Anlotinib in combination with Envorilzumab plus Etoposide for the treatment of EX-SCLC: a case report

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Author contributions
LBS has considered and designed a treatment plan. GHL and WH performed the experiments and wrote the manuscript. WAD, SLX and SYQ proposed changes to the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abstract
Background: Small cell lung cancer (SCLC) is an aggressive malignant tumor with strong immunosuppressive effects, characterized by rapid doubling time and poor prognosis. Currently, effective therapeutic options are urgently needed for Extensive-stage small-cell lung Cancer. Case description: In the present case, a combination therapy of anlotinib, envorilzumab, and etoposide was administered to treat an 80-year-old female patient with extensive-stage SCLC accompanied by mediastinal lymph node and bone metastasis. After two cycles of treatment, the tumor lesions in the right lungs decreased from 5.04*3.44 cm to 1.65*1.42 cm. As of now, no significant mass is seen there and no serious adverse reactions in this patient. Until September 2023, she has survived for 18 months with no disease progression. Conclusions: Research shows that Alectinib, in combination with envorilzumab plus etoposide, could be an original, viable therapeutic option for the treatment option of patients with extensive-stage SCLC.

Keywords: Extensive-stage Small Cell Lung Cancer; anti-angiogenesis; PD-1 inhibitors; Combined treatment; case report

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Background

Small cell lung cancer (SCLC) belongs to high-grade neuroendocrine carcinoma, with rapid proliferation and poor prognosis [1, 2]. Currently, no effective method exists for early detection of SCLC. Low-dose CT screening can detect the growth of non-small cell lung cancers (NSCLC), yet its inclusiveness is limited by the rapid progression of tumor aggression, rendering it ill-suited for the early detection of SCLC [3-5]. NCCN Version 2.2022 recommends combining chemotherapy with immunotherapy as the first choice for extensive-stage small-cell lung cancer patients [6-8]. With the current state of medical technology, the treatment of small-cell lung cancer of extensive-stage is extremely challenging. Envolizumab has become the first domestically approved PD-L1 inhibitor in China, and also the world's first subcutaneous injection PD-L1 inhibitor. Anlotinib is a targeted anti-angiogenic drug that can be used for third-line treatment of advanced lung cancer. In this case, we described for the first time a case report of SCLC with mediastinal lymph node and bone metastasis gave an antineoplastic therapy of erlotinib in combination with evolocumab plus etoposide. After two cycles of treatment, the tumour lesions in the right lungs has decreased from 5.04*3.44 cm to 1.65*1.42 cm. The mediastinal lymph nodes have significantly reduced in size, and the pain in the right rib area has noticeably decreased, and no serious adverse reactions in this patient. Until September 2023, she has survived for 18 months. Our study demonstrates that anlotinib in combination with envolizumab plus etoposide could be a promising and original treatment option for patients with extensive-stage SCLC.

Case presentation

An 80-year-old female patient was admitted to our hospital on 28 March 2022 because of a cough, hemoptysis, and pain in the right rib area. She smoked for 50 years and has no family history of lung cancer. The weight was 53 kg, the height was 163 cm, and the body mass index (the weight in kilograms divided by the square of the height in meters) was 19.94. The patient’s body surface area was calculated to be 1.59. She had a history of ischemic cerebrovascular disease (ICVId) and myocardial ischemia for more than 5 years. Right lung breath sound weakened. Physical examination of the CT chest showed a large mass about 5.04*3.44 cm in size was palpable in the superior lobe of right lung mass (Figure 1). The pathological diagnosis is small cell carcinoma (Figure 2). The results of immunohistochemistry (IHC) staining were positive for Syn, CD56, TTF-1, and CD117, partially positive for CK, small positive CgA, and negative for p40 Ki-67 index approximately 90 %. The Fluoro-deoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) revealed many lymph nodes in the right clavicular area, right side of the inferior mediastinal paratracheal area, and pulmonary hilar of the right, and with high FDG uptake, suggesting lymph node metastasis. Furthermore, high FDG uptake was identified in the 7th rib on the right side, considering the bone metastases. The blood tests showed the following results: Laboratory findings were within the normal range, except for the Cytokeratin-19-fragment (CYFRA21) level of 7.71 ng/mL (normal range, <3.3 ng/mL), the Alpha fetal protein (AFP) level of 9.50 ng/mL (normal range, <9.0 ng/mL), and the Pro-gastrin-releasing peptide (ProGRP) level of 270,31 pg/mL (normal range, <50 ng/mL) in the serum, and the rest were normal. The above findings led to a diagnosis of SCLC with mediastinal lymph node and bone metastasis.

Figure 1 The chest contrast enhancement computed tomography on the first visit revealed. A mass lesion measuring 5.04*3.44 cm in the pulmonary hilumright of superior lobe.

Figure 2 Hematoxylin and eosin staining of transbronchial biopsy showed small cell lung cancer (×100 magnification).
Due to the patient’s advanced age, weak physical condition, long-term cardiovascular and cerebrovascular diseases, and multiple tumor metastases, we have chosen to administer oral ibrutinib instead of intravenous infusion to reduce clinical side effects based on the patient’s physical condition. We have also combined the use of Anlotinib and Enfortumab to further enhance the anti-tumor effect from the perspective of inhibiting vascular endothelial growth factors and activating the immune system. She started treatment of chemotherapy plus targeted therapy and immunotherapy with Etoposide capsule (50 mg po QD *10d), Anlotinib (12 mg po QD *14d), and Envolizumab (200 mg Ih QW *2W) in cycles of 21 days in March 2022. Zoledronic acid is administered to treat the patient’s bone metastasis. After 2 treatment cycles and periodic imaging assessment of efficacy, CT chest showed that the diameter of mass decreased from 5.04*3.44 cm to 1.65*1.42 cm. After 8 cycles of treatment, the tumor disappeared, the mediastinal lymph nodes significantly reduced in size, and the pain in the right rib area noticeably decreased, so the oral chemotherapy drugs were discontinued (Figure 3). Enfortumab, in combination with nivolumab, was continued for consolidation therapy, and the duration of treatment will be extended based on the patient’s physical condition. Figure 4 and Figure 5 illustrate the trend of ProGRP and CYFRA21-1 changes in the duration of therapy. Until March 2023, she has survived for 18 months with no disease progression (PR).

Figure 3 Progressive tumor shrinkage was seen on contrast-enhanced computed tomography scans of the chest during treatment.

Figure 4 Trend of ProGRP changes during treatment from March 2022 to March 2023.

Figure 5 Trend of CYFRA21-1 changes during treatment from March 2022 to March 2022.
SCLC makes up about 15% of lung cancer cases, and is marked by an exceptionally high proliferative rate, strong predilection for early metastasis and poor prognosis [9]. Patients with SCLC typically present with respiratory symptoms such as cough, difficulty breathing, or hemoptysis. Main treatment include surgery, platinum-based chemotherapy, radiotherapy, targeted therapy and immunotherapy. Approximately 25% of early-stage small-cell lung cancer patients can achieve long-term control of the disease through concurrent chemoradiotherapy (CRT) [9]. In the vast majority of patients with metastatic small-cell lung cancer, the efficacy of chemotherapy is temporary, with a median survival of less than 1 year [10]. In this paper, we reported an SCLC patient exhibited poor physical condition thus was not eligible for surgery, and she was treated with oral chemotherapy drugs combined with PD-1 inhibitor and anti-angiogenic drug with remarkable results.

The Serum tumor markers are important clinical indicators that can be used to evaluate the clinical treatment effect and prognosis of patients with SCLC [11]. The pro-gastrin releasing-peptide (pro-GRP) can serve as a tumor marker for early prediction of adenocarcinoma transforming into small-cell lung cancer [12]. The persistent decrease in this patient’s pro-GRP levels could be associated with tumour regression. CYFRA21-1 play a suggestive role in the metastasis occurrence and prediction of poor prognosis in lung cancer [13]. Therefore, routine and dynamic tests of pro-GRP and CYFRA21-1 levels in the serum could be helpful to evaluate prognosis of patients with SCLC.

Some chemotherapy drugs or targeted therapy drugs can enhance anti-tumor immunity by inhibiting the elimination or inactivation of suppressive immune cells [14]. Since the approval of PD/1/PD-L1 monoclonal antibodies in 2014, it has quickly become a hot research topic in cancer treatment. This treatment is offering new options, with a small subset of patients deriving prolonged benefits. Consequently, integrating CT, TT and ICI s positively has become an important and effective method. In this case report, after the administration of combined erlotinib and nivolumab, the primary cancer focus achieved near-complete regression. This suggests that the combination of anotilinib and envelolimab vedotin may have significant therapeutic effects on extensive-stage small-cell lung cancer patients, providing direction for future clinical anti-tumor treatment regimens.

In a randomized, double-blind, placebo-controlled phase 2 study (NCT03059797), Anlotinib demonstrated significant anti-tumor activity and fewer adverse reactions based on a Chinese population sample [15]. The median PFS and OS of the nilotinib group were 4.1 months and 7.3 months, which were better than 0.7 months and 4.9 months in the control group. Combining anti-angiogenic therapy with immunotherapy can enhance the effectiveness of immunotherapy and reduce immune-related adverse reactions [16]. Angiogenic factors play an immunosuppressive role in the tumor microenvironment by inhibiting antigen presentation, inducing vascular abnormalities, or enhancing the immunosuppressive activity of tumor-associated macrophages [17]. Hao et al. reported 36 patients who had received at least one chemotherapy regimen and then underwent treatment with Anlotinib plus PD-1 blockade therapy [18]. The objective response rate (ORR) of these 36 patients was 27.8%, the disease control rate (DCR) was 80.6%, and the median PFS and OS were 4.6 months and 9.3 months, respectively. The combination of Anlotinib and PD-1 blockade therapy provides new treatment possibilities for patients who have received at least one chemotherapy regimen. SCLC has a high mutation rate, suggesting that it may have immunogenicity. Combining immune checkpoint inhibitors with cytotoxic chemotherapy drugs may have a synergistic effect on the treatment of small-cell lung cancer, leading to better anti-tumor effects.

Currently, there are many PD-1/PD-L1 immune therapy methods applied in patients with SCLC, and the safety and effectiveness of this method still need further research. Luis Paz-Ares analyzed the efficacy of Durvalumab plus platinum–etoposide in 268 patients were adults with untreated ES-SCLC. The median overall survival of Durvalumab plus platinum–etoposide was 13.0 months and 10.3 months, and the patients alive at 18 months were 34% and 25%, respectively [7]. Based on data from a pivotal phase II study, KN035-CN-006, nivolumab was included as a Class I recommendation for second-line and beyond the treatment of advanced solid tumors such as MSI-H/dMMR colorectal cancer, class 2A evidence [19]. Just a mere 30s of medication administration can culminate in the subcutaneous injection of envalolimb, to some extent circumventing the adverse reactions inherent in intravenous administration. Such a mode of medication administration enhances patient compliance and mitigates the squandering of medical resources. A single-arm phase 2 study of an open-label included 130 advanced dMMR/MSI-H tumor patients from 25 hospitals in China, who received weekly subcutaneous injections of 150 mg during a 28-day treatment cycle [20]. The median follow-up was 11.5 months. The objective response rate was 42.7%, and disease control rate was 66.0%. The 12-month objective response rate was 92.2%. The median progression-free survival was 11.1 months.

**Conclusion**

Although some breakthroughs have been made in antineoplastic agents combined with recurrent small-cell lung cancer in recent years, how to formulate the most reasonable strategy needs to be addressed. Integrating CT, TT, and ICI s positively has become a major and efficient method. In this case report, we have described a standard sample of Extensive-stage SCLC treating it with a newer combined treatment approach and achieving good results. Integrating chemotherapy, PD-1 inhibitor, and anti-angiogenic drug for extensive-stage SCLC has not been previously reported; it is probable that these three treatments may have synergistic effects and provide even better outcomes.

**References**


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