Six-year survival after oral temozolomide maintenance therapy in limited-stage small cell lung cancer: A case report

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Abstract. Small cell lung cancer (SCLC) accounts for 13-17% of lung cancer cases and is characterized by poor differentiation, high malignancy and a propensity for recurrence and metastasis. Limited-stage SCLC (LS-SCLC) typically has a better prognosis than extensive-stage SCLC due to its localized nature. However, even with standard concurrent chemoradiotherapy, the median overall survival (OS) for LS-SCLC is only 30 months, with a 5-year survival rate of merely 29-34%. The present study reported the case a patient with LS-SCLC who received oral temozolomide (TMZ) maintenance therapy, achieving an impressive 6-year survival without disease progression or significant side effects. Factors contributing to this outcome include the cytotoxic effects of TMZ and its potential preventive and therapeutic roles in managing brain metastases. In addition, durvalumab has been proven to prolong OS as maintenance therapy after first-line chemoradiotherapy in patients with LS-SCLC. In the future, maintenance therapy for SCLC should explore combination drug strategies, as integrating TMZ or poly(ADP-ribose) polymerase inhibitors with immunotherapy may enhance patient survival.

Introduction

Lung cancer was the leading cause of cancer-related death worldwide in 2022, accounting for 18.7% of all cancer fatalities (1). Small-cell lung cancer (SCLC) accounts for 13-17% of all lung cancer cases. Despite a high initial chemotherapy response rate (60-67%) (2), SCLC often recurs rapidly and develops resistance to subsequent treatments, leading to a poor prognosis. Patients with limited-stage SCLC (LS-SCLC) typically have a better prognosis than those with extensive-stage SCLC (ES-SCLC) due to the more localized nature of the disease. However, even with standard concurrent chemoradiotherapy, the median overall survival (OS) for patients with LS-SCLC remains 25-30 months, with a 5-year survival rate of merely 31-34% (3). Maintenance therapy has emerged as a critical strategy for extending survival following first-line treatment. The ADRIATIC study showed that durvalumab maintenance therapy significantly improved OS in patients with LS-SCLC after concurrent chemoradiotherapy [55.9 vs. 33.4 months, hazard ratio (HR)=0.73] (4), underscoring its potential as a new standard of care. The current study presented the case of a patient who received oral temozolomide (TMZ) as maintenance therapy after first-line treatment, achieving an exceptional survival of 6 years without disease recurrence, which highlights the potential of TMZ as a maintenance therapy for LS-SCLC.

Case report

A 57-year-old woman, 165 cm tall and weighing 70 kg, in February 2019 developed various symptoms, including cough, expectoration, chest tightness and fatigue. The symptoms were relieved after self-administered oral antibiotics but recurred in March. The patient had no history of smoking and no family history of cancer. The patient had been previously healthy, without any chronic conditions such as hypertension, diabetes or any history of cardiac, hepatic or renal insufficiency. A chest computed tomography (CT) scan in March 2019 at the Affiliated Hospital of Hebei University of Engineering (Handan, China) revealed a malignant mass in the left hilum (3.0x4.5 cm), along with several enlarged lymph nodes in the regions of group 4L lower paratracheal, group 10 left hilar and group 8 paraesophageal. The enlarged nodes exhibited partial fusion, obscuring precise quantification (the original CT films were inaccessible due to the passage of time. Only

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the CT report and images captured by a mobile phone were retained and submitted as supplementary material) (Fig. 1A; Fig. S1). On March 2019, a bronchoscopy biopsy confirmed SCLC with aspergillus proliferation. Immunohistochemical analysis showed weak cytokeratin positivity, thyroid transcription factor 1 (TTF-1) and cluster of differentiation 56 (CD56) positivity and partial weak positivity for chromogranin A and synaptophysin, while tumor protein p63 (P63), P40 and lithodeoxycholic acid were negative, with a Ki-67 index of 60% (Fig. 2). The clinical staging was $cT_2N_2M_0$, stage IIIA.

The specimens were fixed in 10% neutral buffered formalin at room temperature for 24 to 48 h and embedded in paraffin. The tissue blocks were sectioned into slices of 4 or 5 μm in thickness. H&E staining was performed by staining with hematoxylin for 10 min and eosin for 5 min at room temperature. Elastic fiber staining was conducted using the iron hematoxylin method, also at room temperature (5). A mixture of 5% ethanol hematoxylin, 10% ferric chloride and Verhoeff's iodine solution in a ratio of 20:8:8 drops was prepared and applied to the tissue sections. Counterstaining with eosin was performed for 2 min. Immunohistochemistry was carried out by EnVision system. Antigen retrieval was performed by high pressure treatment at 120˚C for 5 min, followed by blocking endogenous enzyme activity with 3% H_2O_2 for 10 min. The primary antibodies included ALK (clone D5F3; cat. no. K18082; Roche Diagnostics) and TTF-1 (clone SPT24; cat. no. 18092706; OriGene Technologies, Inc.), both diluted at 1:200 and incubated at room temperature for 1 h. The secondary antibody was a horseradish peroxidase labeled polymer (1:2,000 dilution; cat. no. M00855-M01010; Roche Diagnostics), incubated at 37˚C for 30 min. Next, DAB was used for color development at room temperature for 10 min, and hematoxylin was used for counterstaining at room temperature for 10 min. All sections were examined under a light microscope.

The patient was diagnosed with LS-SCLC with mediastinal lymph node metastasis and a concomitant fungal infection. Treatment commenced in March 2019, utilizing a regimen of etoposide and a platinum-based drug for eight cycles (Fig. 1). After two cycles of etoposide (120 mg on days 1-3) and cisplatin (85 mg on day 1), the patient exhibited a partial response (Fig. 1B) but suffered severe nausea and vomiting, necessitating a switch from cisplatin to lobaplatin. The third cycle was completed with etoposide (120 mg on days 1-3) and lobaplatin (40 mg on day 1), alongside 28 sessions of radiotherapy (56 Gy; 2.0 Gy daily, from May to July 2019). The reason for initiating concurrent radiotherapy after the third cycle was that the patient had a combined aspergillus infection. Administering radiotherapy during the first two cycles carried the risk of further compromising the immune system and exacerbating the pulmonary infection. The patient developed grade II myelosuppression, with a white blood cell count of $2.82x10^9$/l (normal ranges, 3.5-9.5x10^9/l), prompting a dosage reduction of etoposide to 100 mg in cycles 4-6 to reduce the risk further of myelosuppression. In cycle 4, during radiotherapy, the patient developed grade III myelosuppression, with a white blood cell count of $1.28x10^9$/l and a neutrophil count of $0.53x10^9$/l (normal range, 1.8-6.3x10^9/l). The National Comprehensive Cancer Network guidelines recommend 4-6 cycles of chemotherapy for SCLC (6). However, clinical practice should be adjusted based on the patient's personal preferences and physical tolerance: Dose reduction or reduced cycles may be considered when chemotherapy is intolerable, while extended cycles could be an option for patients demonstrating adequate tolerance who desire enhanced therapeutic efficacy. Considering the patient's desire for better therapeutic outcomes and physical tolerance, an additional two cycles of chemotherapy were initiated, with treatment intervals extended to 28 days to minimize side effects. Cycles 7 and 8 were completed with etoposide (100 mg on days 1-4) and lobaplatin (75 mg on day 2), resulting in grade III myelosuppression, with a white blood cell count of $1.4x10^9$/l, neutrophil count of $0.37x10^9$/l and platelet count of $27x10^9$/l (normal range, 125-350x10^9/l). After first-line treatment, the patient did not choose prophylactic cranial irradiation due to the risk of cognitive decline and instead opted for regular brain MRI checks to detect potential brain metastases early. In October 2019, following the completion of first-line therapy, the patient commenced oral TMZ maintenance therapy at a dosage of 250 mg, administered on days 1-5 of each 28-day cycle. After 3 cycles of maintenance therapy, a chest CT scan revealed stable disease (Fig. 1C). The patient then continued with regular follow-up assessments, including brain MRI, chest and abdomen CT, and whole-body bone scintigraphy, with the frequency of follow-ups gradually extended from 3 to 6 months, and eventually to once a year. The last follow-up was conducted in February 2025, with the chest CT scan showing a stable lesion (Fig. 1D). The patient has now survived for 6 years since the definitive diagnosis, maintaining a stable condition without significant adverse reactions.

Discussion

This case report highlights the long-term survival of a patient with LS-SCLC receiving oral TMZ as maintenance therapy following first-line treatment. Remarkably, the patient has survived for 6 years without disease recurrence, a rare achievement in SCLC cases. This prolonged survival prompts critical inquiries about the benefits of maintenance therapy and the potential underlying mechanisms that may contribute to this unique outcome.

A 2005 meta-analysis found that maintenance or consolidation therapy increased the 1-year survival rate by 9% (from 30 to 39%), the 2-year survival rate by 4% (from 10 to 14%), the 1-year progression-free survival (PFS) rate by 10% (from 13 to 23%) and the 2-year PFS rate by 3% (from 10 to 13%) (7). In addition, a 2013 meta-analysis indicated that maintenance chemotherapy improved PFS [HR=0.72, 95% confidence interval (CI) 0.58-0.89, P=0.003] in ES-SCLC but did not significantly affect OS (8). Regarding maintenance strategies, conversion strategies, which utilize a regimen different from the initial treatment, showed a trend toward better PFS and OS but without statistical significance. By contrast, continuous strategies that use the same regimen as the initial treatment had no significant impact on OS and even worsened PFS (HR=1.27, 95% CI 1.04-1.54). These findings underscore the importance of maintenance therapy in improving survival outcomes for patients with ES-SCLC, although the optimal strategy is under investigation.

The Concurrent ONce-daily VErsus twice-daily RadioTherapy (CONVERT) trial found that ~30% of patients

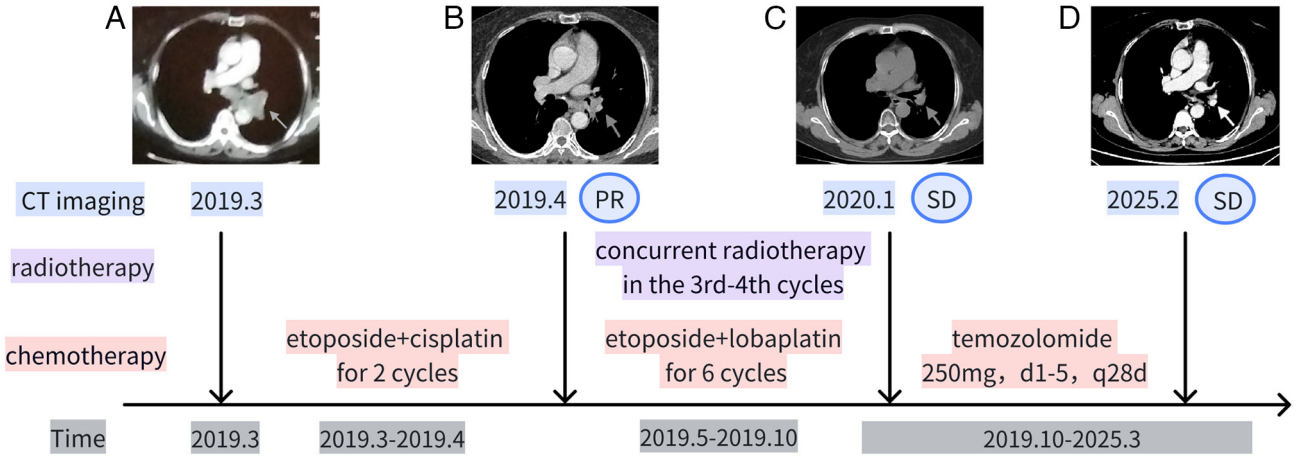

Figure 1. Changes in the treatment and chest CT of the patient. First-line treatment: Etoposide + platinum-based drugs (cisplatin for 2 cycles, lobaplatin for 6 cycles), totaling 8 cycles. Synchronized radiotherapy commenced after the completion of the 3rd chemotherapy cycle and was concluded before the initiation of the 5th chemotherapy cycle. Maintenance therapy: Oral temozolomide, 250 mg/day, days 1-5, every 28 days. Outcome: As of March 2025, the OS of the patient was 72 months. Chest CT imaging: (A) Pre-chemotherapy imaging in March 2019, with the arrow indicating the lesion at the left hilum. (B) After completion of 2 cycles of chemotherapy in April 2019, the lesion at the left hilum (indicated by the arrow) showed PR compared to pre-treatment. (C) After completion of 3 cycles of maintenance therapy in January 2020, the lesion at the left hilum (indicated by the arrow) showed SD. (D) The most recent contrast-enhanced CT imaging in February 2025 shows that the lesion at the left hilum (indicated by the arrow) is in a state of SD. PR, partial response; SD, stable disease; OS, overall survival.

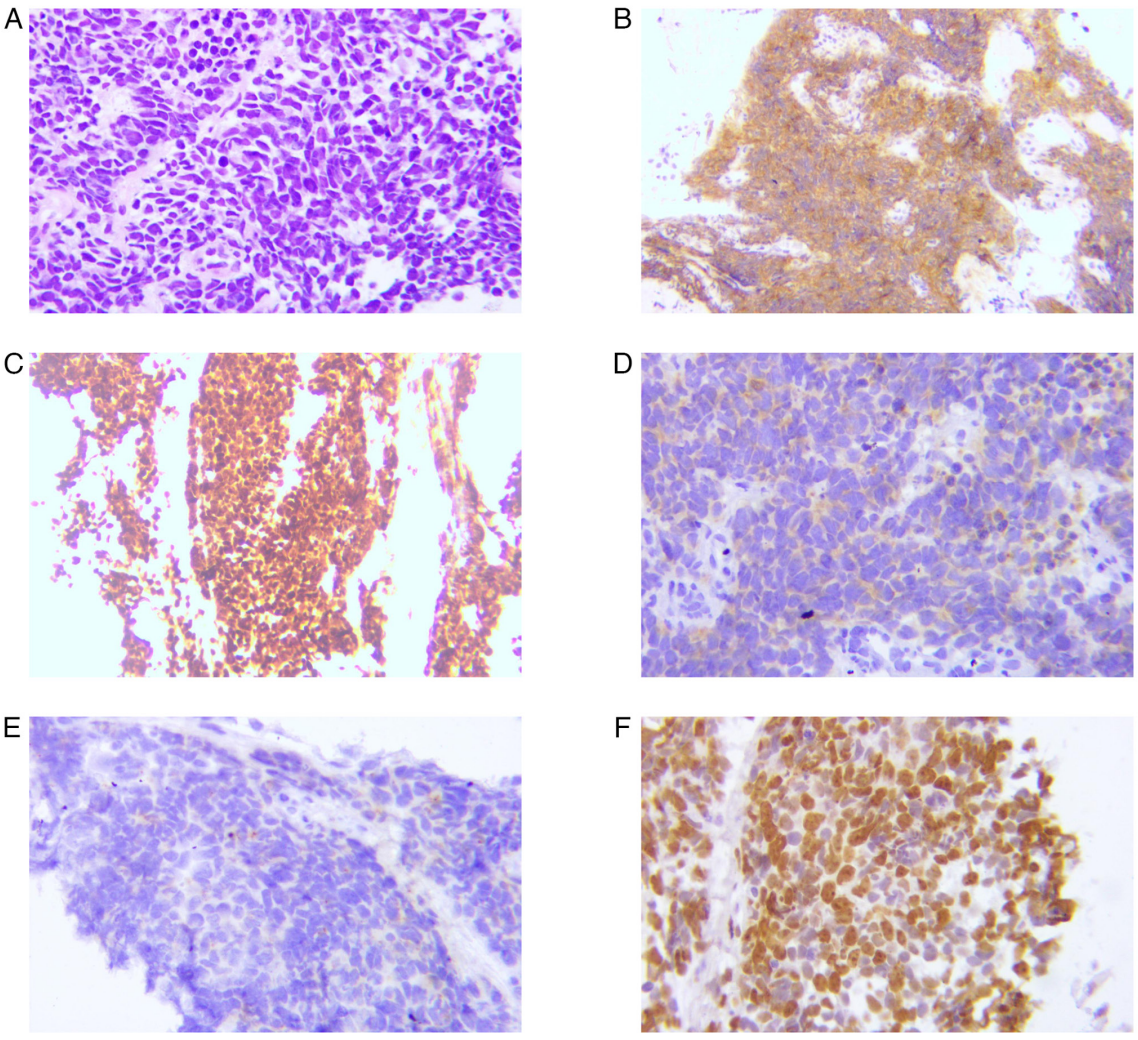

Figure 2. Histopathological images. (A) Histological specimen of the small-cell lung cancer: Small tumor cells are densely packed, with scant cytoplasm, finely granular nuclear chromatin and absence of nucleoli (magnification, x400). (B) CD56 positivity (magnification, x400 magnification). (C) TTF-1 positivity (magnification, x400 magnification). (D) Synaptophysin partial weak positivity (magnification, x400 magnification). (E) Chromogranin A partial weak positivity (magnification, x400). (F) Ki67 index, ~60% (magnification, x400).

with LS-SCLC developed brain metastasis after concurrent chemoradiotherapy, significantly impacting mortality rates in this population (3). By contrast, the patient of the present study survived for 6 years without developing brain metastasis, likely due to TMZ's ability to cross the blood-brain barrier. While there is no direct evidence supporting TMZ as a preventive therapy for brain metastases in SCLC, several studies have explored its efficacy in treating existing brain metastases. One case study reported on a patient with ES-SCLC who achieved complete remission (CR) following whole-brain radiotherapy (WBRT) but developed multiple new brain metastases after 15 months. After treatment with TMZ, the patient attained CR after 6 months with good tolerance (9). Another study involving two patients with SCLC receiving a combination of TMZ and etoposide showed stabilization of central nervous system lesions, both radiologically and clinically, for 12 and 29 weeks, respectively (10). A Phase II study found that TMZ alone controlled the brain disease in 41% of patients with recurrent brain metastasis (11).

The prolonged use of oral TMZ raises concerns about potential adverse effects. Nausea and vomiting, the most common non-hematologic toxicities, affect ~50% of patients, although they are typically mild to moderate in severity (12). Thrombocytopenia and neutropenia are considered dose-limiting toxicities. While TMZ at 150 mg/m^2/day is generally well tolerated in patients with solid tumors, higher doses can lead to severe hematologic toxicity (13). In the present case, the patient took 250 mg/day, which was calculated based on the standard dose of 150 mg/m^2/day (calculation: 165 cm, 70 kg, body surface area of 1.75 m^2, resulting in 1.75 m^2 x 150 mg/m^2/day=262.5 mg/day). The patient's complete blood count, liver and kidney function, as well as symptom changes are being regularly monitored to detect potential adverse reactions. Supportive treatment is provided based on any discomfort the patient experiences. After 65 months of TMZ therapy (as of March 2025), the patient did not experience any grade II or higher myelosuppression. It is noteworthy that challenges arose in obtaining all relevant test results due to the patient consulting at external hospitals. The findings are based on follow-up examinations from the China-Japan Friendship Hospital. In addition, the patient did not experience significant vomiting after the administration of ondansetron to manage nausea, suggesting that long-term oral TMZ is safe and well-tolerated. However, rare toxicities such as aplastic anemia, cholestatic hepatitis, lymphopenia-induced opportunistic infections, myelodysplastic syndromes and leukemia have been reported during TMZ treatment (14). Although these adverse effects are uncommon, their severity and specificity require careful clinical monitoring. Regular assessments of blood counts, as well as liver and kidney function, are crucial during the long-term use of TMZ.

Immunotherapy shows potential as a maintenance treatment for SCLC. Studies suggest that certain medications may improve the effectiveness of immunotherapy, indicating that combination therapies could be a valuable avenue for future research in SCLC maintenance therapies.

A retrospective study found that combining TMZ with programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors resulted in an ORR of 26.19% and a DCR of 64.29% in patients with NSCLC brain metastasis (15). Furthermore, a Phase II trial showed that TMZ combined with nivolumab for treating recurrent or refractory SCLC and advanced neuroendocrine tumors achieved an ORR of 30%, a median PFS of 2.4 months and a median OS of 6.3 months; the median OS was 9 months for patients with brain metastasis (16). The NCT0491938 trial is currently exploring the combination of TMZ with atezolizumab as maintenance therapy for relapsed or refractory ES-SCLC (17).

SCLC cells can repair DNA damage, particularly through the poly(ADP-ribose) polymerase (PARP) pathway. PARP inhibitors can block this repair process, thereby enhancing the cytotoxic effects of TMZ. Research has shown that combining TMZ with talazoparib is more effective than monotherapy in patient-derived xenograft models with high Schlafen family member 11 expression (18). A randomized, double-blinded Phase II trial found that the TMZ and veliparib combination significantly increased the ORR (39 vs. 14%) in patients with relapsed or refractory ES-SCLC; however, no significant differences were found in PFS and OS (19).

PARP inhibitors may enhance the tumor microenvironment, boosting the effectiveness of immunotherapy. Studies suggest that PARP inhibitors may exert immune-modulatory effects by activating the cyclic GMP-AMP synthase /stimulator of interferon genes (STING) pathway, thereby transforming 'cold' tumors into 'hot' tumors and enhancing the anti-tumor activity of immunotherapy in Excision repair cross-complementation group 1-deficient NSCLC (20). In addition, DNA damage response inhibitors such as prexasertib and olaparib can increase PD-L1 expression in SCLC cell lines, promoting CD8+ T-cell infiltration into tumors and anti-tumor immunity through the activation of the STING/TANK-binding kinase 1/interferon regulatory factor 3 pathway, which leads to the production of type I interferons (e.g., interferon-β) and chemokines (e.g., C-X-C motif chemokine ligand 10 and C-C motif chemokine ligand 5) (21). Lurbinectedin has been shown to reduce tumor-associated macrophages and modulate the inflammatory tumor microenvironment (22). Ongoing clinical trials, such as NCT03830918, are investigating the combination of TMZ, niraparib and atezolizumab as maintenance therapy for SCLC, with PFS as the primary endpoint.

In conclusion, this case report details a patient with LS-SCLC who survived for 6 years without disease recurrence after receiving oral TMZ as maintenance therapy. Immunotherapy has emerged as a standard maintenance treatment for SCLC. Future research should explore the combination of immunotherapy with TMZ or PARP inhibitors to enhance treatment outcomes for patients with SCLC.

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Availability of data and materials

All data generated in the present study are included in the figures/tables of this article.

Authors' contributions

DW and HC designed the study. AW, XZ and CW were responsible for patient management and interpreted the patient data. DW, TX, YG and YX acquired and analyzed the data. DW and YX drafted the manuscript. HC and CW revised the manuscript and checked and confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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