

[CASE REPORT]

Whole-brain Radiation and Pembrolizumab Treatment for a Non-small-cell Lung Cancer Patient with Meningeal Carcinomatosis Lacking Driver Oncogenes Led to a Long-term Survival

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Abstract:

We herein report a 66-year-old woman with advanced lung adenocarcinoma [programmed cell death and its ligand 1 (PD-L1) tumor proportion score 60%] lacking driver oncogenes in whom meningeal carcinomatosis, along with sudden onset dizziness, deafness, and consciousness disturbance, appeared after second-line chemotherapy. Whole-brain radiation therapy (WBRT) and Pembrolizumab were subsequently administered, and third-line chemotherapy with Pembrolizumab is now ongoing. At the time of writing, the patient has achieved a 23-month survival without disease progression. Our findings suggest that the combination of WBRT and an immune checkpoint inhibitor is effective for non-small-cell lung cancer patients lacking driver oncogenes who develop meningeal carcinomatosis.

Key words: non-small-cell lung cancer, meningeal carcinomatosis, immune checkpoint inhibitor, Pembrolizumab, whole-brain radiation therapy

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Meningeal carcinomatosis is a severe condition associated with a poor prognosis in non-small-cell lung cancer (NSCLC) patients lacking driver oncogenes, for whom an optimal therapy has yet to be established. Recent studies (1, 2) have demonstrated the efficacy of a combination of brain radiation therapy and administration of an immune checkpoint inhibitor (ICI) for patients with lung cancer brain metastasis, although the effects of such an approach in patients with meningeal carcinomatosis have not been reported.

To our knowledge, this is the first report of a patient with NSCLC lacking driver oncogenes who developed meningeal carcinomatosis and then subsequently received whole-brain radiation therapy (WBRT) and Pembrolizumab, leading to a

long-term survival. Our findings suggest that this combination therapy may be an effective treatment option for such cases.

Case Report

The patient gave her informed consent for the publication of the details concerning her case, including images.

A 66-year-old woman with a 26-year history of smoking was referred to our hospital for the evaluation of abnormal chest radiograph findings. Chest computed tomography (CT) revealed a tumor 30.3 mm in diameter in the left upper lung as well as swelling of the left sub-aortic lymph node (#5). A surgical biopsy of the #5 lymph node showed a poorly differentiated adenocarcinoma lacking driver oncogenes [epidermal growth factor receptor (*EGFR*) mutation-negative, anaplastic lymphoma kinase (*ALK*) fusion gene-negative, c-ros oncogene 1 (*ROS-1*) fusion gene-negative, rearranged

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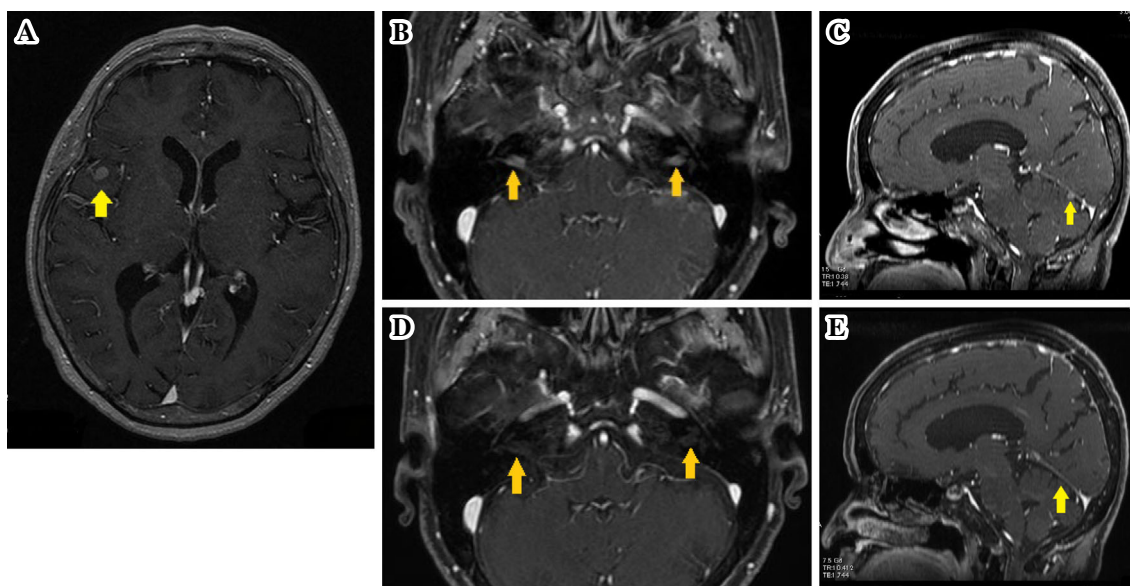


Figure. Brain MRI findings. Solitary brain metastasis in the right frontal lobe at 10 months after the end of chemo-radiotherapy (A: arrow). Abnormal findings of disseminated lesions in both internal auditory canals (B: arrows) and along the meninges (C: arrow) after SBRT and 13 cycles of pemetrexed. Disappearance of previous findings following combination therapy with WBRT and Pembrolizumab (D, E: arrow).

during transfection (*RET*) proto oncogene-negative]. The programmed cell death and its ligand 1 (PD-L1) tumor proportion score (TPS) was 60%. Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) also revealed the FDG uptake in the primary tumor and #5 lymph node, while there was no evidence of distant metastasis (cT2aN2M0: Stage IIIA). Brain magnetic resonance imaging (MRI) before the initiation of chemo-radiotherapy showed no findings of previous central nervous system (CNS) metastasis. Chemo-radiotherapy with cisplatin and pemetrexed was performed, and the patient achieved a complete response.

Ten months later, brain MRI confirmed a solitary metastatic tumor in the right frontal lobe (Figure A), for which stereotactic brain radiation therapy (SBRT; 35 Gy: 7 Gy×5) and second-line chemotherapy with pemetrexed were performed. After 13 cycles of chemotherapy, dizziness and deafness suddenly appeared. Brain MRI revealed disseminated lesions in both internal auditory canals and along the meninges (Figure B), and an adenocarcinoma was confirmed on a cerebrospinal fluid examination. Based on these results, we diagnosed meningeal carcinomatosis and performed WBRT. Although her consciousness worsened for the duration of WBRT (30 Gy: 3 Gy×10), soon after it was finished, third-line chemotherapy with Pembrolizumab was administered. Within three days of the initiation of that chemotherapy regimen, the patient's consciousness recovered. After nine cycles of Pembrolizumab, brain MRI and cerebrospinal fluid examination results were improved (Figure C), although deafness remained. At present, 23 months have passed since the diagnosis of meningeal carcinomatosis, and

chemotherapy with Pembrolizumab is ongoing (30 cycles at the time of writing) without disease progression.

Discussion

The prognosis for NSCLC meningeal carcinomatosis patients lacking driver mutations remains poor, with previous studies (3-5) showing a median overall survival period of 4-6 weeks for cases without any treatment and 2-3 months for those that underwent treatment, such as systemic therapy, intrathecal chemotherapy, or radiation therapy. In contrast, median overall and progression-free survival periods of 3.8-18.0 and 2.0-17.2 months, respectively, have been reported for *EGFR* mutation-positive NSCLC patients with meningeal carcinomatosis who received treatment with an *EGFR* tyrosine kinase inhibitor. This indicates this approach to be an effective treatment option for such cases (6-10) and highlights the need for effective treatment options for NSCLC patients lacking driver oncogenes who develop meningeal carcinomatosis. To our knowledge, this is the first report of such a patient, who has shown a minimum survival period of 23 months without disease progression, indicating the efficacy of this combined therapy.

Previous reports (11-13) have noted that the level of dense tumor-infiltrating lymphocytes (TILs) was high in cases of brain metastasis associated with certain types of cancer, including lung cancer. This high density was shown to be associated with a favorable survival duration. Although the blood-brain barrier (BBB) prevents antibody entry into the CNS (14-16), those results suggest that immune cells ac-

tivated by immune-modulating drugs, such as ICIs, may be effective against CNS metastases. Indeed, previous studies (17-19) of NSCLC brain metastasis treated by ICI reported response rates ranging from 16.6-29.4% and a median OS ranging from 6.5-8.9 months.

Other more recent reports (1, 2) have shown the efficacy of a combination of brain radiation therapy and ICI administration for NSCLC patients with brain metastasis. Radiation augments anti-tumor immune responses via various mechanisms (20). It has been reported that radiation-induced tumor cell necrosis increases the release of tumor neoantigens and the tumor mutation burden (21). Furthermore, radiation also triggers the release of immune-stimulatory damage associated molecular patterns (DAMPs) that promote antigen-presenting cell (APC) recruitment to the tumor microenvironment and antigen presentation to cytotoxic T cells (22, 23). It has also been found that radiation primes CD8-positive T cells by stimulating IFN- γ production and increasing the tumor cell major histocompatibility complex (MHC) class I and Fas expression (24) while also increasing the PD-L1 expression (21, 25). These mechanisms maximize the effects of an ICI given for brain metastasis, regardless of the PD-L1 expression. While those previous studies (1, 2) targeted NSCLC patients with brain metastases, we suspected that the same mechanisms would be applicable to patients with NSCLC and meningeal carcinomatosis and thus performed combination therapy with WBRT and Pembrolizumab in the present case. The results obtained here are important and supports our speculation, although additional research is necessary.

The present findings indicate that the combined administration of WBRT and an ICI is an effective treatment option for NSCLC patients lacking driver oncogenes who develop meningeal carcinomatosis. This treatment could be considered for affected patients.

The authors state that they have no Conflict of Interest (COI).

References

- Schapira E, Hubbeling H, Yeap BY, et al. Improved overall survival and locoregional disease control with concurrent PD-1 pathway inhibitors and stereotactic radiosurgery for lung cancer patients with brain metastases. *Int J Radiat Biol Phys* **101**: 624-629, 2018.
- Chen L, Douglass J, Kleinberg L, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in Non-small cell lung cancer, Melanoma, and Renal cell carcinoma. *Int J Radiat Oncol Biol Phys* **100**: 916-925, 2018.
- Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. *Cancer Treat Rev* **25**: 103-119, 1999.
- Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumor: experience with 90 patients. *Cancer* **49**: 759-772, 1982.
- Chamberlain MC, Kormanik P. Carcinoma meningitis secondary to non-small cell lung cancer: combined modality therapy. *Arch Neurol* **55**: 506-512, 1998.
- Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing challenge in the personalized treatment era. *Cancer Treat Rev* **53**: 128-137, 2017.
- Tamiya A, Tamiya M, Nishihara T, et al. Cerebrospinal fluid penetration rate and efficacy of Afatinib in patients with EGFR mutation-positive non-small cell lung cancer with leptomeningeal carcinomatosis: a multicenter prospective study. *Anticancer Res* **37**: 4177-4182, 2017.
- Saboundji K, Auliac JB, Pérol M, et al. Efficacy of Osimertinib in EGFR-mutated non-small cell lung cancer with leptomeningeal metastases pretreated with EGFR-tyrosine kinase inhibitors. *Target Oncol* **13**: 501-507, 2018.
- Li H, Yu T, Haang M, et al. Treatment response to Osimertinib in EGFR-mutated leptomeningeal metastases from non-small cell lung cancer: a case series. *Onco Targets Ther* **12**: 7785-7790, 2019.
- Abdallah SM, Wong A. Brain metastases in non-small-cell lung cancer: are tyrosine kinase inhibitors and checkpoint inhibitors now viable options? *Curr Oncol* **25**: 103-114, 2018.
- Berghoff AS, Fuchs E, Ricken G, et al. Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival time in patients with brain metastases. *Oncoimmunology* **9**: e1057388, 2015.
- Berghoff AS, Inan C, Ricken G, et al. 1324p Tumor-infiltrating lymphocytes (TILs) and PD-L1 expression in non-small cell lung cancer brain metastasis (BM) and matched primary tumors (PT). *Ann Oncol* **25**: iv465-iv466, 2014.
- Berghoff AS, Ricken G, Wilhelm D, et al. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastasis of small cell lung cancer (SCLC). *J Neurooncol* **130**: 19-29, 2016.
- Lois AL. Monoclonal antibodies in neuro-oncology: getting past the blood-brain barrier. *mAbs* **3**: 153-160, 2011.
- Saunders NR, Ek CJ, Habgood MD, et al. Barriers in the brain. *Trends Neurosci* **31**: 270-286, 2008.
- Eyal S, Hisao P, Unadkat JD. Drug interactions at the blood-brain barrier: fact or fantasy? *Pharmacol Ther* **123**: 80-104, 2009.
- Bidoli P, Chiari R, Catino A, et al. Efficacy and safety data from patients with advanced squamous NSCLC and brain metastases participating in the nivolumab Expanded Access Programme (EAP) in Italy. *Ann Oncol* **27**: 1228, 2016.
- Goldberg S, Mahajan A, Herbst R, et al. Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. *J Clin Oncol* **36** (suppl 15): 2009, 2018.
- Crino L, Bronte G, Bidoli P, et al. Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer. *Lung Cancer* **129**: 35-40, 2019.
- Suneel DK, Priya UK. Immune checkpoint inhibitors for the treatment of central nervous system (CNS) metastatic disease. *Front Oncol* **8**: 414, 2018.
- Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* **74**: 5458-5468, 2014.
- Hodge JW, Guha C, Neefjes J, et al. Synergizing radiation therapy and immunotherapy for curing incurable cancers. Opportunities and challenges. *Oncology* **22**: 1064-1070, 2008.
- Weichselbaum RR, Liang H, Deng L, et al. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol* **14**: 365-379, 2017.
- Tang C, Wang X, Soh H, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? *Cancer Immunol Res* **2**: 831-838, 2014.
- Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* **124**: 687-695, 2014.

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