Case Report

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Camrelizumab Plus Zoledronic Acid Showed Sustained Efficacy in A Patient with Cranial and Spinal Metastases from Lung Adenocarcinoma

Chu Zhang[1], Guangmao Yu[1], Miao Zhang[2*], Wenbin Wu[2]

[1]Department of Thoracic Surgery, Shaoxing People' s Hospital (Shaoxing Hospital, Zhejiang University School of Medicine), Shaoxing, [2]Department of Thoracic Oncology, Xuzhou Central Hospital, Xuzhou, P.R. China

ABSTRACT

The role of anti-programmed cell death protein-1 (PD-1) antibody camrelizumab in brain metastases (BMs) from lung adenocarcinoma is uncertain. Herein, for the first time, we report the efficacy of camrelizumab in a patient with chemotherapy-refractory BMs from lung adenocarcinoma. A 49-year-old male non-smoker was admitted with cough and back pain. Primary lung adenocarcinoma with brain and spinal metastases was diagnosed. The specimen from CT-guided lung biopsy showed positive expression of PD-L1 (~20%). The BMs were enlarged after first-line intravenous pemetrexed/cisplatin and zoledronic acid; whereas second-line camrelizumab demonstrated impressive complete remission of the BMs. The intracranial progression-free survival and overall survival of the patient since immunotherapy were more than 12 months and 20 months, respectively. In addition, we searched PubMed for relevant studies from inception to May 2020, and a total of 23 reports enrolling 1187 patients also indicated the promising efficacy of immunotherapy for BMs from lung cancer. However, more and better evidence is still needed before a definite conclusion could be drawn.

Keywords: Programmed cell death protein-1 (PD-1), Anti-PD-1 monoclonal antibody, Immune checkpoint inhibitors (ICIs), Camrelizumab, Lung adenocarcinoma, Brain metastasis

*Corresponding author:
Miao Zhang,
Department of Thoracic Oncology, Xuzhou Central Hospital, 199 Jiefang South Road, Xuzhou 221009, P.R. China
Tel: +86 189 52171161
Email: zhangmiaodr@163.com

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INTRODUCTION

Brain metastases (BMs) account for 10% of non-small cell lung cancer (NSCLC) patients at initial presentation; whereas 25%~40% of the patients develop BMs during their disease (1). Once formed, BMs hide behind the blood-brain barrier and become inaccessible to chemotherapies. In addition, patients with BMs from NSCLC have largely been excluded from trials. Pemetrexed plus cisplatin is the first-line chemotherapy in nonsquamous NSCLC. However, the efficacy of chemotherapy in BMs is limited by tumor resistance and the blood-brain barrier.

To date, molecular therapy targeting driver genes and immunotherapy have shown efficacy in multiple BMs as compared to surgical resection, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS) (2).

Immune checkpoint inhibitors (ICIs) enhance the immune response of the body through inhibiting cytotoxic T-lymphocyte-associated protein (CTLA-4), programmed cell death protein-1 (PD-1), or program death ligand-1 (PD-L1) to fight against cancers. Camrelizumab (SHR-1210), a PD-1 inhibitor (Jiangsu Hengrui Medicine Co. Ltd., Lianyungang, China), is being investigated as a treatment option for non-squamous NSCLC (3).

To our knowledge, the role of camrelizumab in BMs from lung cancer has never been reported before. Herein, we report the efficacy of camrelizumab in a patient with chemotherapy-refractory BMs from lung adenocarcinoma. Meanwhile, the relevant studies were briefly reviewed.

CASE PRESENTATION

The clinical data were presented anonymously for privacy concerns. A 49-year-old male non-smoker was referred to the local hospital due to 6-week back pain and vomiting in January 2018. His Eastern Cooperative Oncology Group (ECOG) performance status score on admission was 1. Laboratory tests only showed slightly elevated carcinoembryonic antigen (CEA). Further computed tomography (CT) revealed a lung mass and spine metastatic lesions (Figure 1). CT-guided percutaneous lung biopsy confirmed the pathological diagnosis of primary lung adenocarcinoma. In addition, the specimen revealed positive expression of PD-L1 about 20% and negative expression of epidermal growth factor receptor. Further brain magnetic resonance imaging (MRI) showed three isolated lesions <1 cm in diameter without obvious surrounding edema.

After a multidisciplinary evaluation, first-line intravenous pemetrexed (500 mg/m^2 of body surface area) and cisplatin (75 mg/m^2 of

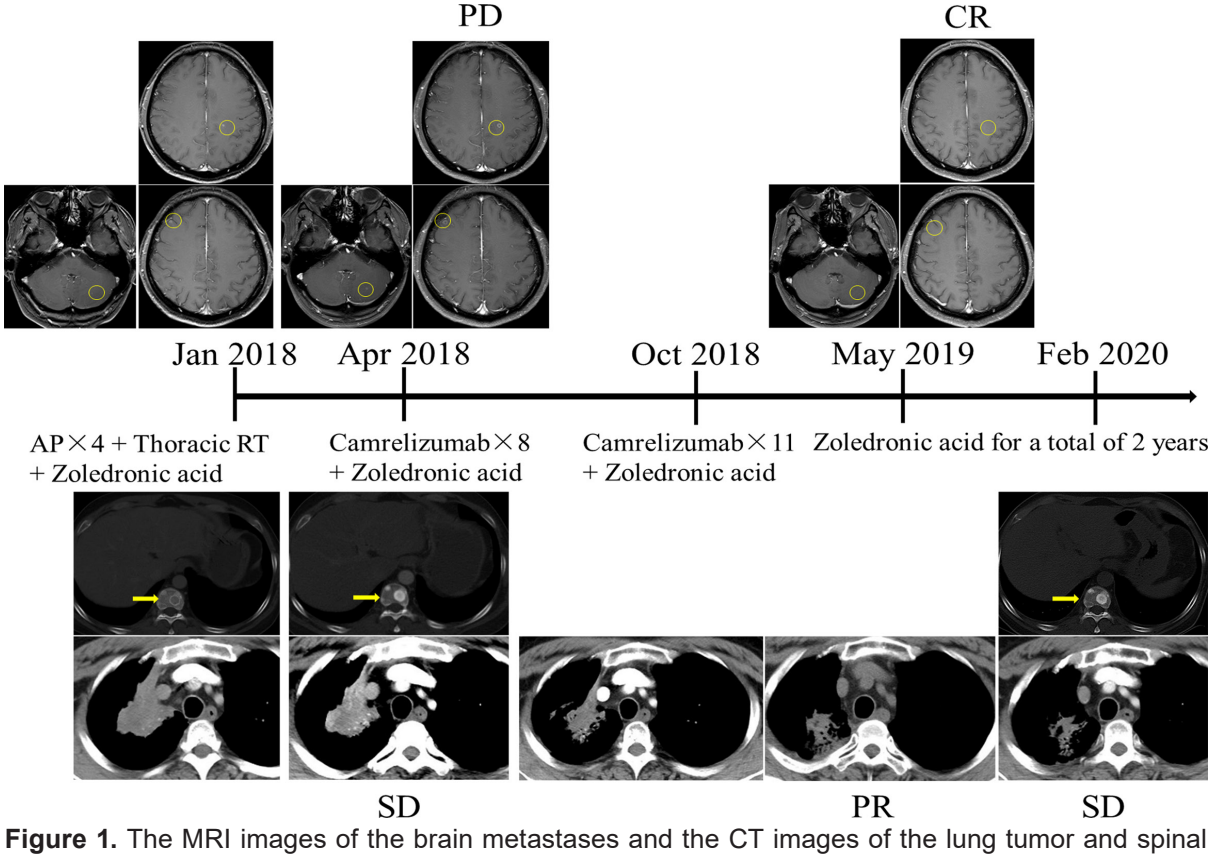

Figure 1. The MRI images of the brain metastases and the CT images of the lung tumor and spinal metastases.
Note: The BMs showed progressive disease after chemotherapy (April 2018) but a complete remission following immunotherapy (May 2019). In addition, a partial remission of the lung tumor and stable disease of the spinal metastases were shown during immunotherapy.

body surface area) plus zoledronic acid (4 mg every month) were administered. Concurrent local thoracic radiotherapy was also initiated (a total of 30 Gy by 10 fractions). The serum CEA was decreased significantly at first but increased after 4 cycles of chemotherapy (Figure 2). Meanwhile, the obvious 3 brain lesions were enlarged (progressed disease, PD) simultaneously; whereas the lung tumor and spine metastases indicated stable diseases (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

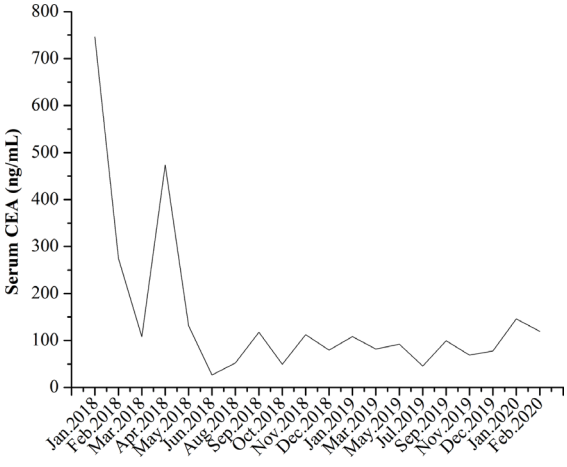

Figure 2. The change of serum carcinoembryonic antigen during the treatment.

The patient refused cranial radiotherapy for personal reasons. Considering his compromised performance status, second-line camrelizumab (200 mg once, every 2 weeks) instead of paclitaxel was started in April 2018, which was scheduled to be continued until PD or intolerable/uncontrolled adverse events. Partial remission of the lung tumor was demonstrated after 8 cycles of immunotherapy. In addition, the serum CEA was decreased significantly and maintained stable (Figure 2). Nevertheless, the camrelizumab was discontinued due to moderate headache of the patient for nearly a month, without hemoptysis, dyspnea, or chest pain. Grade II rashes, leukopenia, and grade III fatigue according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 were recorded. Best supportive care along with granulocyte-colony stimulating factor was administered. Prophylactic antibiotics were avoided due to the continually normal temperature of the patient and the negative culture of the sputum.

One and a half months later, camrelizumab was re-challenged for another 11 cycles. A complete remission (CR) of the 3 cranial lesions was indicated in May 2019. The patient was followed up without further treatment. He showed a satisfactory quality of life. Restaging in February 2020 by chest and abdomen CT did not show newly emerged lesions (Figure 1). Furthermore, the serum CEA remained stable (Figure 2). Thus, the patient got more than 12 months of intracranial progression-free survival (PFS) and 20 months of overall survival (OS) since the initiation of camrelizumab.

DISCUSSION

The present case firstly revealed the efficacy of camrelizumab on BMs from lung adenocarcinoma. There is currently no consensus or guideline concerning the optimal regimen for NSCLC patients with BMs. Only a small percentage of patients could benefit from surgery or SRS. Immunotherapy has shown impressive results in patients with PD-L1 expression in tumor cells, which can be further enhanced by radiotherapy and traditional chemotherapy (4, 5). ICIs have changed the treatment landscape for NSCLC (6). A meta-analysis of 17 studies showed that concurrent SRS and ICIs may improve the efficacy for BMs (7). Similarly, a review indicated that a subset of patients with BMs benefited from the addition of ICIs to radiotherapy and surgery (8).

We searched PubMed and Google Scholar for published articles up to May 2020 regarding ICIs for the treatment of BMs from lung cancer. Finally a total of 23 reports including 2 RCTs (NCT02085070 and NCT02008227), 9 cohort studies, and 12 case reports enrolling 1187 patients were retrieved (Table 1). Some but not all the reports provided detailed survival information.

Table 1. Previous reports of immune checkpoint inhibitors for lung cancer with brain metastases.

First author, year	Study design	No. of pts	Tumor type	PD-L1 expression	Therapeutic regimen	Intracranial disease control rate	Intracranial PFS, months	OS, months	Grade ≥3 AEs (n)
Goldberg, 2016 (9)	Open-label, phase 2 trial (NCT02085070)	18	NSCLC	Positive	Pembrolizumab (10 mg/kg) every 2 weeks	ORR: 33.3% (4 CR and 2 PR)	5.8 (3.2-7.0) in 5 respondents	NR	Colitis, pneumonitis, fatigue and hyperkalemia
Gadgeel, 2019 (10)	Phase 3 trial (NCT02008227)	61	NSCLC	Positive in 42.6% cases	Atezolizumab	NR	NR	16.0	Incidence, 14 (23.3%)
Schapira, 2018 (11)	Cohort study	37	NSCLC	NR	Nivolumab/ pembrolizumab/ atezolizumab + SRS	NR	NR	17.6	Ataxia and headache
Lanier, 2019 (12)	Cohort study	73	Lung cancer	NR	Nivolumab/ pembrolizumab/ ipilimumab after SRS	NR	NR	15.9	1-year neurologic/ non-neurologic death: 9%/29%.
Hendriks, 2019 (13)	Cohort study	255	NSCLC	Positive in 179 (64.9%) cases	PD-1/PD-L1 inhibitors +/- anti-CTLA-4 antibody	ORR: 27.3%	1.7	8.6	NA
Bjørnhart, 2019 (14)	Cohort study	21	NSCLC	Positive	Nivolumab/pembrolizumab	ORR: 33.3% (1 CR and 6 PR)	NR	8.2	Pneumonitis, colitis and hypophysitis
Crinò, 2019 (15)	Cohort study	409	Non-squamous NSCLC	NR	Nivolumab in 118 patients; (nivolumab + radiotherapy) in 74 cases	ORR: 16.6% (4 CR and 64 PR)	NR	8.6 (1-year survival of 43%)	Termination of treatment for AEs: 23 (7%)
Shepard, 2019 (16)	Cohort study	16	NSCLC	NR	Nivolumab/pembrolizumab/ atezolizumab	8 (50%) CR	6.6	NR	None
Koenig, 2019 (17)	Cohort study	45	NSCLC	NR	Ipilimumab/nivolumab/ pembrolizumab/atezolizumab + SRS	NR	NR	Total: 9.4 (1 year survival of 42%)	NR
Zhang, 2020 (18)	Cohort study	32	31 NSCLC; 1 other type	NR	Nivolumab	ORR: 28.1% (2 CR and 7 PR)	2.2	14.8	NR
Hulsbergen, 2020 (19)	Cohort study	48	NSCLC	Positive in 33 cases	NR	NR	NR	26	NR
Gauvain, 2018 (20)	Case series	30	NSCLC	Positive in 5 cases	Nivolumab	ORR: 9%	3.9	NR	Asthenia, diarrhea and anemia

Chen, 2018 (21)	Case series	74	NSCLC	NR	Nivolumab/pembrolizumab/ ipilimumab + SRS	ORR: 88%	Overall: 11.5 (1-24)	NR	NR
Hendriks, 2019 (22)	Case series	19	NSCLC	Positive in 8 cases	Nivolumab/pembrolizumab	NR	2.0 (1.8-2.2)	3.7 (0.9-6.6)	NR
Singh, 2019 (23)	Case series	39	NSCLC	Positive	Nivolumab/pembrolizumab/ (ipilimumab + nivolumab) + SRS	ORR: 94.9% of the 291 lesions	Local: 3.6; distant: 4.67	10 (range: 6~25)	NR
Pluchart, 2017 (24)	Case report	1	Adenocarcinoma	NR	Corticosteroids + 4 courses of nivolumab	PR	4 +	NR	None
Salati, 2018 (25)	Case report	1	Sarcomatoid carcinoma	Positive, ≥ 50%	Nivolumab	CR	22 +	NR	None
Melian, 2018 (26)	Case report	2	NSCLC	Positive < 5%	Ipilimumab + nivolumab	PR	2.5 +	NR	NR
Otsubo, 2018 (27)	Case report	1	Adenocarcinoma	Positive, 100%	Pembrolizumab	PR	4.5	NR	NR
Uprety, 2019 (28)	Case report	1	Adenocarcinoma	Positive, 95%	Pembrolizumab	SD	10 +	NR	NR
Lin, 2019 (29)	Case report	1	Adenocarcinoma	NR	Atezolizumab + SRS	CR	23 +	NR	NR
Jong, 2019 (30)	Case report	1	Adenocarcinoma	Positive, < 1%	Nivolumab for 2 cycles	PR	10	NR	NR
Abid, 2019 (31)	Case report	2	Adenocarcinoma	Positive in 1 case	Pembrolizumab + WBRT; Nivolumab	1 PR; 1 SD	5.5	NR	NR

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CTLA-4, cytotoxic T-lymphocyte antigen 4; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; AEs, adverse events; PSC, pulmonary sarcomatoid carcinoma; ORR, objective response rate; PFS, progression-free survival; iPFS, the PFS estimated according to the change of intracranial metastases; OS, overall survival; ICIs, immune checkpoint inhibitors; NR, not reported.

Table 2. The registered trials of immunotherapy for lung cancer patients with brain metastases.

Identifier	Year	Study design	Genetic status	Regimen	Estimated enrollment	Primary outcomes	Status	Country
NCT01454102	2011	Phase I	Not mentioned	Nivolumab monotherapy	Total, 472	Adverse Events	Active, not recruiting	America
NCT02008227	2013	Phase III	Not mentioned	Atezolizumab vs. docetaxel	Total, 1225	PFS, OS	Completed	America
NCT01846416	2013	Phase II single-arm	PD-L1 (+)	Atezolizumab	138	ORR	Completed	America
NCT02085070	2014	Phase II single-arm	PD-L1 (+)	Pembrolizumab (MK-3475)	Total, 65	ORR	Completed	America
NCT02681549	2016	Phase II single-arm	PD-L1>1%	Pembrolizumab + Bevacizumab	Total, 53	Brain metastasis response rate	Recruiting	America
NCT02696993	2016	Phase I/II	Not mentioned	(Nivolumab ± ipilimumab) + SRS/WBRT	88	Intracranial PFS	Recruiting	America
NCT02978404	2016	Phase II single-arm	Not mentioned	Nivolumab + SRS (15-20 Gy)	60	Intracranial PFS	Recruiting	Canada
NCT02886585	2016	Phase II	Not mentioned	Pembrolizumab + SRS	Total, 102	Intracranial and extra-cranial PFS, OS	Recruiting	America
NCT02858869	2016	Phase II	PD-L1 positivity is not required	Pembrolizumab + SRS	Total, 30	Proportion of dose limiting toxicities	Recruiting	America
NCT03325166	2017	Phase II single-arm	PD-L1>1%	Pembrolizumab + Ferumoxytol	20	Adverse events	Recruiting	America
ChiCTR1800019899	2018	Phase II	PD-L1>1%; EGFR/ALK (-)	Anti-PD-1/PD-L1 + WBRT; or anti-PD-1/PD-L1 monotherapy	76	Intracranial PFS	Not yet recruiting	China
NCT03955198	2019	Phase II	EGFR/ALK (-)	Durvalumab + SRS	100	Intracranial PFS	Recruiting	France
NCT04211090	2019	Phase II single-arm	PD-L1 (+); EGFR/ALK (-)	camrelizumab + pemetrexed/ carboplatin	64	Intracranial ORR	Recruiting	China
NCT04291092	2020	Phase II single-arm	Not mentioned	Camrelizumab (SHR-1210) + local radiotherapy	20	PFS, ORR	Not yet recruiting	China

Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery.

In general, the intracranial objective response rate using immunotherapy was 9%~94.9%; whereas the PFS and OS were 1~24 months and 0.9~26 months, respectively. Major patients showed a positive expression of PD-L1 in the tumor specimen. However, a pooled analysis for prognostic factors of long-term survival such as the expression of PD-L1, serum CEA, and first response time was not applicable due to lacking the original data. Based on the findings from the literature review, ICIs could be considered for selected patients with chemotherapy-refractory BMs from lung cancer. However, considering the overall low quality of the evidence from the retrieved studies, well-designed researches are needed before a guideline or recommendation could be drawn. The registered trials of immunotherapy using ICIs for BMs from lung cancer were shown in Table 2.

In summary, we report the efficacy of camrelizumab in a patient with chemotherapy-refractory metastatic lung adenocarcinoma. Further high-quality trials are warranted.

ETHICS STATEMENT

This case report was written and offered for publication with written informed consent from the patient. The patient gave written informed consent under the Declaration of Helsinki.

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We thank the patient for his permission to publish this case report.

Conflicts of Interest: None declared.

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