Case Report

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Case Report: Anlotinib For Advanced Non-Small Cell Lung Cancer That Has Not Responded To First-And Second-Line Therapy

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LZ, ZL, JL and ZY reviewed the literature and contributed to the manuscript collection and interpretation of the clinical data and material; XL was responsible for the revision of the manuscript for important intellectual content. All authors contributed to the manuscript and approved the final version to be submitted.

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1. Abstract

Primary bronchial lung cancer, referred to as lung cancer, is one of the malignant tumors with high morbidity and mortality in China and other countries in the world, accounting for 20% of the global cancer-related mortality.Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of lung cancer, and most of the patients withNSCLC are found at an advanced stage, and most patients already have locally progressive or metastatic disease at diagnosis. Genetic detection and molecular targeted therapy of NSCLC have become a hot topic in the field of cancer search and therapy in recent years, but patients with wild-type (negative) NSCLC have no benefit. Over the past two decades, molecularly targeted therapies and immunotherapies for non-small cell lung cancer (NSCLC) have significantly improved prognosis. However, the vast majority of advanced NSCLC develop resistance to current treatments and eventually progress. ERlotinib (AL3818) is a novel multi-target tyrosine kinase inhibitor (TKI) for tumor angiogenesis and proliferation signaling. Herein, reported case of advanced NSCLC Adenocarcinoma with pleural, bone, and liver metastases. After first-line treatment with carboplatin, pemetrexed, camrelizumab, and second-line treatment with albumin-paclitaxel, no remission was observed, andoral monotherapy with erlotinib was adopted, and progression-free survival was 10 months. The objective of this study was to investigate the efficacy of anlotinib in the treatment of advanced NSCLC patients after first and second-line treatment failed.

2. Keywords:
Non-small cell lung cancer, An lotinib, Multi-targeted tyrosine kinase inhibitor, Case report

3. Introduction

Lung cancer is classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) based on the size of its characteristic cells. Histologically, NSCLC comprises three subtypes: adenocarcinoma (ADC), large cell lung cancer, and squamous cell carcinoma (SCC). Irrespective of gender, NSCLC is the most prevalent form and occurs in both smokers and non-smokers, with ADCs accounting for 40% of cases[1]. Currently, NSCLC ranks among the most common malignant respiratory diseases in China. Due to its asymptomatic nature during early stages, diagnosis of NSCLC poses challenges. Typically, patients are diagnosed at an advanced stage with a high mortality rate.Although surgical resection is widely utilized in patients with all types of non-small cell lung cancer (NSCLC),approximately 70% of lung cancer patients in China often miss the optimal timing for surgical treatment due to the concealed don set of NSCLC. Consequently, chemotherapy is frequently employed for middle and advanced stages of NSCLC; however, more than 50% of patients survive less than one year, and the 5-year survival rate stands at around 18% [1]. Currently, chemotherapy serves as the primary approach for lung cancer treatment, with platinum-based chemotherapy being used as first-line the rapytoimpede tumorpro life ration and metastasis. Nevertheless, drug resistance exhibited by tumor cells remains a major cause leading to chemotherapy failure and disease progression [2]. Over the past two decades, advancements in immunology and molecular biology have enhanced outcomes for NSCLC patients; nevertheless, novel treatments are still required to significantly improve median overall survival and progression-free survival rates [3]. FDA-approved therapies target processes such as angiogenesis while also addressing the immune checkpoint role in elucidating lung cancer's pathological and physiological characteristics along with its tumor microenvironment-

related properties[1].

For patients with advanced NSCLC with positive driver genes, targeted therapy is mainly adopted, and for patients with advanced NSCLC with negative driver genes, the combination of immunotherapy and platinum-based chemotherapy is mainly adopted. However, there is currently no established standard treatment for patients with advanced NSCLC who experience disease progression following first-line and second-line therapies. Antiangiogenic Drugs Alone Or Combination with other drugs is the recommended treatment. Anti-angiogenic therapy includes macromolecular monoclonal antibodies, recombinant human endostatin, and multi-target small molecule tyrosine kinase inhibitors (TKI). The TS-β-targeted oral drug, anlotinib, has been recommended as a third-line or higher treatment option for patients with relapsed advanced NSCLC (including squamous and non-squamous carcinoma) who have negative driver gene mutation and EGFR gene sensitive mutation [4]. Additionally, the "CSCO Guidelines for the Diagnosis and Treatment of Primary Lung Cancer" (2021) state that anlotinib is a Grade I recommendation for third-line treatment of non-squamous carcinoma and stage IVnon-small cell lung cancer (Class 1 evidence). Anlotinib exerts potent inhibition on protein tyrosine kinase (PTK), competitively binding to the intracellular tyrosine kinase domain to inhibit its phosphorylation process. This block adehinders downstream signal transduction pathways ways activation in cells, thereby suppressing tumor angiogenesis [4]. Therefore, we report a patient with NSCLC who failed first - and second-line therapy with progression-free survival of 10 months after third-line lotini treatment.

4. Case Presentation

A46-year-old man presented with shortness of breath, fatigue for two weeks. Two Weeks Ago, the patient presented with dyspnea, which worsened after exercise, accompanied by weakness, and pain in the left thoracic region. Two Days prior to admission, the patient experienced dyspnea, reduced exercise tolerance, and generalized fatigue. A chest CT scan revealed moderate left-sided pleural effusion necessitating referral to our hospital for further management. Physical examination revealed decreased breath sounds in the left lower lung. The laboratory data revealed the following: Partial pressure of oxygen 68 mmHg, partial pressure of carbon dioxide 39.6 mmHg, and blood oxygen saturation 93.6%. Carcinoembryonic Antigen (CEA) (normalrange0-5ng/ml) 103.70ng/ml, Cytokeratin 19 fragment assay (Cyfra21-1) (normal range 0-3.3ng/ml) 4.41 ng/ml, Neuron-specific enolase (NSE) and squamous cell carcinoma associated antigen assay, showed no significant abnormalities. Chest computed tomography (CT) shows eda tubercle located in the left inferior lobe of the lung adjacent to the mediastinum, as well as apleuraleffusion on the left side (Figure1 C&D. The pleural effusion is pale yellow, pleuralfluidbio biochemistry: ADA 7.6, LDH 148, pleural fluid protein 50.4; Tumor markers in pleural fluid: carcinoembryonic antigen (CEA) 744.90ng/ml, cytokeratin 19 fragment assay (Cyfra21-1) 13.42 ng/ml, neuron-specific enolase (NSE) 2.24ng/ml.

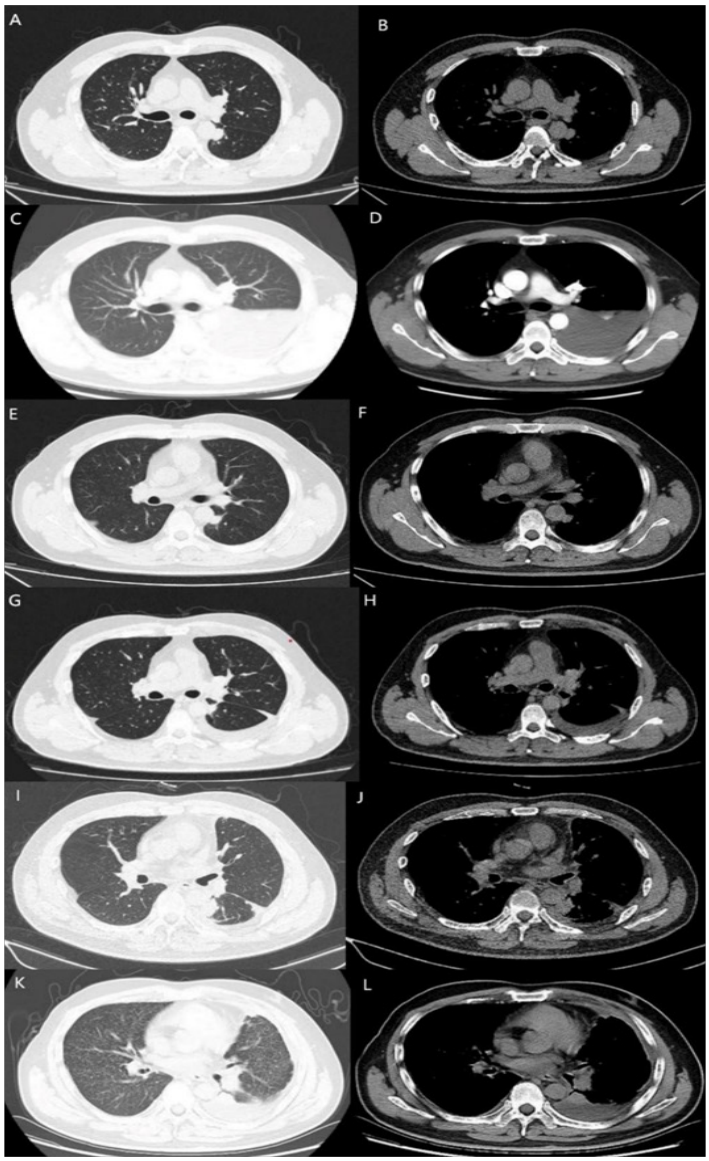

Figure1: Chestcomputed tomography A and B Proximal mediastin altubercle of in feriorlobe of lef tlung C and D Massive pleural effusion on the left E and F After 3 cycles of chemotherapy and immunotherapy G and H After 7 cycles of che mother apyandimmun other apy I and J After 10 cycles of Pemetrexedin combination with camrelizumab K and L After 8 month so for alanlotinib.

Tumor cells were detected in both the pleuralfluid and cellularmass, with immunocytochemical findings supporting adiagnos is of pulmonary adenocarcinoma. The immunohisto chemistry findings were as follows: CK20(-) CK7 (+) CR (-) Napsin-A (+) TTF-1 (+) Ki-67 (+30%) P53 missense mutation (CK5/6) (-). No mutant gene was found in pleural effusion gene detection. The initial chemotherapy regimen consisted of carboplatin at a dose of 400mg combined with pemetrexed at a dose of 800mg, administered every 21 days for a total of 6 cycles. Additionally, the PD-1 inhibitor pembrolizumab was administered intravenously

at a dosage of200mg. After 6 courses of treatment, pemetrexed and camrelizumab were used for 10 courses of treatment. Thepatient's disease was not alleviated Figure 1 I&J, and second-line treatment was selected, carboplatin 600mg combined with albumin-paclitaxel 400mg and camrelizumab 200mg for 2 courses. The patient's condition was not under control, and finally she chose third-line treatment, single drug oral anlotinib 12 mg/ before breakfast, 21 days for 1 cycle, and has been taken orally until now (Figure K&L). After 15 Cycles Oral Anlotinib, the comprehensive efficacy of pulmonary CT (Figure 1 K-L) review was a partial response. So far, the patient's PFS is10 months. The EGFR gene p. L858R mutation was detected in recent blood samples from the patient, who is currently being treated with befotertinib. We will continue to focus on the patient's condition changes in the future.

5. Discussion

NSCLC accounts for 85-90% of all lung malignancies and is the leading cause of death [5]. The 5-year survival rate for patients with advanced NSCLC is less than 20%. Currently, there are various treatment options available, including chemotherapy, radiotherapy, traditional Chinese medicine, targeted therapy, immunotherapy, antibody drug conjugate (ADC), and bispecific antibodies. At present, chemotherapy is the main method for the treatment of lung cancer, and platinum-based dual-drug chemotherapy regimen is the traditional standard regimen for the treatment of advanced NSCLC. However, the chemotherapy regimen has high side effects, and some patients have developed resistance to it. With advancement in molecular targeted therapy research, targeted therapy has gradually been incorporated into clinical practice. Compared to chemotherapy drugs, targeted therapies have fewer adverse reactions and can improve patient survival rates [6]. In the exploration of immune escape mechanisms, programmed cell death protein1 (PD-1) programmed death ligand1 (PD-L1) inhibitors and PD-1/PD-L1 inhibitors combined with che mother apy have become the treatment standard for advanced patients [7]. The PD-1 pathway enables stumor cells to evade immune surveillance by suppressing Tcell in flammatory responsean Impairing Immune System function. Carrellizumab bindsto the PD-1receptor, disrupting the transport pathway of PD-1 and exerting anti-tumor effects, thereby reducing levels of CEA and other related tumor markers. The existence of a chronic inflammatory environment in lung cancer may change or deviate from the differentiation of immune cells, resulting in the imbalance of anti-tumor activity, which is conducive to tumor escape and resistance to ICI. Therefore, PD-L1 expression is high, but a certain proportion of patients receiving ICI do not respond to treatment [8]. Pemetrexed is a TS-β targeted drug that exerts anti-cancer effects by inducing thymidylate deficiency and intracellular nucleotide poolim balance [9]. Powerful drivers of tumor migration and metastasis, such as activation of EMT, cancer cells, and other changes in biomarkers, can cause NSCLC cells to become less sensitive to pemetrexed. In addition, decreased apoptosis, small range of MCV variation, and somemi RNA expression changes may also reduce the efficacy of pemetrexed in NSCLC patients [10].

An lotinib is a multi-target small-molecule targeted drug, whose targets include c-Kit, fibroblast growth factor receptor (FGFR) 1/2/3, vascular endothelial growth factor receptor (VEGFR) 1/2/3, platelets-derived growth factor receptor (PDGFR), etc., showing broad-spectrum anti-tumor and anti-angiogenesis effects. At the same time,anlotinib has a strong inhibitory effect on protein tyrosine kinase (PTK), which can effectively inhibit the massive replication and proliferation of cancer cells, and is widely used in the treatment of ovarian cancer and lung cancer. Anlotinib can not only inhibit tumor growth, but also has anti-tumor angiogenesis effect, which can combine with adenosine triphosphate (ATP) and VEGFR. It can inhibit the phosphory lation of stem cell factor receptor kinase and VEGFR in umbilical vein endothelial cells, thus blocking the conduction of related signaling pathways and playinga role in inhibiting angiogenesis [11-13]. The Phase II trial (ALTE0302) enrolled 117 patients with advanced NSCLC who had previously received EGFR/ALK targeted therapy of two or more chemotherapy regimens and were randomly assigned to anlotinib (n=67 cases) and placebo (n=50 cases). Baseline characteristics were similar between the two groups. Compared with placebo, anlotinib significantly prolonged progression-free survival (PFS) (4.8 months vs1.2 months, $P < 0.0001$), improved overall response rate (ORR) (10%vs0%, $P < 0.0001$), and prolonged overall survival (OS) (11.2 months vs 6.3 months, P=0.2316) inpatients [14]. With The Further Development of the study, a large-scale multicenter Phase III clinical trial (ALTER0303) in China included 437 patients, and the data showed that the median OS in the anlotinib group (n=143) was 3.3 months longer than that in the placebo group (n=294) (9.6 months VS6.3 months, HR=0.68, P=0.002). Median PFS extended by 4.0 months (5.4 months VS1.4 months, HR=0.25, $P < 0.001$). The secondary endpoints such as objective response rate (ORR) (9.2%vs0.7%, $P < P < 0.001$) and disease control rate (DCR) (81.0%vs37.1%, $P < 0.001$) in the anlotinib group were also significantly better than those in the control group [15].

Duan et al. [16] included 134 patients with advanced NSCLC, and divided them into 67 cases in the control group (gemcitabine combined with cisplatin) and 67 cases in the study group. Finally, the clinical efficacy of the study group was superior to that of the control group ($P < 0.05$), and the total clinical effective rate of the study group was 73.13%, which was significantly higher than that of the control group (43.28%, $P<0.05$). Following a one-year follow-up period, boththe1-year progression-free survival rate (58.21% vs 37.31%) and 1-year overall survival rate (65.67% vs 46.27%) exhibited statistically significant differences between the study and control groups ($P < 0.05$) [16]. A meta-analysisof11 studies with a total of 2180 patients was designed to evaluate the efficacy and safety of anlotinib for third-line and above treatment in Chinese patients with advanced NSCLC. The results showed that the PFS, OS and DCR of anlotinib alone or combined with traditional treatment were improved, but the risk of treatment-related adverse events, mainly hypertension, liver dysfunction, diarrhea and hemoptysis, was significantly increased [17]. The most frequently observed non hematological adverse events included hypothyroidism, elevated triglycerides and total cholesterol levels, increased ALT levels, diarrhea, and proteinuria [18]. In General, there

are few studies on the use of anlotinib alone in patients with advanced NSCLC, mainly case reports with limited persuasion and extrapolation, and more large-sample multicenter clinical studies are expected to provide more favorable evidence support in the future. Xu et al.[19] reported that EGFR mutation rate changed from negative to positive in 33.33% of patients before and after chemotherapy. They also found that EGFR mutation status of advanced NSCLC patients may change during chemotherapy.

6. Conclusion

Patients with drivergene-negative NSCLC who have progressed after first- or second-line treatment with platinum, pemetrexed, camrelizumab, and paclitaxel protein-bound can opt for anlotinib as a third-line treatment, which can extend progression-free survival.

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