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Research Progress of Anti-Angiogenic Drugs in First-Line Treatment of Small Cell Lung Cancer

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Abstract

Small Cell Lung Cancer (SCLC) is a low-differentiated neuroendocrine tumor with rapid growth, early metastasis and sensitivity to radiotherapy and chemotherapy. It is highly recurrence rate. And there is lacking effective treatment now. As an active research direction at present, anti-angiogenic drugs are not only widely used in non-small cell lung cancer and other tumors, but also have certain effects in small cell lung cancer combined with chemotherapy. As one of the effective treatment methods for small cell lung cancer, related research is not rare, but there is still inadequacy, such as side effects can not be tolerated, and the timing of treatment can not be accurately assessed. This article will briefly describe the research progress of anti-angiogenic drugs combined with chemotherapy in the first-line treatment of extensive small cell lung cancer.

Keywords

Anti-Angiogenesis, Small Cell Lung Cancer

1. Introduction

Lung cancer ranks first in the world. Compared with other tumors, its prognosis is worse and the mortality rate is higher. As one of the types, the incidence of small cell lung cancer accounts for about 15% - 20% [1]. The degree of malignancy is much higher than that of Non-Small Cell Lung Cancer (NSCLC). It is mainly characterized by atypical early symptoms, rapid growth, high invasiveness and early metastasis [2]. Due to the high proliferation rate, early extensive metastasis and rapidly acquired drug resistance of SCLC, the prognosis of SCLC is still poor, and the 5-year survival rate is less than 7% [3]. In about 98% of pa-

tients, the occurrence of SCLC is closely related to smoking [4], and the main mechanism may be DNA damage [5]. This damage usually occurs in the form of covalent bonds between metabolically activated electrophilic active products and DNA molecules, called "DNA adducts", while the level of DNA adducts in smokers increases [6]. Clinically, most patients are sensitive to first-line chemotherapy and can get a certain objective remission rate in the short term, but at least 80% of patients will have recurrence and metastasis [7]. Tumor drug resistance is one of the most important reasons for recurrence and metastasis. Therefore, it is necessary to choose appropriate therapeutic drugs to delay tumor progression and drug resistance. In recent years, the first-line standard treatment for small cell lung cancer is still platinum-based chemotherapy, and there is no substantial progress. However, with the increasing rise of anti-angiogenic drugs, many researchers have used them in first-line chemotherapy and achieved good results.

2. Discovery of Anti-Angiogenic Drugs

In the 1970s, Folkman first proposed the hypothesis that tumor growth depends on angiogenesis. In 1787, Dr. John Hunter described the concept of angiogenesis until 1990, Terman isolated and purified Vascular Endothelial Growth Factor 2 (VEGFR2), and angiogenesis officially entered people's sight. VEGF (Vascular Endothelial Growth Factor) and VEGFRs (Vascular Endothelial Growth Factor Receptors) were discovered and identified in 1983 and 1992, respectively. Bevacizumab, the first monoclonal antibody drug approved for inhibiting vascular growth, was marketed in the United States in 2004. Nearly 40 years ago, VEGF was identified as a key factor in promoting vascular permeability and angiogenesis. Since then, more than 12 drugs targeting the VEGF/VEGFR pathway have been approved for about 20 solid tumor types, usually in combination with other therapies. These drugs were originally designed to "starve the tumor". However, in clinical studies, it has been found that they temporarily "normalize" tumor blood vessels [8], and increase lymphocyte infiltration and T-cell activation [9]. In addition, vascular normalization can reduce the expansion of Myeloid-Derived Suppressor Cells (MDSCs) and the proliferation and differentiation of regulatory T cells (Treg) [10], eventually leading to the transformation of an immunosuppressive state into an immune-promoting state.

3. Occurrence of Angiogenesis

In the process of malignant tumor, occurrence and development, angiogenesis has become a key driving factor, which includes angiogenesis and angiogenesis. Angiogenesis is a new blood vessel formed by the differentiation of mesoderm-derived vascular cells and endothelial cells. Angiogenesis refers to the formation of new capillaries on existing blood vessels in a budding manner. It is a dynamic process and is closely regulated by the body [11]. However, it can be abnormally activated in many pathological conditions, such as tumors, inflammation, infections and

immune disorders.

SCLC tumors have the characteristics of high microvessel density and extremely rich blood supply. Therefore, VEGF is up-regulated in the serum of most SCLC patients, and is negatively correlated with chemotherapy sensitivity and survival time [12]. Therefore, anti-angiogenic therapy is of great significance to SCLC in principle. Studies have also shown that anti-angiogenic drugs have a clear effect on the treatment of small cell lung cancer [13].

4. Anti-Angiogenesis and Tumor Microenvironment

Tumor Microenvironment (TME) plays a key role in the regulation of tumor angiogenesis, which is mainly reflected in the following aspects: 1) During tumor growth, high oxygen consumption, nutrient deficiency and accumulation of metabolites in cells may produce hypoxic microenvironment that is not suitable for tumor cell growth. Hypoxia-Inducible Factor 1 (HIF-1) is a key transcription factor that mediates the response to hypoxic conditions [14]. Under normal oxygen conditions, HIF-1α is modified by Proline Hydroxylase (PHD) on specific proline residues, which triggers the binding, ubiquitination and proteasome degradation of the tumor suppressor VHL protein [15] [16]. On the contrary, the above effects do not occur under hypoxic conditions, thereby activating angiogenesis genes; 2) In the tumor microenvironment, VEGF binds to receptors (VEGFR1 - 3), activates intracellular signaling pathways, and promotes angiogenesis and vascular permeability [17]; 3) VEGFR can interact with Grab/Src/Gab1/Shb/PKCγ, activate PI3K/AKT signaling pathway and promote the proliferation of endothelial cells [18]; 4) VEGFR can promote EMT-induced (epithelial-mesenchymal transition stimulates) angiogenesis by up-regulating the expression of EMT-related genes. Magnussen believes that vascular normalization may reverse the tumor microenvironment [19].

The growth of neovascularization in TME can be directly inhibited by acting on endothelial cells in vascular growth, or indirectly inhibited by acting on tumor cells or other tumor-associated stromal cells. Therefore, angiogenesis inhibitors can be divided into direct inhibitors and indirect inhibitors [20]. Indirect angiogenesis inhibitors mainly include VEGF/VEGFR molecular targeted drugs, some traditional chemotherapeutic drugs, etc., which can affect angiogenesis by reducing the level of some vasoactive factors, reducing the expression of proto-oncogenes, affecting the microenvironment and inhibiting inflammatory response, such as bevacizumab and anlotinib. Direct angiogenesis inhibitors including endostatin are the main endogenous molecules. Endostatin can interfere with the pathway activated by VEGF and its related receptors, reduce the expression of Transforming Growth Factor-β1 (TGF-β1), and reduce the production of Tumor Necrosis Factor-α (TNF-α) to achieve the purpose of anti-angiogenesis. The most common clinical drugs such as endostar (recombinant human endostatin), some scholars have shown that [21] shows that endostar can reverse the drug resistance of tumor cells, which provides a new perspective for SCLC standard first-line treatment.

5. Several Anti-Angiogenic Agents for First-Line Treatment of SCLC

5.1. Pan-Target Vascular Endothelial Cell Inhibitors

Endostatin is an endogenous pan-target angiogenesis inhibitor. It is the first anti-angiogenic drug independently developed in China. It has achieved gratifying results in the treatment of NSCLC. It has been recommended as the first-line treatment for NSCLC by the National Comprehensive Cancer Network (NCCN) guidelines for three consecutive years. Endostar as VEGFR, hinder the binding of VEGF and endothelial cells, to inhibit vascular endothelial cell proliferation; in addition, endostar can also make VEGF mRNA and protein low expression, so that the VEGFR signal transduction blocked [22], further cut off the oxygen supply of tumor cells, inhibit tumor metastasis and spread; with the deepening of research, some scholars believe that it can also normalize blood vessels, reverse tumor microenvironment [19], and improve tumor prognosis. Endostar, as a direct anti-angiogenic drug, is the least likely to induce acquired drug resistance and can improve the tumor microenvironment, which undoubtedly brings new hope to SCLC patients.

A total of 33 patients with SCLC were enrolled in the Phase II study of endostar combined with chemotherapy by Zhou *et al.* [23]. There were 23 males (69.7%) and 10 females. The overall response rate was 69.7%. Complete Response (CR) was 3%. Partial Response (PR) was 66.7%. Stable Disease (SD) was 15.1%. The median Progression-Free Survival (PFS) was 5 months, the 6-month PFS was 33.3%, and the 1-year Overall Survival (OS) was 38.1%, indicating that Endostar plus Chemotherapy (EP) had a slight improvement in PFS and OS compared with the historical control group receiving chemotherapy alone. However, this is only a Phase II exploratory study of endostar. These results are not enough to define the effect of endostar on SCLC treatment. A domestic study [24] included 47 patients with newly diagnosed SCLC, who were randomly divided into experimental group (EP + Endostar regimen) and control group (EP regimen), 21 days as a cycle. The results showed that the ORR of control group and experimental group were 40% and 68%, PFS were 6.4 months and 5.5 months, median survival were 10.9 months and 10 months, the difference was statistically significant ($P < 0.05$). The 2-phase single-arm multi-center open label trial [25] of endostar combined with EP regimen in the treatment of small cell lung cancer is safe and effective, indicating that anti-angiogenesis plus chemotherapy first-line treatment of SCLC is a good and promising treatment model, related research remains to be further.

5.2. Monoclonal Antibody against VEGF

Bevacizumab is an IgG1 humanized monoclonal antibody against VEGF, which mainly binds to VEGFR-1 and VEGFR-2, thereby closing the angiogenesis pathway signal and inhibiting the mitosis of vascular endothelial cells to reduce neovascularization. Bevacizumab has been approved by the U. S. Food and Drug Administration for the treatment of metastatic NSCLC, colorectal cancer, breast

cancer, renal cell carcinoma and glioblastoma and many other malignant tumors.

The SALUTE experiment [26] was a placebo-controlled, double-blind, randomized, multicenter Phase II clinical trial.102 SCLC patients were randomly assigned to the experimental group (bevacizumab + carboplatin/cisplatin + etoposide) and the control group (placebo + carboplatin/cisplatin + etoposide). The primary endpoint was PFS. The results showed that the median PFS in the bevacizumab group (5.5 months) was higher than that in the placebo group (4.4 months). The OS of the two groups was similar (9.4 months in the bevacizumab group and 10.9 months in the placebo group). The total effective rate of the bevacizumab group was 58%. The placebo group was 48%. A multicenter Phase III randomized study in Italy [27] included 204 patients with ED-SCLC who had not received treatment and were randomly divided into two groups. One group was treated with EP regimen, and the other group was treated with EP + bevacizumab regimen. The primary endpoint was OS. The median OS time of the bevacizumab group and the control group was 9.8 and 8.9 months, respectively, and the PFS was also better than that of the control group (6.7 months VS 5.7 months). There was no significant difference in blood toxicity between the two groups. Both sets of studies are shown in ED-SCLC first-line treatment. The addition of bevacizumab to the EP regimen has acceptable toxicity and leads to a statistically significant improvement in PFS. However, this has not been successfully converted into an increase in OS, indicating that further research on new anti-angiogenesis drugs to replace the original drugs is imperative.

5.3. VEGFR-2 Receptor Antagonists

Apatinib is an anti-angiogenic drug independently developed in China. It competitively inhibits the binding of VEFR to VEGFR-2 by binding to VEGFR-2 and blocks downstream signal transduction, thereby exerting a strong anti-tumor effect [28].

Teng *et al.* [29] conducted a prospective Phase II clinical trial. A total of 12 patients were enrolled in this study. The primary endpoints were OS and PFS. Apatinib (250 mg/day) was used as maintenance therapy during the intermittent period of chemotherapy and after 4 - 6 cycles until disease progression or death. The median PFS was 3.7 months, the median OS was 16.3 months, the objective effective rate was 50.0%, and the disease control rate was 66.7%. Luo *et al.* [30] studied the efficacy and toxicity of apatinib combined with chemotherapy and maintenance therapy in a randomized two-phase trial. The results showed that there was no significant difference in short-term efficacy between the combined chemotherapy group (apatinib + EP/EC) and the chemotherapy group (EP/EC regimen). The long-term efficacy showed that the median PFS of the combined group and the chemotherapy group was 7.8 months and 4.9 months, respectively, and the median OS was 12.1 months and 8.2 months, respectively. In summary, apatinib has shown good efficacy and safety in prolonging OS/PFS in

SCLC patients, so it may become an effective treatment in future clinical practice.

5.4. Tyrosine Kinase Inhibitor (TKI)

1) Sunitinib is a tyrosine kinase inhibitor that inhibits VEGFR and Platelet-Derived Growth Factor Receptor (PDGFR). It also inhibits VEGF-dependent vascular endothelial cell activity to induce the degradation of existing tumor blood vessels and reduce tumor vascular exudation, eventually leading to hypoxia and necrosis of tumor cells. Sunitinib can also directly inhibit the growth of tumor cells by specifically inhibiting kit mutations.

Sunitinib has been studied as a second-line treatment for SCLC patients, but the results were mostly negative [31]. In the EORTC-08061 study [32], a total of 9 SCLC patients were included, of which 2 were untreated and 7 were relapsed after treatment. Among them, 2 patients achieved DCR at 8 weeks, and 1 patient achieved PR after 8 weeks. The overall response of the other 3 patients was SD at 6 weeks. The study was terminated early due to low accumulation. In the randomized Phase II trial of Cancer and Leukemia Group B (CALGB) 30504 [33], patients with small cell lung cancer who had no progression after 4 - 6 cycles of standard chemotherapy (cisplatin or carboplatin + etoposide) were randomized to receive sunitinib or placebo until disease progression. The primary endpoint was PFS.A total of 144 patients were enrolled. Finally, 85 patients weretreated and divided into experimental group (sunitinib n = 44) and control group (placebo n = 41). The median PFS was 2.1 months in the placebo group and 3.7 months in the sunitinib group. The median OS of the placebo group and theexperimental group were 6.9 months and 9.0 months (one-sided P = 0.16), respectively, and 3 of them achieved CR, indicating that sunitinib was safe for first-line maintenance treatment of SCLC and effectively improved PFS. OS did not significantly benefit, but there was still hope.

2) Anlotinib hydrochloride is a new type of small molecule multi-target tyrosine kinase inhibitor. It can also inhibit VEGF subtypes and their receptors (VEGFRs), Platelet-Derived Growth Factor b (PDGFRb) and stem cell factor receptor (c-Kit). Therefore, anlotinib caninhibit angiogenesis and tumor growth in many ways, and is the only approvedthird-line treatment drug for SCLC in China.

ALTER1202 clinical studies have shown that anlotinib can significantly prolong PFS and OS in patients with advanced SCLC and improve Disease Control Rate (DCR). WU [34] and other clinical studies enrolled 48 SCLC patients without chemotherapy. The subjects were randomly divided into study group (EP regimen chemotherapy) and control group (EP + anlotinib) in a 1:1 ratio. The ORR of the study group and the control group was 19% and 11%, respectively, and the DCR was 21% and 14%, respectively, indicating that the efficacy and safety of anlotinib combined with chemotherapy in the first-line treatment of SCLC were ideal. A prospective Phase II clinical study [35] showed that anlotinib was effective

in patients with recurrent SCLC, with tolerable side effects and observed longer OS and PFS.

6. Conclusion and Prospect

In recent decades, more and more anti-angiogenic drugs have been discovered and applied in clinical practice. So far, the efficacy of angiogenesis inhibitors in SCLC is relatively limited: Bevacizumab combined with first-line chemotherapy can improve PFS, but cannot prolong OS. Anlotinib has reliable clinical efficacy and safety as the first-line treatment for Chinese SCLC patients, while Endostar combined with chemotherapy requires a lot of data to support. Although anti-angiogenic drugs can further prolong the survival of patients, there are still many problems: 1) How to grasp the timing of treatment and how to maximize the efficacy of anti-angiogenic drugs; 2) How the efficacy of treatment is evaluated and measured; 3) Anti-tumor drugs have certain side effects, how to minimize this reaction, so that patients can have better compliance; 4) Drug resistance is a very serious problem, drug use to a certain extent, there must be drug resistance, then how to solve; 5) How to choose the combination regimen, single drug or combined chemotherapy, immunization or radiotherapy; 6) The mechanism of anti-angiogenic drugs for SCLC-related research is not perfect; 7) Combination of angiogenesis inhibitors with other treatments may improve their efficacy, but further studies are needed to provide a theoretical basis and relevant data support. From the current theory, anti-angiogenic drugs in the treatment of SCLC are clear and effective, and anti-angiogenic drugs in the treatment of SCLC have broad prospects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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