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Prolonged Response of Meningeal Carcinomatosis from Non-small Cell Lung Cancer to Salvage Intrathecal Etoposide Subsequent to Failure of First-Line Methotrexate: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADEF **Min Jae Park**

Division of Hematology-Oncology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Korea

Corresponding Author: Min Jae Park, e-mail: zoloft77@naver.com
Conflict of interest: None declared

Patient: Male, 58
Final Diagnosis: Non-small cell lung cancer with meningeal carcinomatosis
Symptoms: Headache
Medication: Etoposide
Clinical Procedure: Intraventricular chemotherapy
Specialty: Oncology

Objective: Unusual setting of medical care

Background: As the incidence of meningeal carcinomatosis (MC) in non-small cell lung cancer (NSCLC) patients has been increasing, MC has recently become an important clinical problem in the management of NSCLC. However, development of new treatments is lacking and a standard treatment guideline is not yet available. Research on salvage intrathecal chemotherapy after failure of first-line treatment for NSCLC patients with MC has rarely been reported in the literature. Here, we report the case of an NSCLC patient with MC who showed durable response to salvage intrathecal etoposide subsequent to failure of first-line methotrexate.

Case Report: A 58-year-old Asian man with lung adenocarcinoma with bone metastasis presented gait disturbance, diplopia, and progressively increasing headache. The diagnosis of MC was made by brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology. After MC progression was suspected during the first-line treatment of intrathecal MTx, intrathecal etoposide was used as a salvage treatment. Brain MRI performed after 2 months of the treatment demonstrated disappearance of enhancing lesions along the ependymal lining of the lateral ventricles. His clinical status markedly improved from Eastern Cooperative Oncology Group performance status of 4 to 2. Stable neurologic status was maintained and CSF cytology remained negative while weekly injection of etoposide was continued for 19 weeks. However, hepatic metastatic lesions persistently progressed despite systemic palliative chemotherapy and the patient died of the disease.

Conclusions: To our knowledge, this is the first case report in which intrathecal etoposide was successfully used to treat MC from NSCLC after failure of MTx. This case report might provide preliminary evidence of the feasibility of intrathecal etoposide as salvage intrathecal chemotherapy (ITC). Further clinical trials including larger numbers of patients are necessary to evaluate the role of this ITC regimen for NSCLC patients with MC.

MeSH Keywords: Etoposide • Injections, Intraventricular • Injections, Spinal • Lung Neoplasms

Abbreviations: **CNS** – central nervous system; **CSF** – cerebrospinal fluid; **ITC** – Intrathecal chemotherapy; **NSCLC** – non-small cell lung cancer; **MRI** – magnetic resonance imaging; **MTx** – methotrexate

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/894061

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Background

Meningeal carcinomatosis (MC) is dissemination and infiltration of malignant cells throughout the arachnoid and pia mater of the central nervous system (CNS); it is associated with devastating neurologic complications and dismal prognosis [1]. Recent advances in systemic chemotherapy and targeted agents contributed to improved clinical outcomes in NSCLC patients. However, their prolonged survival has led to a relative increase in the risk of CNS metastasis and progression, in which the blood-brain barrier impedes the passage of effective systemic agents [2].

Despite recent developments in treatment of NSCLC, little improvement has been made in the clinical outcome of NSCLC patients with MC. The prognosis remains poor, with a median survival of less than 3 months after diagnosis of MC [3]. Conventional treatment options for MC include intrathecal chemotherapy (ITC), systemic chemotherapy, targeted agents, and radiotherapy. Of these, ITC has been regarded as the most reliable way to deliver chemotherapeutic agents into subarachnoidal space. However, there are a limited number of therapeutic agents currently available for ITC and the optimal dose and scheduling of the agents remain elusive. Commonly used agents for first-line ITC against newly diagnosed MC include methotrexate (MTX), cytarabine, liposomal cytarabine, and thiotepa [4]. In spite of ITC and multimodal treatments, nearly all NSCLC patients with MC experience treatment failure with neurologic progression within several weeks. Selected fit patients with good performance status need salvage treatment for preventing further neurologic deficit and prolonging overall survival. Unfortunately, research on salvage ITC after failure of first-line treatment for NSCLC patients with MC is scarce in the literature. Here, we report the case of an NSCLC patient with MC who achieved durable response to salvage intrathecal etoposide subsequent to failure of MTx.

Case Report

A 58-year-old Asian man with a 30-pack/year history of smoking was diagnosed with lung adenocarcinoma with bone metastasis. Molecular biomarker assays revealed the tumor had no epidermal growth factor receptor gene mutation and anaplastic lymphoma kinase gene rearrangement. As a palliative, systemic chemotherapy, 4 cycles of pemetrexed/cisplatin followed by 8 cycles of pemetrexed maintenance therapy were administered, with tumor response of stable disease according to Response Evaluation Criteria In Solid Tumors 1.1 [5], until the patient developed gait disturbance, diplopia, and progressively increasing headache. Brain magnetic resonance imaging (MRI) demonstrated enhancing lesions along the ependymal lining of the lateral ventricles (Figure 1A). A lumbar puncture was performed and the cerebrospinal fluid (CSF) examination showed high opening pressure of 230 mmH_2O, elevated protein level (86 mg/dL), normal glucose level, and the presence of malignant cells, diagnostic of MC. Systemic imaging evaluation demonstrated newly developed liver metastasis (Figure 2A).

Intrathecal MTx 15 mg was administered bi-weekly via an Ommaya reservoir as a first-line ITC. Despite 2 weeks of the treatment, neurological deficits progressed. The follow-up CSF

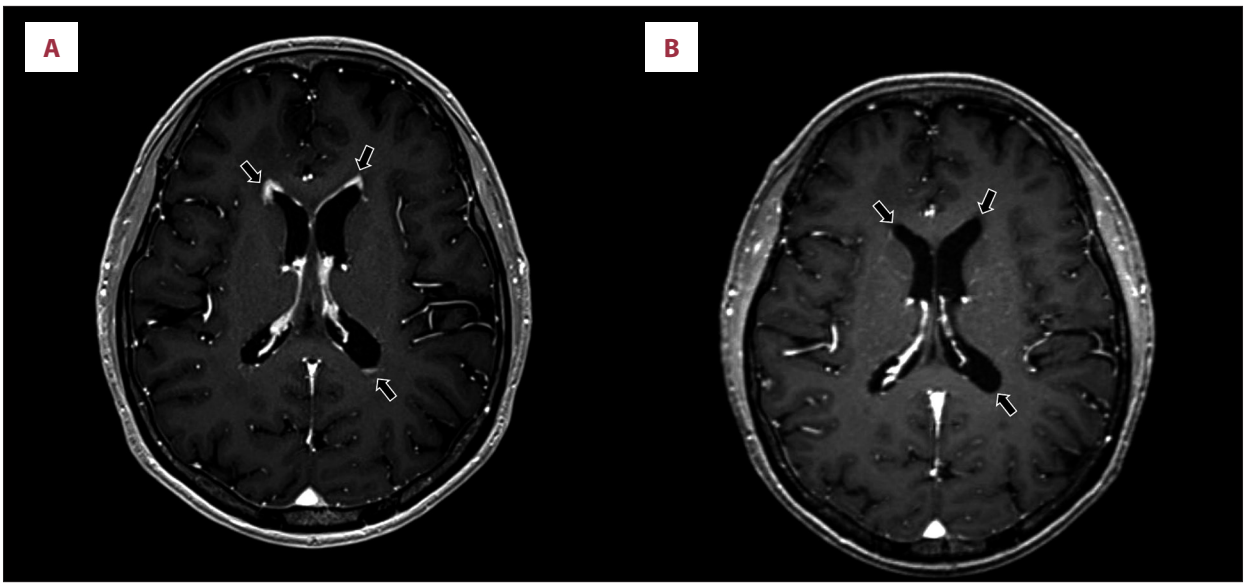

Figure 1. (**A**) Brain magnetic resonance imaging (MRI) revealed enhancing lesions along the ependymal lining of the lateral ventricles. (**B**) MRI performed after 2 months of salvage intrathecal etoposide demonstrated disappearance of enhancing lesions along the ependymal lining of the lateral ventricles.

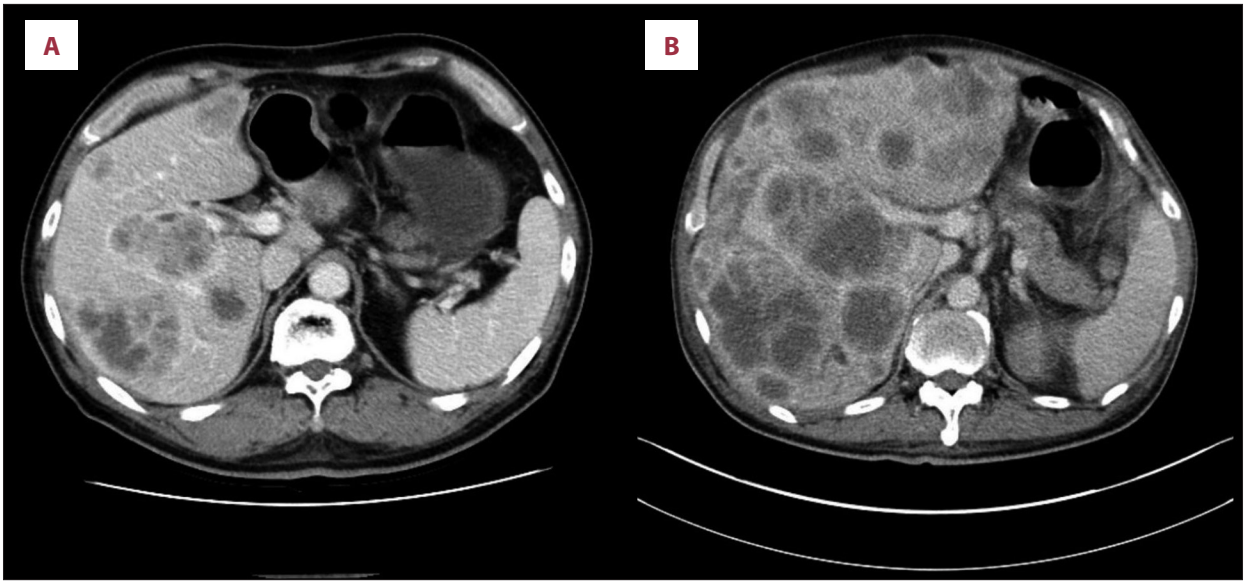

Figure 2. (**A**) Abdominal computed tomography (CT) at the time of diagnosis of meningeal carcinomatosis showed newly developed hepatic metastases. (**B**) Metastatic lesions in liver progressed despite systemic palliative chemotherapy, being considered as a main cause of deterioration of the patient.

analysis showed high opening pressure of 240 mmH_2O, further increased protein (314 mg/dL), and persistent malignant cells. MTx failure was highly suspected. There was no specific recommended salvage treatment for MC progression subsequent to first-line therapy in the literature. After explaining the experimental nature of salvage treatment, written informed consent was obtained from the patient and his family. Based on previous clinical trials to evaluate intrathecal etoposide for MC in metastatic brain tumors [4,6], etoposide was administered for salvage ITC.

For intrathecal administration, a 5-ml vial containing 100 mg of etoposide (E.P.S®, Boryung Pharm Co., Ltd., Seoul, Korea) was diluted with normal saline, yielding a final concentration of 0.2 mg per ml. The final solution of 5 mL containing etoposide 1 mg was injected over a 2-minute period after draining of 5 ml of CSF from the reservoir for discarding. The treatment was given weekly through an Ommaya reservoir. Corticosteroid was administered as a prophylaxis of chemical arachnoiditis.

After the third injection of etoposide, the patient showed neurological improvements. CSF cytology turned negative after the fifth ITC. No adverse event related to intrathecal etoposide was been observed. Brain MRI performed after 2 months of the treatment demonstrated disappearance of enhancing lesions along the ependymal lining of the lateral ventricles (Figure 1B). Clinical status markedly improved, with Eastern Cooperative Oncology Group performance status of 2 and gemcitabine was started as second-line systemic chemotherapy.

The patient maintained stable neurologic status and CSF cytology remained negative while weekly injection of etoposide was continued for 19 weeks. However, hepatic metastatic lesions persistently progressed despite systemic palliative chemotherapy (Figure 2B) and the patient died of the disease 5 months after the diagnosis of MC.

Discussion

As the incidence of MC in NSCLC patients has been increasing, MC has become an important clinical problem in the management of NSCLC. However, development of new treatment is lacking and a standard treatment guideline is not yet available. ITC, systemic chemotherapy, targeted therapy, and radiotherapy are the conventional treatment options for MC in NSCLC patients. Due to its advantage of distributing effective anti-tumor drugs into CSF, ITC has become the mainstay of treatment for MC in NSCLC patients [7]. Despite ITC and other combined treatments, most of the treated patients have neurologic deterioration within several weeks and salvage therapy is required for selected patients to prevent worsening neurologic deficit and to prolong survival [8]. However, salvage ITC for NSCLC patients with MC has rarely been reported in the literature. Future research is imperative to evaluate salvage ITC after failure of first-line treatment in NSCLC patients with MC to meet growing clinical demands.

Two clinical trials evaluated the feasibility of intraventricularly administered etoposide in patients with relapsed metastatic brain tumors and demonstrated that etoposide was well

tolerated for ITC without significant adverse events [4,6]. Based on these data, in this case we chose etoposide as salvage ITC subsequent to failure of MTx, because there was no particular salvage regimen recommended for NSCLC patients with MC. Instead of the previously published regimen of 5 consecutive days of intrathecal etoposide, we devised a weekly administration scheme. A single injection per once per week is more simple and convenient in clinical practice than 5 days of injection and 2 to 4 weeks of rest, which was the previously evaluated dosing schedule for intrathecal etoposide.

This case showed durable response to the modified intrathecal administration of etoposide and he continued the treatment for 19 weeks until poor performance status from progression of liver metastasis did not allow further ITC. Neurologic signs related to MC progression had not been detected and normal CSF analysis profile with negative cytology was maintained on serial CSF examinations. Overall survival was 186 days from the diagnosis of MC; the patient did not die directly from MC progression, but rather from systemic progression of the disease. To the best of our knowledge, this is the first case report of salvage intrathecal etoposide after failure of first-line MTx, leading to prolonged response and successful palliation of MC from NSCLC. More clinical studies are required to investigate the effectiveness and safety of intrathecal etoposide for NSCLC patients with MC as an additional ITC regimen.

Conclusions

To our knowledge, this is the first case report in which intrathecal etoposide was successfully used to treat MC from NSCLC after failure of MTx. It is also unique in that we a devised weekly administration scheme of intrathecal etoposide, instead of the previously published 5 consecutive days of administration and 2 to 4 weeks of rest. This case report might provide preliminary evidence of the feasibility of intrathecal etoposide as salvage ITC. Further clinical trials including larger numbers of patients are necessary to evaluate the role of this ITC regimen for NSCLC patients with MC.

Competing interests

The authors have declared that no competing interests exist.

References:

1. Leal T, Chang JE, Mehta M et al: Leptomeningeal metastasis: challenges in diagnosis and treatment. Curr Cancer Ther Rev, 2011; 7(4): 319–27
2. Lee SJ, Lee J-I, Nam D-H et al: Leptomeningeal carcinomatosis in non-small-cell lung cancer patients: impact on survival and correlated prognostic factors. J Thorac Oncol, 2013; 8(2): 185–91
3. Gwak H-S, Joo J, Kim S et al: Analysis of treatment outcomes of intraventricular chemotherapy in 105 patients for leptomeningeal carcinomatosis from non-small-cell lung cancer. J Thorac Oncol, 2013; 8(5): 599–605
4. Fleischhack G, Reif S, Hasan C et al: Feasibility of intraventricular administration of etoposide in patients with metastatic brain tumours. Br J Cancer, 2001; 84(11): 1453–59
5. Eisenhauer EA, Therasse P, Bogaerts J et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer, 2009; 45(2): 228–47
6. Slavc I, Schuller E, Falger J et al: Feasibility of long-term intraventricular therapy with mafosfamide (n=26) and etoposide (n=11): experience in 26 children with disseminated malignant brain tumors. J Neurooncol, 2003; 64(3): 239–47
7. Christoph DC, Reckamp KL: Intraventricular chemotherapy for leptomeningeal carcinomatosis from lung cancer: a feasible and beneficial treatment option? J Thorac Oncol, 2013; 8(5): 523–24
8. Park JH, Kim YJ, Lee J-O et al: Clinical outcomes of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era. Lung Cancer, 2012; 76(3): 387–92