Intramedullary Spinal Cord Metastases from Small Cell Lung Cancer: Report of One Case and Review of the Literature

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Research Article

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Abstract

Purpose

Spinal cord intramedullary metastasis (ISCM) is a rare malignant tumor of the nervous system. Small cell lung cancer (SCLC) accounts for about 15% of lung cancer, and the incidence of brain metastasis is high, but intramedullary spinal cord metastasis is rare. In recent years, the first-line treatment of patients with ISCM from SCLC has been controversial. For these patients with ISCM, the options are usually depending on the progression of the disease. However, the outcome of treatments are not satisfied. Thus, We try to identify the use of immunotherapy in ISCM from SCLC.

Methods

In our review, we focused on clinical trials of immunotherapy, especially in relation to ISCM in SCLC.

Results

A patient was diagnosed as ISCM from SCLC. Radiotherapy for ISCM was started on January 11, 2021. Apatinib was taken orally after radiotherapy. The overall survival was almost 8 months, and there was only 1 month after ISCM was diagnosed.

Conclusion

Finding practical treatment options for SCLC is an important goal. Previous trials have shown that immunotherapy with checkpoint inhibitors may be an effective approach for long-term disease control and a new breakthrough in the treatment of ISCM from SCLC.

Introduction

Spinal cord intramedullary metastasis (ISCM) is a rare malignant tumor of the nervous system. Its incidence accounts for 4.2–8.5% of all central nervous system metastases^{1,2}, and nearly 3.5% of spinal metastases, approximately 0.9–2.1% tumor-related deaths are related to ISCM^{2,3}, the incidence of ISCM in lung cancer and breast cancer is higher than other malignant tumor⁴.

Small cell lung cancer (SCLC) accounts for about 15% of lung cancer⁵, and the incidence of brain metastasis is high, but intramedullary spinal cord metastasis is rare. ISCM is one of the rare causes of death in SCLC patients. Japanese scholars reported an elderly patient with ISCM who received radiotherapy combined with systemic corticosteroids and had a poor prognosis⁶; Professor Gazzeri et al reported 43 patients of intradural spinal cord extramedullary metastases (IESM) surgical related

complications and prognosis⁷. ISCM has limited methods and poor prognosis. The main options are surgery, radiotherapy, and drugs, of which radiotherapy is the main option for ISCM. In our case report, we reported a patient who developed ISCM from SCLC after receiving concurrent radiotherapy and chemotherapy. The effect of radiotherapy and systemic treatment was poor, and we reviewed the literature of ISCM research.

Case Presentation

Case presentation

A 58-year-old man was admitted to our hospital with numbness and pain in the right lower limb on 2020-04-10. He was a current smoker. The 5th vertebral body increased metabolism from the Whole-body bone imaging, considering vertebral metastasis, and chest CT scan revealed that right lung space with mediastinum Multiple swollen lymph nodes and pleural effusion on the right side.

Small cell lung cancer was diagnosed on 2020-05-26. IHC:TTF-1 (+), Syn (+), CD56 (+), NSE (partial +), Ki-67 (+75%). He received EP regimen chemotherapy (etoposide 0.1gd1-5+ Cisplatin 30mgd1-4) on 2020-05-29. Metastasis vertebral accepted radiotherapy on 2020-06-08, the prescribed dose of 95% PTV3000Gy/10 fraction, then received the two cycles of EP regimen chemotherapy on 2020-06-27, 2020-07-18, and concurrent thorax chemo-radiotherapy on July 27, Prescription dose: 100%GTV60Gy/30F, 90% PTV60Gy/30F, then he continued the original EP regimen chemotherapy (etoposide 0.1gd1-5 + cisplatin 30mgd1-4) on 2020-09-18. Magnetic resonance imaging (MRI) revealed multiple intracranial metastases on 2020-10-09. Whole-brain radiotherapy and concurrent EP treatment regimen chemotherapy were started On October 14th, 2020. IMRT plan: 6Mv-X 95%PTV 40Gy/2Gy/20F. He was given 2 cycles of paclitaxel 240mg single-agent chemotherapy On November 7, 2020, and December 7, 2020. The intracranial lesions were smaller than before On November 30, 2020. The patient developed weakness of the right lower limb, no dizziness, vomiting, and other discomforts on 2021.1.1. MRI of the vertebral indicated that the lumbar 5 bone destruction was required to compress the spinal cord and T10-L1 Intramedullary spinal cord metastasis (ISCM). Radiotherapy for ISCM was started on January 11, 2021. The prescribed dose was 95%. PTV 30Gy/10F, and he received rehabilitation treatment at the same time. Apatinib was taken orally after radiotherapy. After radiotherapy, the symptoms of the right lower limb were improved, but the patient died of respiratory failure due to lung infection on February 1, 2021. The overall survival was almost 8 months, and there was only 1 month after ISCM was diagnosed.

Review Of Literature

Epidemic analyses of ISCM

Spinal cord intramedullary metastasis (ISCM) is a rare malignant tumor of the nervous system. Goyal, A.et al.reported the incidence accounts for 4.2–8.5% of all central nervous system metastases^{1,2}. Payer, S.et al .indicated that the the incidence of ISCM is nearly 3.5% in spinal metastases, and approximately

0.9–2.1% tumor-related deaths are related to ISCM^{2,3}. ISCMs constitute 1–3% of all intramedullary tumors and 0.6% of all spinal cord tumor, which is much lower than soft meningeal metastases^{8,9}.

Among the patients with malignant tumor metastasis, lung cancer and breast cancer have the highest rate of ISCM⁴, the rates are as follows: lung cancer (50%), breast cancer (11%), colorectal cancer (3%), kidney cancer (10%), melanoma (8%) and lymphoma (4%)^{10,11}. Studies have shown that there may be three possible ways to cause ISCM. 1. Blood dissemination through arteries and/or veins is the main factor; 2. Meningeal circulation through cerebrospinal fluid is another important mechanism; 3. In addition, bone metastasis Causing epidural spinal cord compression and then invading the spinal cord parenchyma through the dura is also an important mechanism leading to ISCM^{10,12,13}. Other researcher have confirmed that direct invasion is also an important way of ISCM¹⁴. We know that the incidence of brain metastases from small cell lung cancer is high, but the incidence of ISCM is low. At present, there is no research that indicate the reason on different incidence, and there is a lack of a large amount of research to support the mechanism, and further studies are needed. In this study, a rare case of intramedullary spinal cord metastasis in a patient from small cell lung cancer was reported, and the difference between brain metastasis of small cell lung cancer and spinal cord intramedullary metastasis was explored.

Treatment options of ISCM

ISCM has limited treatment options. It is difficult to compare the results and prognosis of different treatment methods. Therefore, the best treatment plan is currently still Controversial¹⁵. Generally, individualized treatment is performed according to the patient's tumor burden and the clinician's judgment. Treatment often depends on the severity of symptoms and the physician's clinical experience. Current treatment options include microsurgical resection, radiotherapy, and drugs.

Surgical resection

Microsurgery is the main method of ISCM. Its purpose is to improve symptoms and evaluate tumors from the histological aspect, most patients can undergo surgery after initial treatment¹⁶. Studies have shown that survival can be prolonged by analyzing 22 cases of ISCM undergoing surgery, whether postoperative radiotherapy or chemotherapy¹⁷. With the advancement of microsurgery techniques and instruments, ISCM patients' symptoms can be improved after surgery, and survival can be Prolonged¹⁰. In the comparison of the treatment plan and results of 301 ISCM patients, it was found that 33% of patients' neurological symptoms had been significantly improved after surgery¹⁸. In the subsequent follow-up, 120 patients had a longer survival¹⁸, obviously, Microsurgery can prevent the deterioration of the nervous system and improve the quality of life. However, the postoperative outcome and survival after resection are largely affected by the scope of resection, and with the increase of the patient's tumor burden, the risk of microsurgery increases, and it is often not as a first-line treatment option. At present, for microsurgery to ISCM, it is necessary to combine radiotherapy and drug therapy to prolong the survival¹⁹.

Radiotherapy

Radiotherapy is another main method for ISCM treatment besides surgery. Due to the small number of cases, whether radiotherapy is the first-line treatment is still controversial. Studies have pointed out that radiotherapy can significantly improve the neurological symptoms of ISCM, especially in tumors that are sensitive to radiotherapy. Most patients use 1.8/2.0/2.5/3.0 Gy of conventional fractionated dose, and the symptoms have also been obviously improved. This may be partly due to most patients are radiosensitive tumors such as small cell lung cancer and breast cancer^{18, 20}. Radiotherapy can be used as a separate option or as supplementary treatment plan after operation in the treatment of ISCM patients. No research has pointed out the difference in survival and neurological symptoms between radiotherapy and surgery in ISCM. However, when surgery and drug treatment fail to achieve a good effect, radiotherapy can improve the patient's neurological symptoms¹⁹. Complications of radiotherapy include radiation myelopathy and radiation spinal cord necrosis. The effect or risk of radiotherapy is controversial, because the maximum allowable radiation dose of the spinal cord is limited and often does not meet the criteria for radical ISCM. At present, stereotactic radiotherapy can avoid complications and prolong the survival, which is a new idea for ISCM treatment²¹.

Chemotherapy

Drugs as the second choice for ISCM treatment, including chemotherapy, immunotherapy, and targeted therapy. Due to the blood-spinal cord barrier, chemotherapy has almost no effect on the treatment of ISCM, it has been unable to prolong the survival of ISCM patients^{13, 22}. Chemotherapy is currently used for chemotherapy-sensitive tumors (such as small cell lung cancer and hematological tumors) or as adjuvant treatment of radiotherapy or surgery. Immunotherapy is currently the main program of drug therapy, and it has a good effect on relapsed, metastatic, and refractory ISCM. For cases that no genetic mutations are found, immune checkpoint inhibitors are recommended²³. In the distant metastasis of non-small cell lung cancer caused by oncogenes, such as EGFR, ALK and ROS1 mutations^{23, 24}. The EGFR tyrosine kinase inhibitors gefitinib, erlotinib or afatinib are very effective and can be used as first-line drugs. In addition, Anti-angiogenesis such as apatinib can also inhibit tumor growth and reduce patient tumor burden

Anti-angiogenesis

The growth of tumors is vessel-dependent. Large blood vessels provide sufficient nutrition and oxygen for tumors. Therefore, there is a hypothesis that anti-vessels of tumor can inhibit the occurrence and development of tumors²⁵.

As an Anti-angiogenesis, apatinib is a safe and effective oral drug after the failure of standard chemotherapy for advanced gastric cancer, which can significantly prolong the survival of patients²⁶. Apatinib as maintenance after chemotherapy in 23 extensive-stage small-cell lung cancer patients, It was found that after taking 250 mg of apatinib, the median PFS after maintenance treatment was 4.1 months (95% confidence interval 3.63–4.57 months). The median OS after maintenance treatment was 12.5 months (95% confidence interval was 5.51–19.49 months). The results of the study suggest that apatinib

can make SCLC patients get longer OS and PFS as maintenance treatment after chemotherapy, there were 8 patients with brain metastases, accounting for 34.8% in this study. Although these 8 patients with brain metastases have not been individually analyzed for efficacy, we can speculate that apatinib has a certain anti-tumor activity in patients with small cell brain metastases²⁷.

As a new type of small molecule multi-target tyrosine kinase inhibitor, Anlotinib can strongly inhibit VEGFR, PDGFR, FGFR and other multi-targets²⁸. In research of 45 SCLC patients who received Anlotinib, 16 patients of brain metastases were included, accounting for 36%. The median PFS of these patients was 4.1 months, the median OS was 6.1 months, ORR was 11% and DCR was 67%. SCLC patients who received Anlotinib had longer survival²⁹. Anti-angiogenic drugs have anti-tumor effects in small cell lung cancer with brain metastases, but there are fewer patients in this study, the evidence is limited, and there is no direct evidence in ISCM. We reported this case. Although apatinib was taken orally after the spinal cord metastasis received radiotherapy, because of the short oral administration time, the effect could not be evaluated.

The anti-PD-1/PD-L1 pathway

PD-1/PD-L1 can inhibit T cell activation and proliferation, trigger T cell apoptosis, induce and maintain immune function, tumor immune tolerance and escape³⁰, thus blocking PD-1/PD-L1 signal Can promote immune response³¹. At present, there are mainly pembrolizumab, nivolumab, Durvalumab, Atezolizumab, all of which can inhibit PD-1/ PD-L1, inhibit tumor progression³².

As a PD-1 inhibitor, pembrolizumab can be used for unresectable or metastatic melanoma, and it also has a positive effect on the treatment of small cell lung cancer. In the analysis of 83 cases of SCLC receiving pembrolizumab treatment after two or more lines of therapy, median PFS was 2.0 months, and median OS was 7.7 months, There were 13 brain metastases, accounting for about 15.7%.The sum of the target disease sizes was reduced from baseline in 33 (44%).22 patients (29%) who had at least a 30% reduction in tumor size³³.

Nivolumab has a positive effect on small cell lung cancer. In the follow-up of 109 SCLC patients treated with nivolumab in third line, it was found that with a median follow-up of 28.3 months (from the first administration to the database lock), objective response rate was 11.9% (95% confidence interval: 6.5–19.5), and the median duration of response was 17.9 months (range 3.0–42.1). At 6 months, 17.2% of patients had no progression³⁴. Phillips reported a patient received Nivolumab to treat ISCM. A 67-year-old female ISCM patient with a 50-year history of smoking was received Nivolumab 3 mg/kg every 2 weeks, combined with surgery and radiotherapy. The patients'clinical manifestations tend to be stable, with no obvious progression of the tumor³⁵. Nivolumab may be suitable for ISCM with minimal changes. These studies have confirmed that nivolumab can prolong the survival of patients with small cell lung cancer and can also be used for ISCM from small cell lung cancer.

In a study of 268 SCLC patients treated with durvalumab +platinum + etoposide in first line, it was found that 28 patients with brain metastases, accounting for about 10%.The median OS was 13.0 months. The

12-month overall survival rate was 54% (47.4-59.5) and the predicted 18-month overall survival rate was 34% (26.9-41.0). The survival period of the patients was significantly longer compared to control group³⁶. Durvalumab has positive significance for the treatment of SCLC.

Atezolizumab is a monoclonal antibody of PD-L1. Atezolizumab monotherapy is safe and effective for many tumor types. In a retrospective study of 201 SCLC patients who received Atezolizumab in first line, 35 of the 201 patients had brain metastases. It was found that the median OS was 12.3 months. At the 18th month, 34% of the patients were still alive. ORR in the Atezolizumab+CP/ET group was 60.2% (95% CI, 53.1 to 67.0) and median DOR in the Atezolizumab+CP/ET group was 4.2 months (95% CI, 4.1 to 4.5). Patients treated with Atezolizumab have a significantly prolonged survival³⁷.

Now, PD-1/PD-L1 checkpoint inhibitors can prolong survival in small cell lung cancer, but there is a lack of head-to-head research data on brain metastases. The efficacy of PD-1/PD-L1 checkpoint inhibitors in small cell lung cancer brain metastasis needs more clinical research. Although there are reports on the efficacy of PD-1/PD-L1 checkpoint inhibitor on ISCM, there is a lack of a large amount of research data, and more research is needed.

There are two limitations in our case report. Firstly, the patient had died eventually because of lung infection. Thus, we were unable to assess the effects of chemo-radiotherapy and anti-angiogenesis on ISCM from SCLC. Secondly, our case report needs more cases of ISCM to analyse the difference between multiple treatment options for ISCM.

Conclusion

There are few patients with ISCM from SCLC, and no standard treatment plan for ISCM. It is necessary to formulate an individualized plan based on the patient's general conditions, tumor burden, and clinicians' experience. Surgery, radiotherapy, immunotherapy and targeted therapy are the main options for ISCM. Although surgery and radiotherapy can prolong survival of ISCM, there are often not as a first-line treatment option based on risk. Stereotactic radiotherapy maybe as a new idea for ISCM treatment. PD-1/PD-L1 checkpoint inhibitors and anti-angiogenesis can make small cell lung cancer achieve longer survival, but this research did not analyze brain metastases. Whether drug treatment can reduce the probability of brain metastases and prolong the survival with brain metastases in SCLC was not analyzed, but the treatment of brain metastases, and the different incidence of ISCM and brain metastases in SCLC is the follow-up goal of this research. In conclusion, finding practical treatment options for SCLC is an important goal. Previous trials have shown that immunotherapy with checkpoint inhibitors may be an effective approach for long-term disease control and a new breakthrough in the treatment of ISCM from SCLC.

Declarations

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Data Availability statement

The datasets generated during and/or analysed during the current study are available in the Pubmed repository, <https://pubmed.ncbi.nlm.nih.gov>

Disclosure of potential conflicts of interest: The authors report no conflicts of interest for this work.

Research involving Human Participants and/or Animals: The research involving human participants.

Informed consent: Informed consent was obtained from all individual participants included in this case report. The ethics committee of AnHui no 2 provincial people's Hospital approved this case report. The study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki.

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Figures

Figure 1
Chest CT scan at baseline

Figure 2

Magnetic resonance image (MRI) of the 5th vertebral metastases

Figure 3

Magnetic resonance image (MRI) of brain metastases

Figure 4

Magnetic resonance image (MRI) of the Spinal cord intramedullary metastasis (ISCM): A sagittal contrast enhanced T1 weighted and T2 weighted MRI of the cervical spine shows intramedullary lesion from the level of T10 to L1 (red arrows).