiting EGFR phosphorylation, subsequently diminishing the activity of mitogen-activated protein kinase, and significantly enhancing the induction of apoptosis.

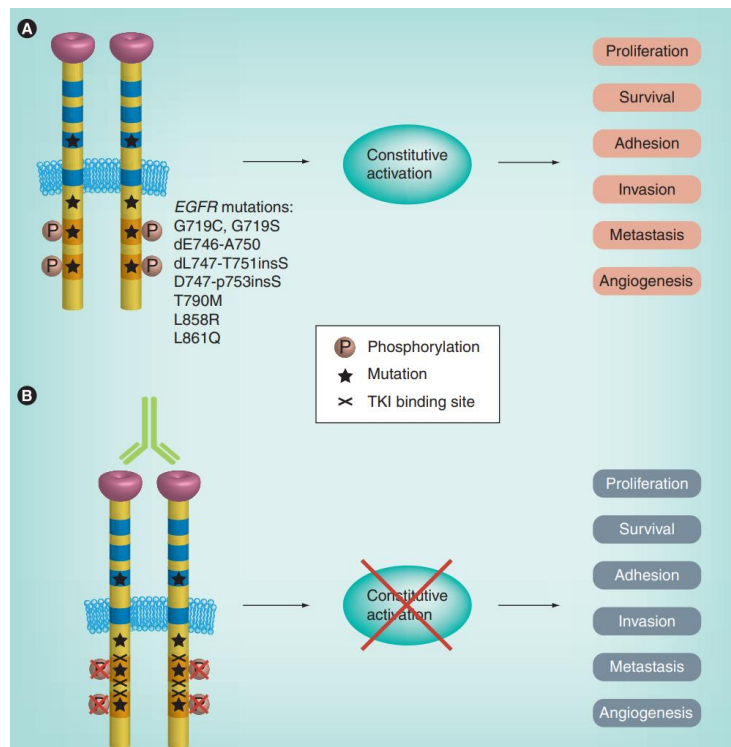


Figure 3. Mechanism of EGFR-activating mutations(A) and EGFR-targeted therapy(B). (A) shows the mutations in the EGFR. These mutations render EGFR-TK activated. And (B) shows that Gefitinib binds the TKI binding sites. Therefore, Gefitinib completely prevents EGFR phosphorylation. Then the functions of EGFR will not be implemented. Reproduced from [2]. Copyright 2011, Informa UK Limited.

An objective examination of the complex mechanisms underlying EGFR-activating mutations and the effectiveness of EGFR-targeted therapies reveals two pivotal scenarios. As shown in **Figure 3**, (A) vividly illustrates the occurrence of mutations within EGFR, specifically within its tyrosine kinase (TK) domain. These mutations, often referred to as 'driver' mutations, effectively transform the EGFR-TK from its quiescent state into a constitutively activated form. This perpetual activation triggers an unchecked cascade of signaling events, ultimately promoting cellular proliferation, and survival, and potentially contributing to the development of malignancies. In (B), the strategic intervention of Gefitinib, a targeted therapeutic agent specifically designed to bind to the tyrosine kinase inhibitor (TKI) binding sites of mutated EGFR, is observable. By occupying these critical sites, Gefitinib effectively blocks the ability of EGFR to undergo phosphorylation, a crucial step in activating its downstream signaling pathways. This blockade not only halts the propagation of oncogenic signals but also renders the mutated EGFR incapable of executing its pathological functions, thereby inhibiting tumor growth and progression. In essence, the harmonious interplay between the understanding of EGFR-activating mutations and the precision of EGFR-targeted therapies, exemplified by Gefitinib, underscores the importance of personalized medicine in combating cancers driven by EGFR abnormalities. By precisely targeting the mutated receptor and its associated signaling machinery, oncogenic processes can be disrupted, facilitating the development of more efficacious and individualized treatment approaches.

The treatment in clinical application, is mainly used for treatment after chemotherapy failure of patients with locally advanced or metastatic NSCLC. Especially in East Asia in the crowd, as well as with EGFR mutations, such as lack of exon 19 and exon 21 L858R mutations in patients with NSCLC, for he showed higher efficacy. These patients usually have a significant objective response to Gefitinib therapy, including tumor shrinkage and symptomatic improvement. However, the treatment of Gefitinib also faces several challenges and limitations. First, not all NSCLC patients are sensitive to Gefitinib, and only those with specific EGFR mutations benefit from it. Second, long-term use of Gefitinib may lead to the development of drug resistance, which limits its long-term efficacy. In addition, Gefitinib may also cause some adverse reactions, such as rash, diarrhea, and abnormal liver function, which need to be closely monitored and managed. Nevertheless, Gefitinib, as one of the representative drugs of EGFR-TKI, plays an important role in the targeted therapy of NSCLC. With the in-depth study of the EGFR signaling pathway and its regulatory mechanism, as well as the continuous emergence of new EGFR-TKIs, Gefitinib, and its similar drugs are still promising in the treatment of NSCLC.

3.3. Mode of Delivery

Gefitinib is an oral drug. Oral administration is the most convenient, safest, and economical, so it is the most commonly used method of administration.

4. Bevacizumab

4.1. The Structure of Drug

Bevacizumab is a monoclonal antibody drug. The structure of it is complex.

4.2. Description of Drug Targets and how their function is affected by drugs

Vascular endothelial growth factor (VEGF) is a growth factor crucial in tumor angiogenesis, promoting endothelial cell proliferation, migration, and survival, thereby facilitating tumor vascularization. Tumor cells usually lose the tight control normal cells have over their growth. Ordinary cells proliferate to a limited extent when stimulated by certain growth factors, while tumor cells may ignore normal growth inhibition mechanisms, resulting in abnormally rapid proliferation. Since tumor metabolism requires high nutrient and oxygen requirements and metabolic wastes require vascular processing to metabolize them, tumors largely rely on the supply of nutrients and oxygen brought about by angiogenesis and the function of their metabolic wastes. Among the diverse array of pro-angiogenic factors secreted by tumor cells, VEGF emerges as a paramount player, exerting a crucial role in fostering the growth of new blood vessels within tumors. Its distinct ability to stimulate endothelial multiplication of cells, cellular

displacement, and neovascularization underscores its significance in tumor progression and metastasis, making VEGF a prime target for anticancer therapies aimed at curbing tumor angiogenesis [3].

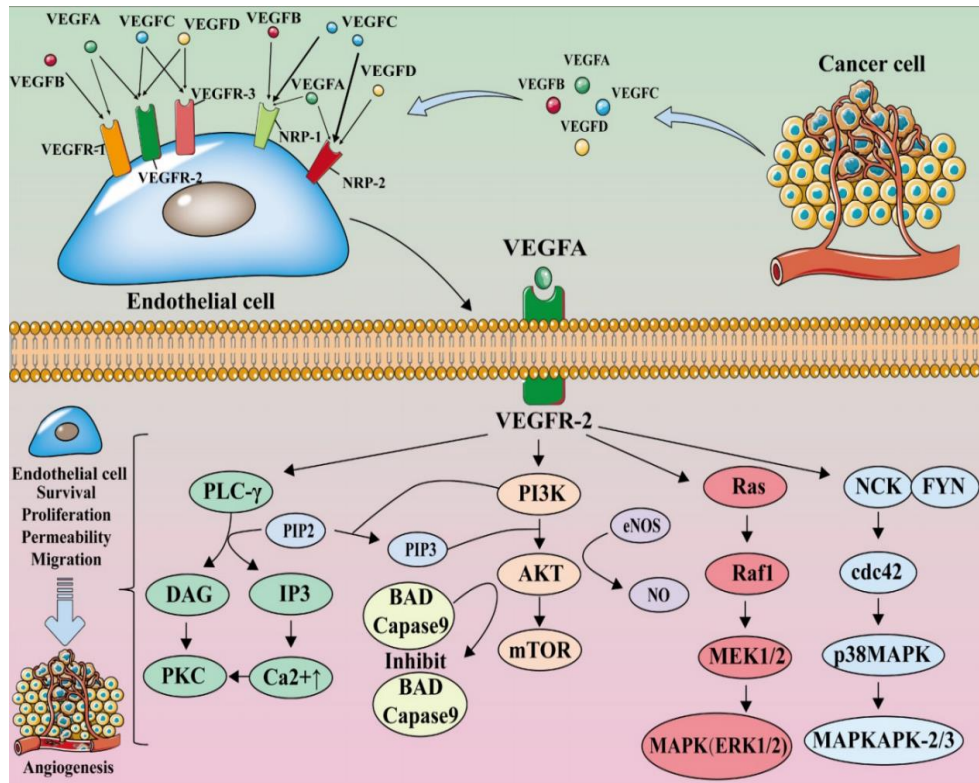


Figure 5. The VEGF-VEGFR signaling pathway. VEGF-A binds to VEGFR-2 and activates signaling cascades involving pathways such as mTOR and MAPK/MEK, promoting endothelial cell survival, proliferation, permeability, and migration essential for tumor angiogenesis. Reproduced from [9]. Copyright 2022, Ivyspring International Publisher.

Regarding Figure 5, here is an introduction to the picture:

VEGFR-2: Vascular endothelial growth factor receptor-2, the key receptor that responds to VEGFs and regulates angiogenesis.

VEGFs (e.g., VEGF-A, VEGF-B, VEGF-C): ligands of VEGFR-2, which promote angiogenesis and cell proliferation.

NRP-1/2: Neuropilin receptor, which acts as a co-receptor to enhance VEGF binding to VEGFR-2.

Endothelial cells: the main cell type of VEGFR-2 action and constitute the vessel wall.

PLC- γ , PI3K: the enzyme activated by VEGFR-2 generates DAG/IP3 and PIP3, respectively, which further activate downstream signals.

MAPK signaling pathway (Ras, Raf, MEK, ERK): promotes cell proliferation and differentiation.

p38MAPK: regulates cellular stress response, inflammation, and apoptosis.

eNOS: produces nitric oxide, regulates vasodilation, and is anti-inflammatory.

AKT, mTOR: regulates cell survival, proliferation, and metabolism.

PKC: involved in the regulation of cell proliferation, migration, and survival.

BAD, Caspase-9: associated with apoptosis, VEGFR-2 signaling inhibits its activity to promote survival.

NCK, FYN, CDC42, Ca^{2+} : involved in cytoskeleton rearrangement, migration, and cycle regulation.

This picture demonstrates the process by which VEGFR-2 regulates angiogenesis, cell proliferation, migration, and survival in endothelial cells by activating multiple signaling pathways in response to VEGFs.

VEGF-A binds to VEGFR-2, triggering its dimerization, autophosphorylation, and subsequent activation. This cascade leads to a profound impact on endothelial cells, fostering their survival, proliferation, increased permeability, and migration. Additionally, VEGF-A signaling activates downstream pathways such as the mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) cascades, including MAP kinase (MEK), further amplifying its effects on endothelial function and tumor angiogenesis.

Bevacizumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody. As a monoclonal antibody, Bevacizumab binds to VEGF, preventing its binding to receptors, thereby inhibiting angiogenesis (an angiogenesis inhibitor), reducing tumor blood supply, and limiting tumor growth and metastasis. It has to do with soluble VEGF - type A combination of all circulation. Bevacizumab does not bind to VEGFR, which directly blocks tumor cell angiogenesis. By specifically binding to VEGF-A and blocking its interaction with VEGFR, Bevacizumab effectively inhibits the activation of the VEGF signaling pathway, which is a key driver of neovascularization. In vivo studies have conclusively showcased Bevacizumab's remarkable potency in suppressing vessel growth, triggering regression of newly formed blood vessels, and thereby normalizing the tumor vasculature [3]. This normalization of the tumor vasculature not only significantly improves the delivery of cytotoxic chemotherapy to the tumor site, but also exerts direct antitumor effects on the tumor cells themselves, thereby highlighting Bevacizumab's dual-modality therapeutic potential.

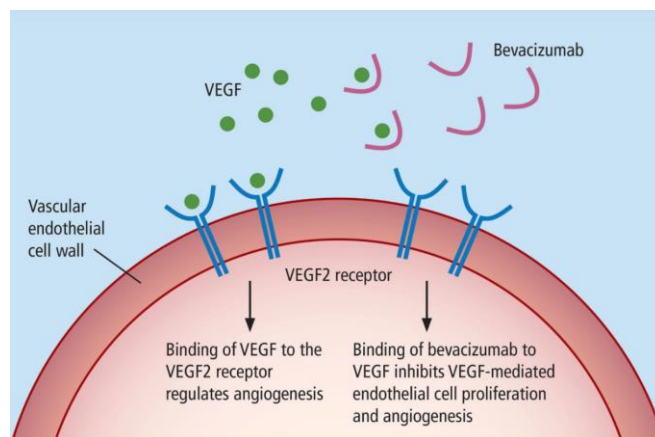


Figure 6. Mechanism of action of Bevacizumab. Bevacizumab can bind with VEGF so VGFR can not bind with its receptor. It acts like a kind of competitive inhibition. Bevacizumab can inhibit the growth of malignant cells and the formation of blood vessels by blocking the interaction between VEGF and its receptor VEGFR, thus playing an anti-tumor role. Reproduced from [10]. Copyright 2020, John Wiley & Sons, Inc or related companies.

Bevacizumab ushered in a new era of antiangiogenic therapy as the first approved inhibitor of angiogenesis. Since its initial approval for the treatment of metastatic colorectal cancer, indications for Bevacizumab have expanded to include a variety of solid tumors. The role of VEGF in the tumor microenvironment, especially in the regulation of angiogenesis and tumor-induced immunosuppression of the dual role of related found for Bevacizumab and immunotherapy of joint application provides a new Angle of view and has set up in NSCLC and the treatment of hepatocellular carcinoma showed clinical benefit. Overall, Bevacizumab not only occupies an important position in cancer treatment due to its established efficacy but also shows great potential as a candidate for novel targeted combination therapy.

4.3. Mode of Delivery

Bevacizumab is an intravenous drug. Intravenous administration is the best method of accurate and rapid administration, which is easy to regulate and can exert systemic effects. When administered orally, most

drugs undergo chemical structural changes (metabolism) in the wall of the small intestine and liver, reducing the amounts of drugs in the blood. Thus, intravenous administration of the drug requires a smaller dose to achieve the same effect.

5. Drug combination

EGFR holds paramount significance in regulating cell proliferation, differentiation, migration, and survival. Notably, EGFR mutations, especially exon 19 deletions and exon 21 L858R point mutations, are prevalent in NSCLC, imparting heightened sensitivity to EGFR-TKIs, thereby offering a promising therapeutic avenue for this malignancy [11]. VEGF, on the other hand, is a key mediator of angiogenesis. The VEGF pathway is often upregulated in cancer, and its inhibition has been proven effective in cancer treatment.

The pivotal small molecule compound example in lung cancer treatment is Gefitinib, which exhibits antitumor effects as monotherapy or combined with chemotherapy, impacting cell proliferation, apoptosis, and angiogenesis in EGFR-expressing cancer cell lines. Its development stemmed from investigations into EGFR-TK inhibition, identifying 4-anilinoquinazoline as a promising class of inhibitors. In contrast, monoclonal antibodies like Bevacizumab act by binding to VEGF-A, disrupting its interaction with VEGFR, thereby inhibiting neovascularization-promoting VEGF signaling. Bevacizumab inhibits vessel growth, induces vessel regression, normalizes vasculature to enhance chemotherapy delivery, and exerts direct antitumor effects.

The dual inhibition of EGFR and VEGFR signaling represents a promising therapeutic strategy, grounded on two key rationales: Firstly, EGFR exerts a crucial regulatory influence on VEGFR signaling, exemplified by its ability to enhance VEGF production upon activation [12].

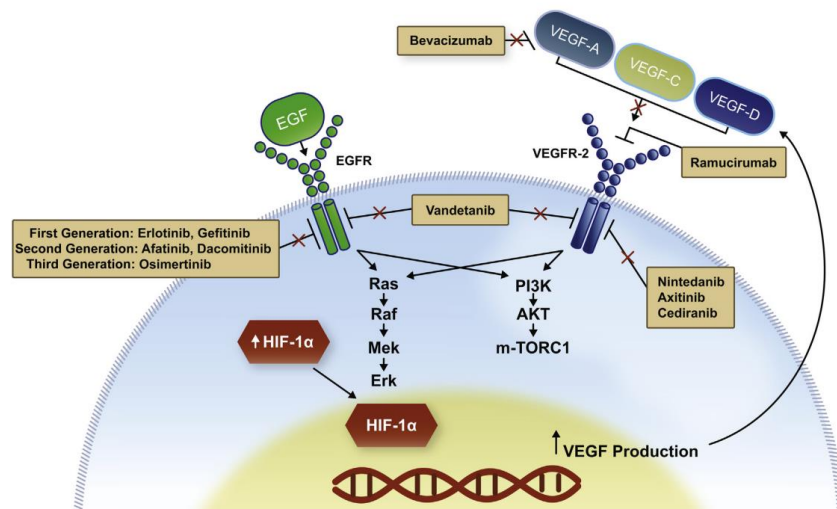


Figure 7. Cross-talk between and inhibition of the VEGF and EGFR pathways. EGFR and VEGFR-2 signaling activate PI3K/AKT and RAS/RAF/ERK pathways. Hypoxia-inducible factor-1 α (HIF-1 α), which is a vital transcriptional regulator of hypoxic responses, binds to DNA to stimulate the production of Vascular Endothelial Growth Factor (VEGF). EGFR activation upregulates HIF-1 α , fostering VEGF expression in a positive feedback loop. In NSCLC with EGFR mutations, increased EGFR signaling enhances VEGF expression through non-hypoxic mechanisms, thereby promoting resistance to EGFR-TKIs. Reproduced from [13]. Copyright 2021 Elsevier B.V., its licensors, and contributors.

Figure 7 illustrates the complexity and importance of VEGF signaling. HIF-1 α , shown in this figure, is a transcription factor that plays an important role in the cell's response to hypoxic environments. It is considered to be the "master transcriptional regulator" of cells and tissues under hypoxic conditions. HIF-1 α binds to DNA and initiates transcription of a range of genes, including the gene that encodes VEGF. Therefore, after EGFR is activated, it can up-regulate the expression of HIF-1 α through a series

of complex intracellular signaling mechanisms and finally promote the transcription and expression of the VEGF gene, increasing VEGF production. This process creates a positive feedback loop that enhances the role of EGFR signaling. The EGFR mutation is one of the common genetic variants in NSCLC. These mutations can lead to abnormal activation of the EGFR signaling pathway, which in turn promotes the growth of solid tumors [14].

EGFR and VEGF pathways converge on common downstream signaling cascades, such as PI3K/Akt and MAPK, which regulate cellular growth, proliferation, and survival. By inhibiting both pathways, one can more effectively disrupt these signaling networks and impair tumor growth. In EGFR-mutant NSCLC, EGFR signaling upregulation leads to increased VEGF expression, which contributes to resistance to EGFR TKIs [15]. By inhibiting VEGF, one can disrupt this resistance mechanism and maintain sensitivity to EGFR TKIs. During the development of resistance to EGFR TKIs, the VEGF pathway can function independently of EGFR signaling to sustain tumor growth. By inhibiting VEGF in addition to EGFR, one can prevent this compensatory mechanism and delay the onset of resistance.

Both Gefitinib and Bevacizumab can inhibit the formation of tumor cells, but the targets they bind are different. Thus, they do not competitively impede the binding of each other to the target. On the contrary, their inhibition of the target of action promotes the inhibition of the target of the other side;

Secondly, the distinct adverse effect profiles of Gefitinib and Bevacizumab facilitate the development of a more individualized and tolerable treatment plan [12]. The most common (more than 20%) adverse reactions to Gefitinib were diarrhea, rash, pruritus, dry skin, and acne, typically occurring within the first month of administration and usually reversible. Bevacizumab's side effects include anemia, pain, headaches, digestive issues, infections, breathing problems, skin irritation, and proteinuria. Monitoring is crucial.

Numerous preclinical investigations have consistently demonstrated the effectiveness of dual EGFR/VEGFR inhibition across a broad spectrum of cancer types. Specifically, the combination of Gefitinib and Bevacizumab, employed as a frontline therapeutic approach, has yielded promising efficacy and favorable tolerability profiles in individuals with advanced NSCLC harboring EGFR gene mutations [12]. Notably, this combination therapy has been particularly beneficial for patients exhibiting EGFR exon 19 deletion mutations, underscoring its targeted and potent therapeutic potential in this specific patient subgroup.

6. Conclusion

NSCLC is a prevalent form of lung cancer, accounting for 85% of lung tumors. Two targeted therapies, Gefitinib and Bevacizumab, show promise in treating NSCLC. Gefitinib, an EGFR-TKI, targets the proliferation of cancer cells by blocking EGFR signaling, thereby limiting their growth. This approach minimizes damage to normal cells. In contrast, Bevacizumab targets the tumor's "lifeline"—blood vessels—by inhibiting angiogenesis, and cutting off nutrient and oxygen supply. Both drugs offer distinct strategies for NSCLC treatment, providing hope for patients and advancing the field of precision medicine.

References

- [1] Non-small-cell lung cancer. (2015). *Nature Reviews Disease Primers*, 1(1).
- [2] Cheng, L., Zhang, S., Alexander, R., Yao, Y., MacLennan, G. T., Pan, C. X., . . . Lopez-Beltran, A. (2011). The landscape of EGFR pathways and personalized management of non-small-cell lung cancer. *Future Oncol*, 7(4), 519-541.
- [3] Garcia, J., Hurwitz, H. I., Sandler, A. B., Miles, D., Coleman, R. L., Deurloo, R., & Chinot, O. L. (2020). Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treatment Reviews*, 86.
- [4] Nicholson, A. G., Tsao, M. S., Beasley, M. B., Borczuk, A. C., Brambilla, E., Cooper, W. A., . . . Travis, W. D. (2022). The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. *Journal of Thoracic Oncology*, 17(3), 362-387.

- [5] Chinese expert consensus on immunotherapy for advanced non-small cell lung cancer with oncogenic driver mutations (2023 edition). (2024). *Chin Med J (Engl)*, 137(9), 1016-1018.
- [6] Herbst, R. S., O'Neill, V. J., Fehrenbacher, L., Belani, C. P., Bonomi, P. D., Hart, L., . . . Sandler, A. (2007). Phase II Study of Efficacy and Safety of Bevacizumab in Combination With Chemotherapy or Erlotinib Compared With Chemotherapy Alone for Treatment of Recurrent or Refractory Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, 25(30), 4743-4750.
- [7] Raben, D., Helfrich, B., Ciardiello, F., & Bunn, P. A. (2003). Understanding the mechanisms of action of EGFR inhibitors in NSCLC: what we know and what we do not know. *Lung Cancer*, 41, 15-22.
- [8] Herbst, R. S., Fukuoka, M., & Baselga, J. (2004). Gefitinib — a novel targeted approach to treating cancer. *Nature Reviews Cancer*, 4(12), 956-965.
- [9] Zhao, Y., Guo, S., Deng, J., Shen, J., Du, F., Wu, X., . . . Xiao, Z. (2022). VEGF/VEGFR-Targeted Therapy and Immunotherapy in Non-small Cell Lung Cancer: Targeting the Tumor Microenvironment. *International Journal of Biological Sciences*, 18(9), 3845-3858.
- [10] Dorrans, B., & Llano, A. (2020). Bevacizumab. *Practical Diabetes*, 37(2), 70-71.
- [11] Lu, X., Yu, L., Zhang, Z., Ren, X., Smaill, J. B., & Ding, K. (2018). Targeting EGFR L858R/T790M and EGFR L858R/T790M/C797S resistance mutations in NSCLC: Current developments in medicinal chemistry. *Medicinal Research Reviews*, 38(5), 1550-1581.
- [12] Ichihara, E., Hotta, K., Nogami, N., Kuyama, S., Kishino, D., Fujii, M., . . . Kiura, K. (2015). Phase II Trial of Gefitinib in Combination with Bevacizumab as First-Line Therapy for Advanced Non-Small Cell Lung Cancer with Activating EGFR Gene Mutations: The Okayama Lung Cancer Study Group Trial 1001. *Journal of Thoracic Oncology*, 10(3), 486-491.
- [13] Le, X., Nilsson, M., Goldman, J., Reck, M., Nakagawa, K., Kato, T., . . . Garon, E. B. (2021). Dual EGFR-VEGF Pathway Inhibition: A Promising Strategy for Patients With EGFR-Mutant NSCLC. *Journal of Thoracic Oncology*, 16(2), 205-215.
- [14] Seshacharyulu, P., Ponnusamy, M. P., Haridas, D., Jain, M., Ganti, A. K., & Batra, S. K. (2012). Targeting the EGFR signaling pathway in cancer therapy. *Expert Opinion on Therapeutic Targets*, 16(1), 15-31.
- [15] Lin, J. J., Cardarella, S., Lydon, C. A., Dahlberg, S. E., Jackman, D. M., Jänne, P. A., & Johnson, B. E. (2016). Five-Year Survival in EGFR-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs. *Journal of Thoracic Oncology*, 11(4), 556-565.