Case Report

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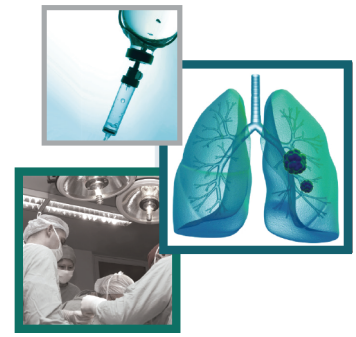
Lung Cancer Management



Achieving long-term survival in extensive-stage SCLC: a case report and mini literature review

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Managing extensive-stage SCLC (ES-SCLC) has long been challenging for clinicians and oncologists due to its aggressive nature and poor prognosis. We report a case of a 41-year-old female with ES-SCLC who survived for six years, defying the disease's typically poor prognosis. Through a heavy treatment strategy involving chemotherapy, targeted therapy, and immunotherapy, the patient experienced robust responses and avoided distant metastasis, including brain involvement. The long-term survival case in SCLC highlights the need for further research into personalized strategies and prognostic biomarkers. This case holds significant value for both clinicians and researchers as it challenges the conventional strategies for ES-SCLC and sets the stage for future evidence-based studies aimed at extending survival in SCLC.

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Despite continuous advancements and innovations in oncology that have gradually increased survival rates across various cancer types, lung cancer remains a formidable global health challenge, holding its rank as the foremost cause of cancer-related deaths [1]. SCLC, which accounts for roughly 15% of all lung cancer cases, is particularly ominous due to its marked aggressiveness, propensity for early metastasis, and bleak prognosis [2]. Statistical insights indicate that an alarming 60–70% of SCLC patients are diagnosed at the extensive-stage SCLC (ES-SCLC), characterized by the tumor's invasion into the opposite side of the chest or distant metastases [3]. The conventional chemotherapy protocols, such as the combination of etoposide and cisplatin, offer a median overall survival (OS) of 7–12 months [3,4]. Retrospective analysis of patient data from 1973 to 1991 involving 1714 subjects revealed a 5-year survival rate of 2.3% and a 10-year survival rate of 1.2% for ES-SCLC [5], underscoring that a minority of patients achieve long-term survival. These exceptional cases not only unveil the intrinsic heterogeneity of the disease but also shed light on promising avenues for future therapeutic exploration.

Pursuing long-term survival has become a shared goal among many patients and clinical oncologists. While modern medicine has yet to achieve a complete "cure" for lung cancer, the chronic management of the disease is steadily evolving into a mainstream approach. However, the treatment of ES-SCLC remains one of the most perplexing challenges in oncology. Over the past three decades, platinum-based chemotherapy has been the cornerstone of treatment, with a dismal 3-year survival rate of less than 6% [6,7]. In recent years, immunotherapies, such as programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors, have shown promise in extending the survival of ES-SCLC patients, elevating the 3-year survival rate to 17.6% [7]. Likewise, the IMpower133 study reported a 5-year survival rate of 12% with atezolizumab combined with carboplatin-etoposide [8]. These percentages represent a marked improvement and suggest a shifting paradigm in the management of ES-SCLC. Despite these advances, the absence of reliable prognostic biomarkers means that the overall therapeutic outcomes are still far from optimistic.

In this report, we present a case of ES-SCLC that achieved long-term survival following multiline systemic therapy and further synthesize the relevant literature. By delving into this rare successful case, we aim to explore new therapeutic directions for ES-SCLC, offering insights and guidance for future clinical practice.

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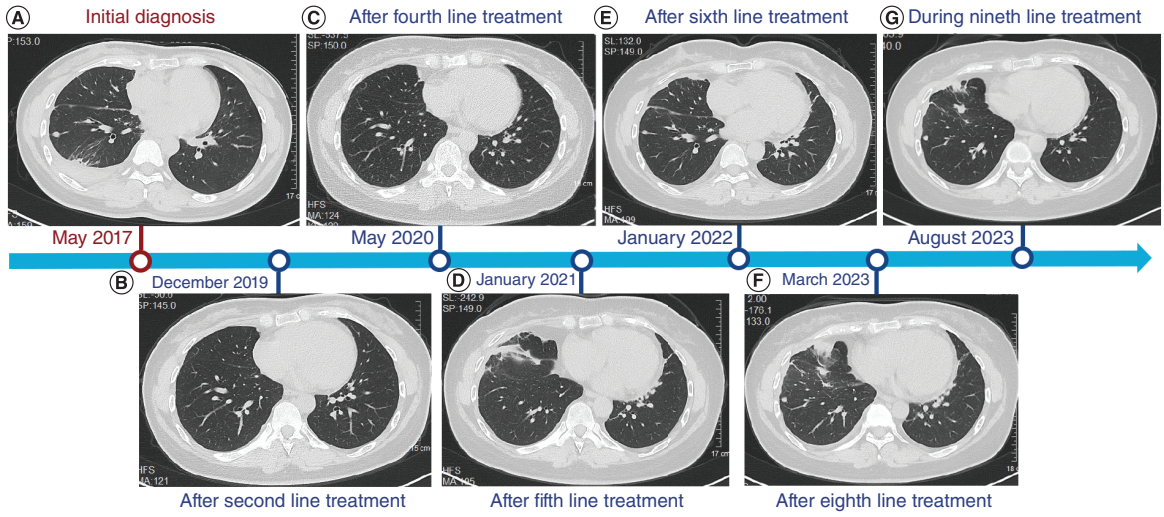

Figure 1. Change in maximum tumor size by chest CT scans.
(A) CT image at the time of initial diagnosis. **(B)** Image after second line treatment. **(C)** Image after fourth line treatment. **(D)** Image after fifth line treatment. **(E)** Image after sixth line treatment. **(F)** Image after eighth line treatment. **(G)** Image during ninth line treatment.

Case presentation

In May 2017, a 41-year-old female presented to Fuzhou Pulmonary Hospital with coughing, chest pain, and dyspnea. The patient underwent a thyroidectomy five years ago due to thyroid papillary carcinoma (T2N0M0), with subsequent long-term maintenance therapy with levothyroxine, follow-up examinations during this period revealed no particular abnormalities. She had no history of smoking or other chronic illnesses, and her physical examination was unremarkable besides thyroid deficiency. A chest CT scan displayed a 1.52 cm × 0.89 cm mass on the right pleural side, associated with pleural thickening and adhesion, and scattered satellite lesions; a minimal right pleural effusion; several mediastinal lymph nodes, the largest measuring approximately 1.01 cm × 1.78 cm; pericardial effusion; and no evident anomalies in the left thoracic cavity (Figure 1A). Fine-needle aspiration biopsy of the tumor revealed small, ill-defined cells with poor differentiation, consistent with the morphological features of small-cell carcinoma. Immunohistochemistry findings were as follows: CK(+), CD56(+), SYN(-), D2-40(-), TTF-1(-), Ki-67(90%+), CR(-), LCA(-), CK5/6(-), P63(-), confirming a diagnosis of small cell lung cancer (Figure 2). Cranial CT, comprehensive abdominal ultrasound, and a bone ECT scan showed no abnormalities. Integrating the radiological and histopathological results, the patient was diagnosed with "Extensive-stage Right Lung Small-Cell Lung Cancer T4N2M1 Stage IVa (right pleura, pericardium involved), ECOG performance status (PS) 1".

Since the definitive diagnosis, the patient has undergone nine lines of systemic treatments, with detailed treatment procedures in Figure 3 and radiological images in Figure 1. The patient initially received four lines of systemic chemotherapy: etoposide plus cisplatin (EP) regimen (1st/2nd lines, progression-free survival [PFS] of 19 and 12 months, best response both PR) and irinotecan plus cisplatin (IP regimen), along with single-agent docetaxel, with the latter two lines achieving a best response of progressive disease (PD). After the first line of treatment was completed, prophylactic cranial irradiation (PCI) was administered [9]. Due to a diminished response to systemic chemotherapy, anlotinib monotherapy was selected as a fifth-line treatment, resulting in a PFS of 7 months, with the best response of SD. In January 2021, due to disease progression, the PD-L1 inhibitor atezolizumab was introduced as a sixth-line monotherapy, achieving a partial response (PR) response, but progression occurred again after one year. The seventh line treatment consisted of gemcitabine plus PD-1 inhibitor sintilimab, but the disease progressed again after four cycles. Considering the correlation between the high vascularization of SCLC and its malignancy, targeted VEGF therapy with bevacizumab in combination with temozolomide plus lobaplatin was implemented as the eighth line treatment [10], with the best response of PR and a PFS of 10 months. However, in March 2023, the disease progressed again. Referencing the ASTRUM-005 study [11], the ninth line treatment was serplulimab combined with etoposide plus cisplatin. Two cycles of the combined treatment led to a radiological indication of PR, which has been maintained as of the writing of this article (August 2023). During treatment, we observed

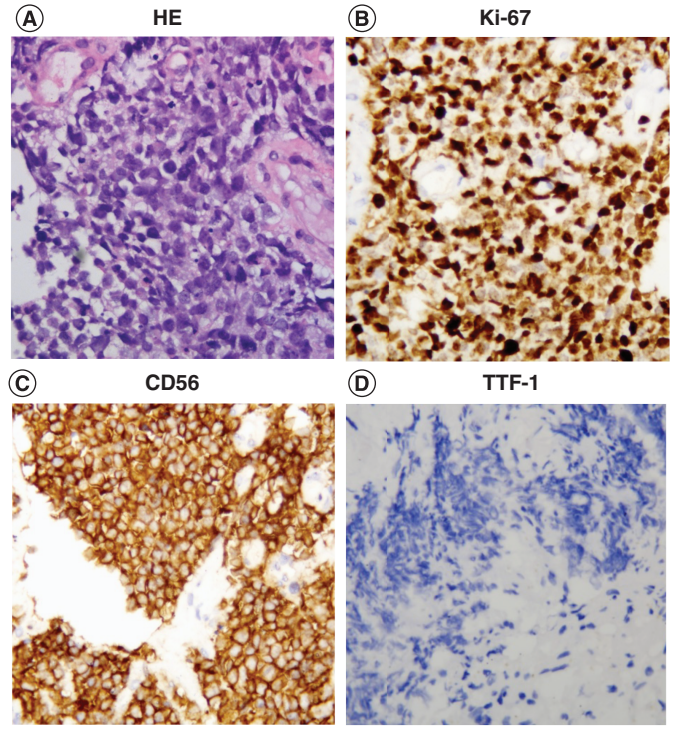

Figure 2. HE and immunohistochemistry staining of tumor.
HE: hematoxylin-eosin; TTF-1: thyroid transcription factor-1. All images were shown at 400×.

changes in the patient's peripheral blood lymphocyte subsets (Figure 4). Specifically, there was a gradual decline in CD3, CD4, and CD8 T cells starting from the third line of therapy, suggesting potential T-cell exhaustion as the treatment progressed [12]. Conversely, CD19 B cells, $CD16^{+}CD56$ NK cells, and CD45 cells showed a significant increase upon initiation of immunotherapy but declined after the seventh line of treatment, correlating well with the patient's response to therapy. Notably, there was a slight uptick in CD19 B cells and $CD16^{+}CD56$ NK cells following the ninth-line serplulimab-based immunochemotherapy, consistent with the patient's favorable response to the serplulimab regimen. All anti-tumor therapies for the patient are detailed in Table 1. The patient has survived six years since diagnosis and is currently in good general condition, with an ECOG PS score of 1.

Discussion

SCLC, originating from neuroendocrine cells, is characterized by rapid growth and high malignancy. It is generally considered closely associated with tobacco exposure, with only 2% of patients having no smoking history [13]. SCLC patients often have a dominant objective response rate (70–80%) to initial chemotherapy and radiation therapy but are highly prone to developing resistance and disease progression, leading to poor OS [13,14]. This article reports a patient with no smoking history diagnosed with ES-SCLC, who has undergone nine lines of systemic treatments and is still alive in good general condition, with a survival period exceeding six years. Notably, this patient had been diagnosed with thyroid cancer five years before the SCLC diagnosis and had undergone a thyroidectomy. Through histopathology, distant thyroid cancer recurrence was excluded, reinforcing the diagnosis of SCLC. This confirmed that the SCLC diagnosis was unrelated to the previous thyroid cancer, and that the two malignancies exhibited completely distinct tumor biological behaviors and treatment strategies [15–18]. This case is particularly notable as it features several clinical characteristics generally associated with better outcomes in ES-SCLC, such as young, female, non-smoking, and Asian ethnicity, which may have collectively contributed to the extended survival [19,20]. Additionally, research suggests that elevated lactate dehydrogenase (LDH) levels at diagnosis correlate negatively with prognosis [21]; however, in our case, the patient's LDH levels were within normal ranges (data not shown), potentially offering further explanation for the favorable prognosis observed. Even with the complex treatment background, this successful case may provide invaluable insights and recommendations for the clinical treatment of ES-SCLC, potentially contributing to the realization of chronic disease management for small cell lung cancer.

Before the US FDA approved the PD-L1 inhibitor atezolizumab in 2019, the standard treatment for ES-SCLC was the EP regimen, accompanied by PCI for patients achieving complete response (CR) or partial response

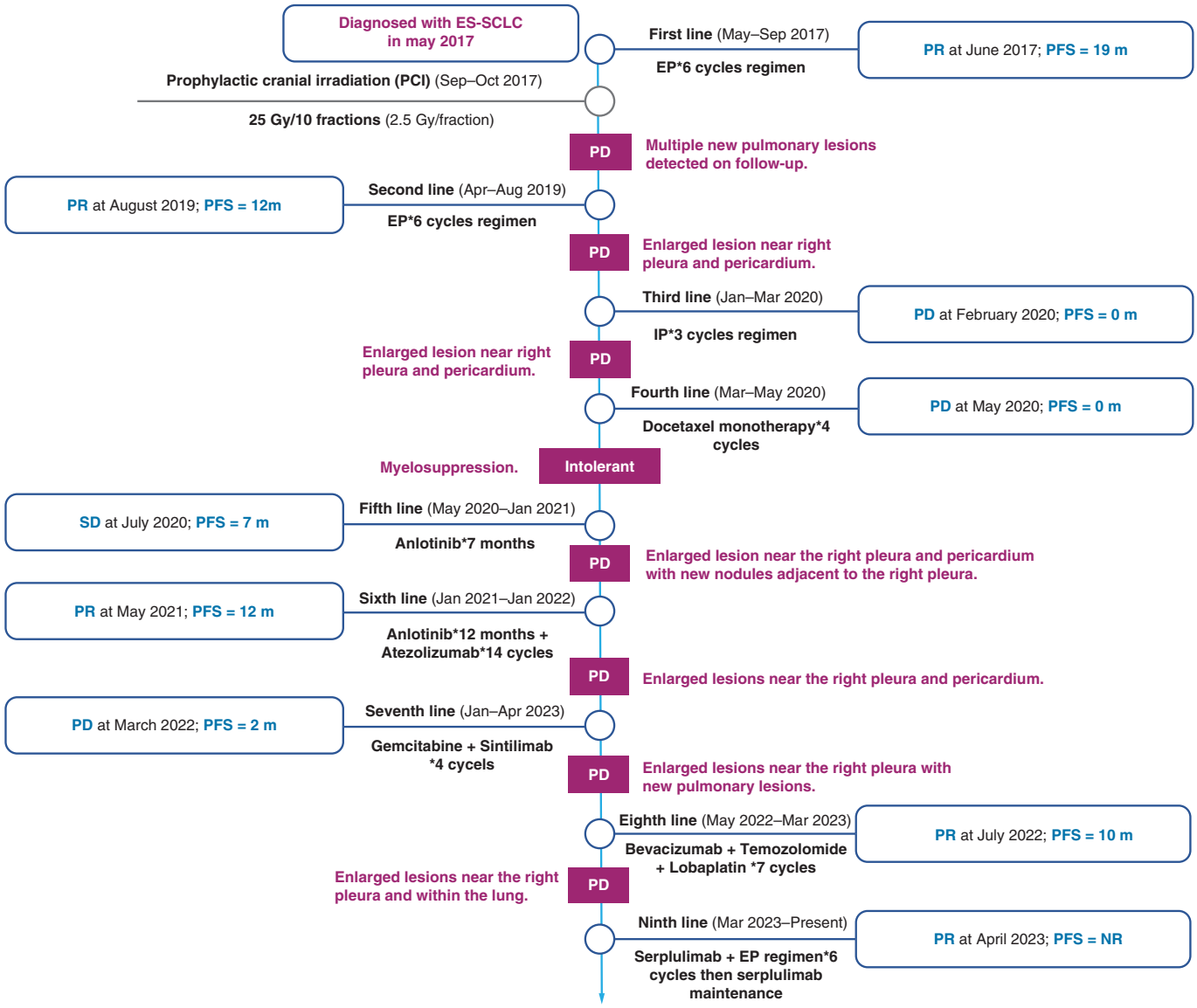

Figure 3. Treatment timeline. The efficacy evaluation was judged according to the Response Evaluation Criteria in Solid Tumours (RECIST) (Version 1.1).
EP: etoposide plus cisplatin; IP: irinotecan plus cisplatin; PR: partial response; PD: progressive disease; SD: stable disease.

(PR) [9,22]. A study has reported that patients with longer disease control times after first-line treatment tend to respond better to second-line therapy [23]. Therefore, for patients who relapse six months after completing the first-line treatment, the EP regimen is commonly re-selected for second-line therapy [24]. In this case, the patient's first and second-line treatments were the EP regimen, achieving a favorable response that significantly exceeded the historically reported 4–5 months of PFS. However, after the failure of two lines of the EP regimen, the patient's response to the IP regimen and single-agent docetaxel declined rapidly, leading to the consideration that further chemotherapy might offer limited benefit.

Angiogenesis plays a vital role in the growth and metastasis of SCLC and, compared with NSCLC, SCLC exhibits a higher degree of vascularization [10,25]. Therefore, anti-angiogenic combination therapies were employed multiple times throughout this patient's prolonged treatment. Currently, bevacizumab, a monoclonal antibody targeting VEGF, is the most extensively studied anti-angiogenic drug in ES-SCLC and is typically used in conjunction with etoposide and cisplatin [26–28]. Although two randomized studies confirmed a certain anti-tumor activity of bevacizumab in SCLC, it failed to prolong OS [29,30]. Results from many other combination therapy regimens

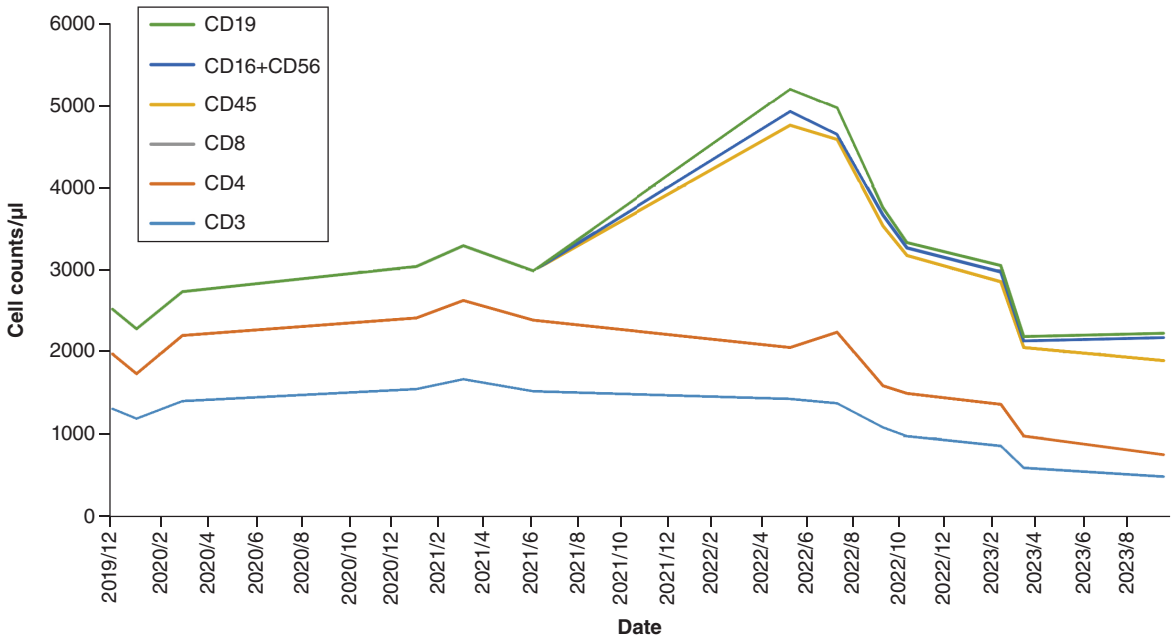

Figure 4. Dynamic changes in peripheral blood lymphocyte subpopulations during the treatment. Data were acquired using flow cytometry. CD19 represents B cells, $CD16^{+}CD56$ represents natural killer cells, CD45 represents common leukocyte antigen, CD8 represents cytotoxic T cells, CD4 represents helper T cells, and CD3 represents total T cells. The y-axis represents the number of cells/ml of blood.

Table 1. The anti-cancer treatments of this patient.

Line of therapy	Treatments
First line	EP regimen was administered intravenously in a 21-day cycle for six cycles Etoposide, a fixed dose of 100 mg on days 1–5 of each cycle Cisplatin, a fixed dose of 120 mg on day 1 of each cycle
Second line	EP regimen was administered intravenously in a 21-day cycle for six cycles Etoposide, a fixed dose of 100 mg on days 1–5 of each cycle Cisplatin, a fixed dose of 120 mg on day 1 of each cycle
Third line	IP regimen was administered intravenously in a 21-day cycle for three cycles Irinotecan, 65 mg/m^2 on days 1 and 8 of each cycle Cisplatin, 75 mg/m^2 on day 1 of each cycle
Fourth line	Docetaxel monotherapy was administered intravenously in a 21-day cycle for four cycles Docetaxel, a fixed dose of 100 mg on day 1 of each cycle
Fifth line	Anlotinib monotherapy was administered orally daily for 7 months Anlotinib, 12 mg daily for 3 months, followed by a reduction to 8 mg daily for 4 months due to foot pain
Sixth line	Anlotinib was administered orally at 8 mg daily for 12 months Atezolizumab was administered intravenously at a fixed dose of 1200 mg on day 1 of every 21-day cycle for 14 cycles
Seventh line	Gemcitabine and sintilimab were administered intravenously at 1000 mg/m^2 and 200 mg on day 1 of every 21-day cycle for four cycles, respectively
Eighth line	Bevacizumab, temozolomide, and lobaplatin were administered intravenously in a 28-day cycle for seven cycles Bevacizumab, 15 mg/kg on day 1 of each cycle Temozolomide, 150 mg/m^2 on days 1–5 of each cycle Lobaplatin, 50 mg/m^2 on day 1 of each cycle
Ninth line	Serplulimab combined with EP regimen were administered intravenously in a 21-day cycle for six cycles Serplulimab, a fixed dose of 300 mg on day 1 of each cycle Etoposide, 100 mg/m^2 on days 1–3 of each cycle Cisplatin, 75 mg/m^2 on day 1 of each cycle

have been disappointing, such as first-line treatment with endostar [31], sunitinib [32], sorafenib [33], vandetanib [34], and thalidomide [35] combined with chemotherapy, maintenance therapy with sunitinib [36], and monotherapy or combined therapy with cediranib [37], and nintedanib [38]. However, anlotinib as a third-line treatment for Chinese SCLC patients has improved both OS and PFS [39,40]. The ALTER1202 study, a randomized, double-blind,

placebo-controlled phase II trial involving 120 Chinese patients with advanced SCLC, demonstrated median PFS of 4.3 months and 0.7 months in the anlotinib and placebo groups, respectively (HR, 0.19; $p < 0.0001$), with anlotinib also prolonging OS (7.3 months vs 4.9 months) and improving the disease control rate (DCR) (71.6% vs 13.2%) [40]. Additionally, a retrospective study by Yu *et al.* suggested that the combination of anlotinib and PD-1/PD-L1 blockade demonstrates promising efficacy and safety as second-line or subsequent therapy for SCLC [41]. Furthermore, the results from the phase III ETER701 trial (NCT04234607) showed that a first-line treatment regimen combining a PD-L1 inhibitor benmelstobart (TQB2450), anlotinib, and platinum-etoposide extended the mOS to 19.32 months for patients with ES-SCLC [42]. In this case, the patient tried anlotinib monotherapy as a fifth-line treatment. Although no significant tumor reduction was observed, the disease remained stable for seven months. In the eighth line of treatment, bevacizumab combined with temozolomide and lobaplatin resulted in a PR, with a PFS of 10 months. Such outcomes emphasize the variability in individual patient responses and draw our attention to the potential existence of yet-to-be-identified prognostic biomarkers that could guide more personalized treatment strategies.

The advent of immune checkpoint inhibitors has revolutionized the standard treatment regimens for many solid tumors, including SCLC. In the IMpower133 trial, combining the PD-L1 inhibitor atezolizumab with chemotherapy significantly improved the survival rate in patients with ES-SCLC [43]. The median OS in the atezolizumab group and placebo group was 12.3 and 10.3 months, respectively (HR: 0.70; 95% CI: 0.54–0.91), and was associated with a significant improvement in PFS (HR: 0.77; 95% CI: 0.62–0.9). The IMpower133 trial marked the first demonstration of survival benefits from PD-L1 inhibitor treatment in patients with ES-SCLC. The global randomized, open-label phase III CASPIAN trial showed that first-line treatment with durvalumab plus EP significantly improved OS in patients with ES-SCLC (HR: 0.73; 95% CI: 0.59–0.91) [44]. The CAPSTONE-1 trial compared the PD-L1 inhibitor adebrelimab combined with placebo and chemotherapy as a first-line treatment for ES-SCLC, with median OS of 15.3 and 12.8 months in the adebrelimab and chemotherapy groups, respectively (HR: 0.72; 95% CI: 0.58–0.90; $p = 0.0017$) [45]. The CAPSTONE-1, IMpower133, and CASPIAN trial results support the efficacy of PD-L1 inhibitors plus chemotherapy for SCLC.

Simultaneously, serplulimab is a recombinant anti-PD-1 humanized monoclonal antibody capable of blocking the immune suppression dependent on the binding pathway of PD-1 and its ligands. This stimulates activated $CD4^+$ T cells, enhancing T-cell proliferation and the production of more IL-2 cytokines and activating the tumor immune microenvironment to kill tumor cells. The international, multicenter, phase III ASTRUM-005 trial studied the effects of serplulimab or a placebo with chemotherapy for ES-SCLC patients [11]. Combining serplulimab with chemotherapy extended the OS of ES-SCLC patients by 4.5 months and significantly reduced the risk of death (15.4 and 10.9 months, respectively; HR: 0.63; 95% CI: 0.49–0.82; $p < 0.001$). While other PD-1 inhibitors like pembrolizumab have shown efficacy against ES-SCLC, only serplulimab has been approved for this specific indication worldwide [46,47]. Although the current evidence generally recommends immunotherapy in combination with chemotherapy in a first-line setting and the limited efficacy of atezolizumab in the second-line setting [48], our case had already progressed beyond multiple lines of chemotherapy and targeted therapies. In the absence of remaining standard options, and after considering the favorable risk-benefit profile of immunotherapy, treatment with PD-1/PD-L1 inhibitors was initiated. This decision was also informed by the patient's preference and the rapidly evolving landscape of immunotherapy in treating ES-SCLC. In this case, the patient began the sixth-line treatment with the PD-L1 inhibitor-atezolizumab, achieving a PR with a surprising PFS of 12 months. Subsequent treatment with sintilimab (PD-1 inhibitor) combined with gemcitabine chemotherapy was ineffective. However, serplulimab treatment displayed encouraging anti-tumor activity, reducing the patient's tumor size and maintaining a PR to the present. Such evidence underscores the importance of individualized treatment responses, especially when there are no contraindications to therapy.

The patient demonstrated textbook-level favorable responses to most systemic treatments in this case. Within the six years since the diagnosis of SCLC, no distant metastases were observed except in the pericardium and pleura. Even brain metastases, common in small cell lung cancer patients, were not detected in this patient, possibly due to PCI following first-line treatment [49]. Some studies have reported on the tumor microenvironment of long-term survivors of SCLC, suggesting that tumor-infiltrating lymphocytes (TILs) are a promising prognostic marker for SCLC patients [50]. In other words, long-term survivors have an increase in TILs that exert tumor-suppressive effects and a decrease in suppressive cells and factors, along with a lower ratio of inhibitory immune cells to CD3-positive lymphocytes [51] and an increase in $CD45RO^+$ TILs in patients with brain metastases [52]. Research has also shown that the ratio of effector T cells to regulatory T cells is higher in long-term survivors and lower

in recurrent patients [53]. During the long-term follow-up of our patient, it was found that the number of CD3 and CD45 positive cells in the patient continued to decrease, but the cytokine levels were normal, including IL-2, IL-4, IL-8, IL-10, and IL-17a (data not shown). This further validates the possibility of the above conclusions. Of course, it cannot be ruled out that the patient will have lymphocyte depletion in the long-term anti-tumor process. Exploratory analyses from the IMpower133 study demonstrated a trend toward improved outcomes in patients whose tumor immune microenvironments were characterized by inflammatory cells, thereby delineating an 'inflamed' SCLC subtype (SCLC-I) [54]. Moreover, Rudin *et al.* conducted a *post hoc* analysis based on the CheckMate 032 study aimed at identifying unique biomarkers that could predict the clinical benefits of ICI in SCLC patients, seeking to uncover biomarkers associated with increased longevity post-immunotherapy [55]. Their analysis concluded that while SCLC subtypes (SCLC-A, -N, -P, and -Y) did not relate to survival outcomes, tumor antigen processing and presentation were significantly correlated with patient prognosis. Unfortunately, this patient did not undergo additional examinations to avoid overtreatment and reduce patient burden. Therefore, it is not possible to confirm whether the tumor immune microenvironment was involved in this process, nor was new insight obtained to explore the reasons for the patient's prolonged PFS during complex treatment.

While the study has its limitations, such as being unable to fully elucidate the underlying mechanisms for the patient's exceptional long-term survival or identify definitive prognostic markers, it nonetheless serves as a seminal case in the evolving landscape of ES-SCLC treatment. This case not only demonstrates the potential for achieving long-term survival in ES-SCLC through multifaceted therapeutic strategies but also challenges conventional therapeutic paradigms, warranting further investigation from both clinical and research perspectives. As we advance in our understanding of small cell lung cancer, this case sets a precedent and provides an invaluable reference for future studies aiming to improve long-term survival rates among this patient population.

Author contributions

Y Mao was responsible for the study concept and design. M Huang and J Liu contributed to data collection and clinical insights. The manuscript was drafted by Y Mao. All authors have critically reviewed and approved the final version of the manuscript.

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Competing interests disclosure

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Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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•• **Sixty percent to 70% of patients with SCLC have extensive-stage disease at the time of diagnosis. With chemotherapy, ORR ranges from 40% to 70%, and the mOS ranges from 7 to 12 months, with a 2-year survival of <5% and a 5-year survival rate of <2%.**

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• **The median overall survival was significantly longer in the serplulimab group (15.4 months [95% CI: 13.3 months-not evaluable]) than in the placebo group (10.9 months [95% CI: 10.0–14.3 months]) (hazard ratio, 0.63 [95% CI: 0.49–0.82]; P < 0.001).**

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