Case Report

Intracranial complete response to toripalimab and anlotinib in a patient with recurrent brain metastases of small cell lung cancer after failure of second-line maintenance therapy: a case report

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Background: Approximately 10–25% of patients with small cell lung cancer (SCLC) have brain metastases at the time of diagnosis. Radiotherapy is a common treatment for brain metastases, but the relapse rates are high. Accumulating evidence suggests that immunotherapy may have a better therapeutic effect for brain metastases. Here, we reported a patient with limited-stage SCLC and relapsed brain metastases who achieved sustained intracranial complete response (CR) to programmed cell death-1 (PD-1) inhibitor toripalimab and multikinase inhibitor anlotinib.

Case Description: A 59-year-old female patient developed brain metastases after initial treatment for limited stage SCLC. CR of brain lesions was achieved after intensity-modulated radiation therapy followed by chemotherapy with irinotecan plus lobaplatin and concurrent anlotinib. PD-1 inhibitor sintilimab combined with anlotinib were given as maintenance therapy. Small and asymptomatic brain lesions relapsed 2.5 months after achieving CR. Another three cycles of sintilimab combined with anlotinib failed to control the relapsed brain lesions. Following two cycles of another PD-1 inhibitor toripalimab combined with anlotinib, the relapsed brain metastases disappeared. Then the patient received another seven cycles of this regimen with sustained CR, and no serious adverse reactions occurred. Interestingly, the primary lung tumor achieved sustained CR from the end of initial treatment to the last follow-up.

Conclusions: This case suggests that toripalimab in combination with anlotinib may be a promising treatment option for patients with brain metastases from SCLC.

Keywords: Small cell lung cancer (SCLC); toripalimab; brain metastases; case report

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Introduction

Small cell lung cancer (SCLC), which accounts for approximately 13–15% of lung cancers, is a highly aggressive neuroendocrine tumor characterized by rapid growth (1). SCLC can be divided into limited and extensive stages. Chemotherapy and radiotherapy are the main treatment methods for SCLC. However, early recurrence occurred in majority of patients within the first year of treatment, leading to poor prognosis. Approximately 10–25% of patients with SCLC have symptomatic or asymptomatic brain metastases at initial diagnosis, and more than 50% will develop brain metastases during the disease course (2). Radiotherapy is commonly used for the treatment of brain metastases from SCLC, with a local control rate up to 93% (3). However, the survival was still dismal, with a 12-month overall survival (OS) rate of 39% (3). In recent years, immune checkpoint inhibitors

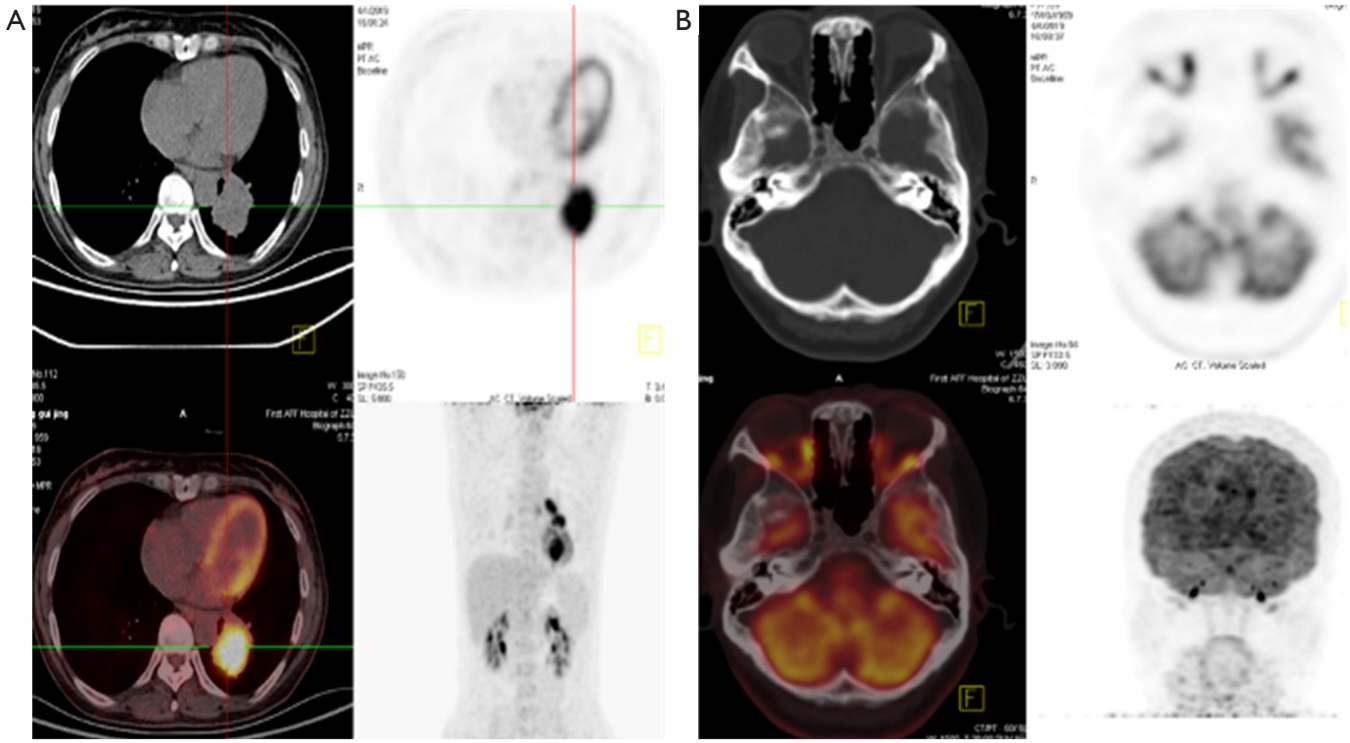

Figure 1 Positron emission tomography-computed tomography of chest (A) and brain (B) when the patient was diagnosed.

(ICIs) have changed the treatment paradigm for solid tumors (4). The IMpower133 and CASPIAN studies showed that ICIs combined with chemotherapy significantly prolonged OS in patients with extensive-stage SCLC compared with chemotherapy alone as first-line treatment (5,6). However, the therapeutic effect of antibody treatments like ICIs on brain metastases is limited because of the blood-brain barrier. Therefore, new treatment modalities need to be explored for SCLC patients with brain metastases.

Here, we reported a patient with multiline-treated SCLC whose primary lung tumor achieved sustained complete response (CR) throughout the treatment period, but with relapsed brain metastases. After failure of programmed cell death-1 (PD-1) inhibitor sintilimab combined with multikinase inhibitor anlotinib as second-line maintenance therapy for brain metastases, the patient was treated with another PD-1 inhibitor toripalimab in combination with anlotinib, and sustained CR for brain metastases was achieved. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-666/rc).

Case presentation

A 59-year-old female patient visited our hospital because of "cough with left back pain" in March 2019. Positron emission tomography-computed tomography (PET-CT) revealed a metabolically active soft tissue mass in the left lower lobe of lung, with a size of approximately 3.3 cm × 3.6 cm (*Figure 1A*,*1B*). Multiple lymphadenopathies in seven mediastinal regions and the left hilum were metabolically active, with size of approximately 1.7–2.1 cm for the larger ones, indicating metastases. No evidence of brain metastases was found. Electronic bronchoscopic biopsy results suggested SCLC. The patient was diagnosed with limited-stage small cell carcinoma of the left lower lung.

Initial chemotherapy with six cycles of etoposide and nedaplatin was given. The patient achieved CR according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by chest computed tomography (CT) and cranial enhanced magnetic resonance imaging (MRI) (*Figure 2A*). Then thoracic-adapted intensity-modulated radiation therapy (IMRT) (45 Gy in 30 fractions) and prophylactic brain radiotherapy (25 Gy in 10 fractions) were sequentially delivered. Approximately 3 months after the

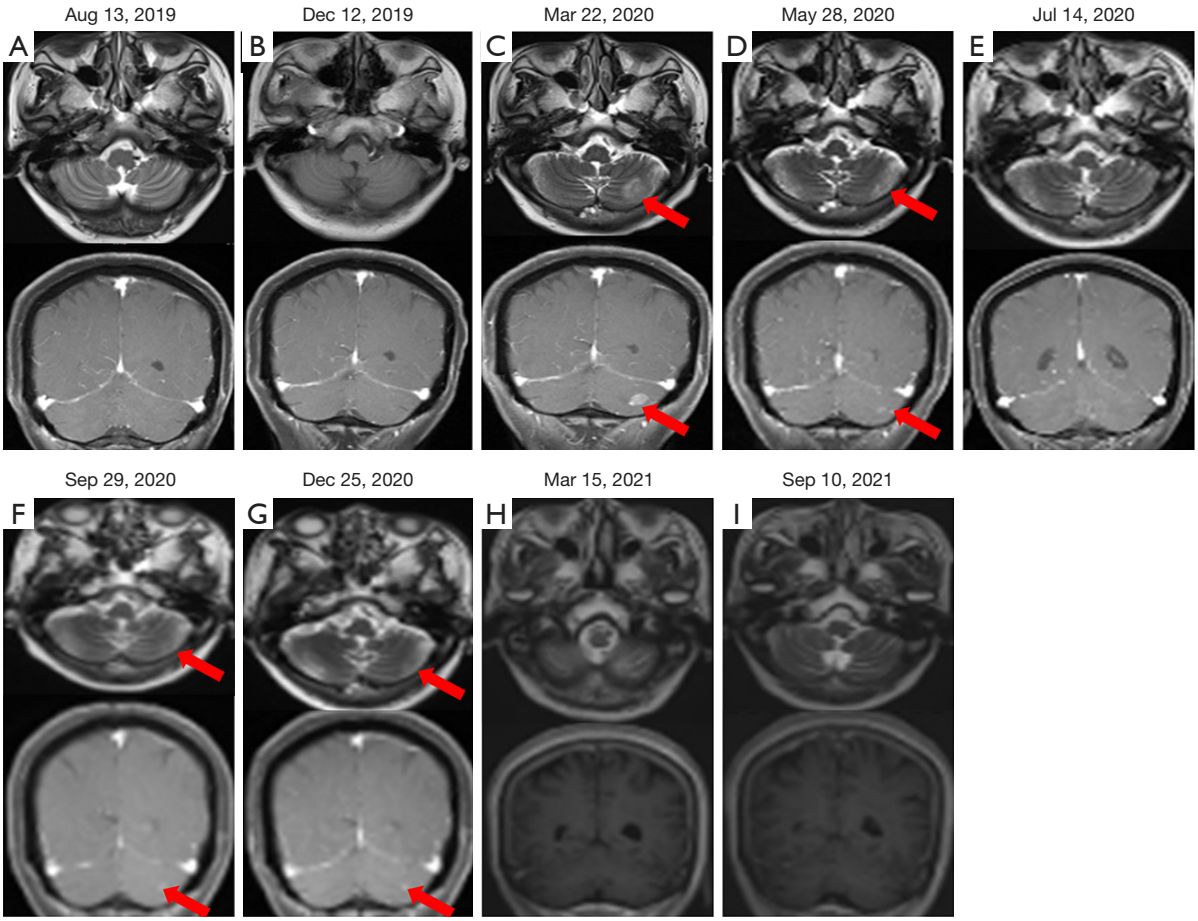

Figure 2 Brain magnetic resonance imaging images at different time points during treatment. Red arrows indicate the location of brain lesion.

end of radiotherapy, the patient was still in CR as confirmed by chest CT and brain enhanced MRI (*Figure 2B*).

Approximately 6 months after the end of radiotherapy, the patient was noted to have cranial enhanced MRI findings of abnormal signals in the left cerebellar hemisphere, indicating brain metastases (*Figure 2C*). CT and ultrasound of cervical lymph nodes, liver, gallbladder, spleen and pancreas did not show other sites of disease recurrence. After consultation with experts in the radiotherapy department, IMRT for target brain metastases were performed (40 Gy in 10 fractions). Anti-angiogenic drug anlotinib (12 mg, once daily) was given concurrently during IMRT. Irinotecan and lobaplatin were added to anlotinib after the end of IMRT. Enhanced MRI of the brain lesions showed partial response (PR) after one cycle of this regimen (*Figure 2D*), and showed CR after four cycles (*Figure 2E*).

Since grade 3 adverse reactions occurred, the patient received sintilimab (200 mg, once every 3 weeks) combined with anlotinib as maintenance therapy for three cycles. However, brain metastases relapsed again 2.5 months after achieving CR (*Figure 2F*). Considering the small relapsed lesions without symptoms, sintilimab combined with anlotinib was continued for another three cycles. Cranial enhanced MRI showed no changes in target lesions (*Figure 2G*).

After obtaining consent from the patient, sintilimab was switched to toripalimab (240 mg, once every 3 weeks). The relapsed brain metastases achieved CR after two cycles of toripalimab combined with anlotinib (*Figure 2H*). With another seven cycles of this regimen, CR had been maintained for 6 months (*Figure 2I*). The safety was manageable during treatment with toripalimab combined with anlotinib, without serious adverse reactions. Interestingly, the primary lung lesions remained in CR throughout the treatment period after the initial treatment.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Here, we reported a patient with limited-stage SCLC with recurrent brain metastases after the failure of second-line maintenance therapy and who achieved sustained CR after treatment with toripalimab in combination with anlotinib.

More than 50% of patients with SCLC will develop brain metastases during the disease course (2), leading to worse prognosis. The IMpower133 and CASPIAN studies demonstrated that ICIs combined with chemotherapy significantly improved the OS in patients with extensive-stage SCLC compared with chemotherapy alone as first-line treatment (5,6). However, no optimal treatment has been established for SCLC after failure of standard treatment, and studies on ICIs in brain metastases from SCLC are limited.

Toripalimab, a humanized anti-PD-1 monoclonal antibody, disrupts the binding of PD-1 and programmed cell death-ligand 1 (PD-L1) to programmed cell death-ligand 2 (PD-L2) and induces the endocytosis of PD-1 protein, relieving the inhibitory effect of PD-1 on T cells; this leads to complete restoration of T cells and complete immune normalization (7,8). The anti-tumor activity and safety of toripalimab monotherapy has been investigated in non-small cell lung cancer (NSCLC) (9), but data on toripalimab monotherapy in SCLC are lacking. Anti-angiogenic inhibitors that target both vascular endothelial growth factor (VEGF) and angiogenin 2 (ANG2) induce vascular normalization of abnormal blood vessels in tumors, thereby limiting the growth of tumor cells and have the advantage of regulating the tumor immune microenvironment, so they are suitable to be combined with ICIs. At the tumor site, the numbers of myeloid-derived suppressor cells and Treg cells decrease along with enhanced cytotoxic T cell infiltration, which makes the tumor immune microenvironment suitable for anti-PD-(L)1 immunotherapy (10). A phase II trial of toripalimab plus surufatinib [an inhibitor of VEGF receptor (VEGFR) 1–3, fibroblast growth factor receptor (FGFR) 1 and colony-stimulating factor-1 receptor (CSF-1R)] in 19 patients with advanced SCLC who had failed first-line systemic chemotherapy showed that the confirmed objective response rate (ORR) and disease control rate (DCR) were 10.5% and 94.7% (11), respectively. The median PFS was 3.0 months and median OS was 10.9 months (11). Another phase II trial enrolled 11 patients with extensive-stage SCLC who received toripalimab plus anlotinib as maintenance therapy after disease control with platinum-based chemotherapy (12). All patients achieved PR or stable disease, but the median PFS was not reached due to the short follow-up time (4.6 months) (12). In a phase II study of 16 patients with extensive-stage SCLC treated with first-line toripalimab combined with etoposide, carboplatin/cisplatin, and anlotinib, 100% of patients achieved objective response (1 CR and 15 PR) (13), and the median progression-free survival (PFS) was 13.3 months (14). Toripalimab combined with anti-angiogenic drug with or without chemotherapy has been investigated in SCLC. The present case supplemented the evidence on toripalimab plus anlotinib in patients with SCLC and brain metastases, which deserves further investigation.

In this case, MRI found no changes in target lesions during treatment with sintilimab plus anlotinib, indicating that PD-1 inhibitor might still have some effects on disease control. In addition, no immune-related adverse events occurred during the treatment. We speculated that switching another PD-1 inhibitor might bring more benefits and the patient could tolerate continued immunotherapy. After obtaining consent from the patient, sintilimab was switched to toripalimab. The sustained CR with toripalimab plus anlotinib indicated that this decision was correct, which also suggested the possibility of switching another PD-1 inhibitor as immunotherapy rechallenge. The differences in the molecular structure and mechanism of action among anti-PD-1 monoclonal antibodies might also contribute to the difference in efficacy, as supported by studies of various anti-PD-1 antibodies in similar populations with the same type of tumor.

Anlotinib is a small molecule multi-target tyrosine kinase inhibitor, which can effectively inhibit VEGFR, platelet-derived growth factor receptor (PDGFR), FGFR, c-Kit and other kinases with significant inhibitory activity, thus exerting anti-tumor angiogenesis and inhibiting tumor growth and metastasis through multiple pathways (15,16). The application of anti-angiogenic drug can improve cerebral edema, which is caused by brain metastases and radiotherapy (17). Some studies have also demonstrated the synergistic effect of radiotherapy combined with

anlotinib for patients with NSCLC and brain metastases (18,19). In addition, angiogenesis and VEGF-VEGFR pathway play important roles in brain metastases, and the inhibition of VEGFR pathway can inhibit brain metastatic tumor growth (20,21). The subgroup analysis of ALTER 1202 study showed that third- or further-line anlotinib could bring significant survival benefit for patients with brain metastases at baseline compared with placebo (22). The combination of anlotinib with chemotherapy as first-line treatment for extensive-stage SCLC also showed promising clinical benefits (ORR: 80–89%; median PFS: 9.4–11.4 months) in previous phase II trials (23,24). Thus, anlotinib was given concurrently with radiotherapy and subsequent chemotherapy when brain metastases were found in the present patient. On the other hand, considering the synergistic effect of ICI and anti-angiogenic drug (10), anlotinib was still continued when sintilimab was switched to toripalimab.

In conclusion, the results observed from this case suggest that the combination of toripalimab and anlotinib may be an alternative promising treatment for patients with brain metastases from SCLC. Further clinical studies to evaluate this potential treatment strategy and the difference in efficacy among PD-1 inhibitors for this population are required.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-666/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-666/coif). LM reports that since the initial planning of the work, this study was funded by Henan Medical Science and Technology Research Joint Construction Project (No. LHGJ20190206), Key Research Projects of Henan Higher Education Institutions (No. 20A320058), and Youth Innovation Fund of the First Affiliated Hospital of Zhengzhou University (No. YNQN2017170). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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