First-line pemetrexed and carboplatin plus anlotinib for epidermal growth factor receptor wild-type and anaplastic lymphoma kinase-negative lung adenocarcinoma with brain metastasis

A case report and review of the literature

Chu Zhang, MDa, Feng-Wei Kong, BScb, Wen-Bin Wu, PhDc, Miao Zhang, MDc, Guang-Mao Yu, PhDa, Xiang Wang, MDc, Yuan-Yuan Liu, PhDc,∗

Abstract

Rationale: Brain metastasis (BM) is a serious complication in non-small cell lung cancer (NSCLC) patients. Pemetrexed is one of the preferred agents in nonsquamous NSCLC with BM; however, the traditional chemotherapy demonstrated limited efficacy partly due to drug resistance and the blood-brain barrier.

Patient concerns: A 52-year-old male non-smoker was admitted for irritating cough, chest distress, and back pain.

Diagnoses: Epidermal growth factor receptor wild-type, anaplastic lymphoma kinase-negative primary lung adenocarcinoma with an asymptomatic solitary BM (cTxNxM1b, IVA).

Interventions: Pemetrexed (500 mg/m² of body surface area) and carboplatin (area under the curve of 5) were firstly administered every 3 weeks for 3 cycles, followed by pemetrexed/carboplatin plus anlotinib (12 mg daily; 2 weeks on and 1 week off) for another 3 cycles. Then maintenance anlotinib monotherapy was continued for a year, without unacceptable adverse events.

Outcomes: The BM was slightly enlarged after 3 cycles of pemetrexed/carboplatin; however, a complete remission was achieved after the combination therapy. His intracranial progression-free survival was more than 2 years.

Lessons: Pemetrexed/carboplatin plus anlotinib could be considered for the treatment of epidermal growth factor receptor wild-type, anaplastic lymphoma kinase-negative lung adenocarcinoma with BM. Further well-designed trials are warranted to verify this occasional finding.

Abbreviations: EGFR = epidermal growth factor receptor, OS = overall survival, PFS = progression-free survival, TKI = tyrosine kinase inhibitor.

Keywords: anlotinib (AL3818), lung cancer, pemetrexed, targeted therapy, tyrosine kinase inhibitor, vascular endothelial growth factor receptor
1. Introduction

Anlotinib (AL3818) is a tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor, fibroblast growth factor receptor, platelet-derived growth factor receptors, and c-kit. Anlotinib has been approved in China for locally advanced or metastatic non-small cell lung cancer (NSCLC) patients who have undergone tumor progression or recurrence after ≥2 lines of systemic chemotherapy,[1] which is based on a significant improved overall survival (OS) with anlotinib versus the placebo. It is reported that the major toxicities of anlotinib include hypertension (67.4%), hand-foot syndrome (43.9%), hemoptysis (14.0%), thyroid stimulating hormone elevation (46.6%), and corrected QT interval prolongation (26.2%).[2] At the dose of 12mg once daily at the 2-week on and 1-week off schedule, anlotinib displays manageable toxicity, long circulation, and broad-spectrum antitumor efficacy.[3] In detail, the plasma concentrations of anlotinib reached its maximum on day 14 and decreased subsequently until the next cycle of treatment. Although it improves the progression-free survival (PFS) and OS of the patients with advanced NSCLC, anlotinib has a significantly lower incidence of grade 3 or higher side effects compared to sunitinib.[4]

However, for epidermal growth factor receptor (EGFR) wild-type NSCLC patients, the therapeutic options for brain metastasis (BM) are limited. Pemetrexed (combined with cisplatin or carboplatin) is the first-line agent for lung adenocarcinoma according to the National Comprehensive Cancer Network guideline for NSCLC, Version 1.2020[5]; nevertheless, the efficacy of this traditional chemotherapy regimen in EGFR-negative, nonsquamous NSCLC patients with BM is somewhat uncertain.

To the best of our knowledge, the evidence concerning the efficacy of first-line pemetrexed plus anlotinib for BM from nonsquamous NSCLC is still lacking. Herein we presented a lung adenocarcinoma patient who demonstrated a complete remission of a solitary BM for 2 years after pemetrexed/cisplatin plus anlotinib. Furthermore, the relevant reports and the registered trials in terms of the TKI-based treatments for BM from lung cancer were briefly reviewed.

2. Case presentation

The clinical data were treated anonymously for privacy concern. A 52-year-old male nonsmoker was admitted due to irritating cough, chest distress, and back pain in November 2015. The chest x-ray indicated left-sided pleural effusion and atelectasis of the left lower pulmonary lobe (Fig. 1A). Laboratory tests indicated mainly normal serum neuron-specific enolase, carcinoembryonic antigen, carbohydrate antigen 724/125, alkaline phosphatase, cytokeratin-19 fragment, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, lactic dehydrogenase, and albumin.

The patient was initially diagnosed as spontaneous hydro pneumothorax empirically. Further contrast-enhanced computed tomography after chest tube drainage showed atelectasis (Fig. 1B). In addition, malignant tumor cells were detected in the pleural effusion (Fig. 1C), which supported the pathological diagnosis of primary lung adenocarcinoma. Moreover, the cranial magnetic resonance imaging revealed a solitary BM in the left cerebrum (Fig. 2A); whereas the whole-body emission computed tomography excluded other metastases. However, a definite diagnosis was not obtained, because a thoracoscopic biopsy was not performed to avoid unnecessary injury and to diminish the risk of iatrogenic tumor dissemination. Based on these findings, this case was staged as cTxNxM1b, IV A according to the 8th edition of tumor, node, and metastasis staging system for lung cancer.[6] Liquid biopsy showed wild-type EGFR, human epidermal growth factor receptor 2 and vascular endothelial growth factor, followed by negative echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (ALK) fusion gene.

After a multidisciplinary evaluation, first-line systemic anticancer treatment, instead of surgery for the cranial oligometastasis, was scheduled. Informed consent was obtained from the patient before treatment. The efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1; meanwhile, the adverse events were recorded and staged in line with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Initially, the patient was given first-line pemetrexed (500mg/m² of body surface area) and carboplatin (Area under curve (AUC) = 5) every 21 days following the prophylactic folinic acid and vitamin B12 for 3 cycles. There was no newly-emerged lung or pleural lesions, which might revealed the efficacy of intravenous pemetrexed/cisplatin in lung adenocarcinoma. However, the solitary BM showed stable disease after the first 3 cycles of chemotherapy (Fig. 2B).

After another multidisciplinary consultation, pemetrexed/carboplatin plus oral anlotinib (12mg once daily at 2-week-on and 1-week-off schedule) was administered. Reimaging of the chest x-ray radiography showed left-sided pleural effusion and atelectasis of the left lower lobe (November 2015); (B) The computed tomography indicated the atelectasis of the left lower lobe after closed thoracic drainage; (C) The cytology of the drained effusion revealed malignant cells (hematoxylin-eosin staining, × 400).
brain after another 3 cycles of combination therapy demonstrated an impressive complete remission of the BM (Fig. 2C). Subsequently, maintenance anlotinib monotherapy, instead of pemetrexed, was continued for 1 year. During the follow up, there was no detectable pleural effusion, newly-onset lung lesion, or distant metastasis. The adverse events were mainly well tolerated. Grade 2/3 hypertension and hand-foot syndrome were controlled effectively. No grade 4 toxicities were observed in this case. The patient obtained an intracranial PFS of more than 2 years till February 2018; however, he was lost to follow up thereafter.

3. Discussion

BM from lung cancer is associated with poor survival of the patients. The incidence of BM has continued to rise, as most patients develop resistance to targeted agents.[7] About 10% of NSCLC patients have BM at diagnosis while 25% to 40% of them develop BM; however, the conventional chemotherapy does not cross the blood-brain barrier.[8] To date, the established management approaches for BM include stereotactic radiosurgery, fractionated radiation therapy, and surgical resection[9]; nevertheless, the optimal regimen for achieving long-term control of BM is yet to be elucidated. In the present case, anlotinib plus pemetrexed/carboplatin demonstrated enduring efficacy in lung adenocarcinoma with solitary BM.

Pemetrexed disodium is effective in various solid tumors. However, the distribution of pemetrexed into the central nervous system is truly limited, probably due to an efflux clearance process.[10] Another research revealed that pemetrexed could distribute from the plasma to the cerebrospinal fluid (CSF) within 1 to 4 hours, but the concentrations of this agent in the CSF was less than 5% of that in the plasma; therefore, the limited anti-tumor activity of intravenous pemetrexed might partly due

| First author, yr | No. of patients | Gene mutation status | Treatment lines | Therapeutic regimen | Median PFS, months | Median iPFS, mo | Median OS, mo |
|------------------|-----------------|----------------------|-----------------|--------------------|--------------------|---------------|--|
| Omlin, 2009[19]  | 1               | NA                   | 4th             | Pemetrexed         | 8.4                | NA            | NA           |
| Bearz, 2010[20]  | 39              | NA                   | 2nd or 4th      | Pemetrexed         | NA                | 10            |              |
| Barlesi, 2011[21]| 43              | NA                   | 1st             | Pemetrexed + carboplatin +/- radiotherapy | 4.0            | 7.4           |              |
| Bailon, 2012[22]| 30              | NA                   | 1st             | Pemetrexed + carboplatin | 7.2            | 9.1           |              |
| Ito, 2012[23]    | 1               | NA                   | 1st             | Pemetrexed          | 16                | NA            |              |
| Yuan, 2012[24]   | 1               | EGFR/ALK-mutated     | 2nd             | Pemetrexed + gefitinib | 6              | NA            | 9            |
| Liang, 2012[25]  | 1               | EGFR/ALK-negative    | 1st             | Pemetrexed + cisplatin + radiotherapy + Cetuximab | NA            | NA            | NA           |
| Ochi, 2012[26]   | 2               | EGFR/ALK-negative    | 3rd and beyond  | Pemetrexed +/- cisplatin | 30            | NA            | NA           |
| Kumthekar, 2013[27]| 4            | NA                   | 2nd/3rd         | Pemetrexed          | NA                | NA            |              |
| Zhang, 2014[28]  | 9               | EGFR wild-type       | 1st and beyond  | Pemetrexed + cisplatin + erlotinib | 4.9            | 6.0           | 6.6          |
| Zhu, 2015[29]    | 30              | NA                   | 1st             | Pemetrexed + cisplatin/carboplatin | 5.0            | 6.0           | 11.0         |
| Zhang, 2015[30]  | 1               | ALK-positive         | 2nd             | Pemetrexed + cotelizib + radiotherapy | > 7.0         | NA            |              |
| He, 2016[31]     | 31              | EGFR-mutated         | 2nd/3rd         | Pemetrexed          | 3.4              | NA            | NA           |
| He, 2016[32]     | 1               | unknown              | 1st             | Pemetrexed + carboplatin + radiotherapy | NA            | Complete remission | NA     |
| Stefanou, 2016[33]| 11            | NA                   | 1st             | Pemetrexed + bevacizumab | 9.2            | NA            | 14.0         |
| Tian, 2019[34]   | 26              | EGFR-mutated, EGFR wild-type, unknown | 1st | Pemetrexed + bevacizumab | 9.2            | 24.3          | NA           |
| Yu, 2019[35]     | 138             | 49 EGFR wild-type, 89 unknown | 1st | Pemetrexed-based chemotherapy +/- radiotherapy | NA            | 9.5           | 21.0         |

iPFS = estimated as PFS estimated according to the change of intracranial metastases. NA = not available, OS = overall survival, PFS = progression-free survival.
to its low concentration in the CSF. Novel therapeutic agents must cross the blood vessel wall to reach cancer cells in adequate quantities and overcome the acquired drug resistance. The studies of BM could uncover new therapeutic targets and identify treatment approaches. A deep understanding of the blood-brain barrier and blood-tumor barrier would enable personalized management for primary brain malignancies and BMs, because the utilization of small-molecules drugs or proteins for the treatment of central nervous system tumors is significantly restricted by the blood-brain barrier.

Table 2
The registered trials regarding anlotinib (AL3818) in the treatment of lung cancer with brain metastases.

| Registration identifier | Year | Tumor type | Driver-gene mutation status | Treatment line | Regimen | Estimated enrollment | Primary outcomes | Status | Country |
|------------------------|------|------------|-----------------------------|----------------|--------|---------------------|-----------------|-------|---------|
| ChiCTR1800017929       | 2018 | NSCLC      | NA                          | 2nd            | Anlotinib | 20                  | Local control rate | Recruiting | China    |
| ChiCTR1800019580       | 2018 | NSCLC      | Unknown or wild-type EGFR/ALK/ROS1/T790M | 3rd and beyond 1st | Anlotinib + stereotactic radiosurgery | 50 | Local control rate | Not yet recruiting | China |
| ChiCTR1900002391       | 2019 | NSCLC      | NA                          | 3rd and beyond 2nd and 3rd | Anlotinib + whole-brain radiotherapy | 30 | PFS | Not yet recruiting | China |
| ChiCTR1900000459       | 2019 | SCLC       | NA                          | 3rd            | Anlotinib + radiotherapy | 25 | Adverse events, tumor inhibition rate | Not yet recruiting | China |
| NCT01447728 (Revision-001) | 2019 | NSCLC      | NA                          | 3rd and beyond 2nd and 3rd | Anlotinib + whole-brain radiotherapy | 28 | Intracranial PFS (IPFS) | Not yet recruiting | China |

DCR = disease control rate, NA = not available, NSCLC = non-small cell lung cancer, ORR = objective response rate, PFS = progression-free survival, SCLC = small-cell lung cancer.

Table 3
The registered trials of pemetrexed for lung cancer patients with brain metastases.

| Identifier               | Year | Tumor type | Treatment line | Regimen                    | Estimated enrollment | Primary outcomes                  | Status          | Country   |
|-------------------------|------|------------|----------------|----------------------------|---------------------|-----------------------------------|-----------------|-----------|
| NCT00227019             | 2005 | NSCLC      | 2nd            | Pemetrexed + bevacizumab   | 16                  | Incidence of brain metastases     | Completed       | America   |
| NCT00363415             | 2006 | SCLC       | NA             | Pemetrexed + carboplatin   | 908                 | OS                                | Completed       | America   |
| NCT00312722             | 2006 | Non-squamous NSCLC | 2nd and beyond | Pemetrexed + bevacizumab   | 115                 | Adverse events                    | Completed       | Switzerland |
| NCT00289748             | 2006 | NSCLC      | NA             | Pemetrexed + whole brain radiotherapy | 10 | Response of brain metastases ORR of brain metastasis | Completed | America |
| NCT007744900 (GFPC-07-01) | 2008 | NSCLC      | 1st            | Pemetrexed + cisplatin     | 45                  | DFS                               | Completed       | France |
| NCT00800819             | 2008 | Non-squamous NSCLC | NA            | Pemetrexed + nintedanib (BIBF1120) | 718 | Adverse events, tumor inhibition rate | Completed | Germany |
| NCT014474102 (CheckMate 012) | 2011 | NSCLC      | 1st and beyond | Pemetrexed + nivolumab     | A total of 472       | Adverse events                    | Active, not recruiting | America |
| NCT01578666             | 2012 | Adenocarcinoma | NA            | Pemetrexed + cisplatin + erlotinib | 69 | ORR of brain metastasis Intracranial PFS | Completed | China |
| NCT01951482             | 2013 | Non-squamous NSCLC | 1st            | Pemetrexed + cisplatin +/- bevacizumab | 108 | Intracranial PFS | Recruiting | China |
| NCT01951469             | 2013 | NSCLC      | 1st            | Pemetrexed + cisplatin + gefitinib or gefitinib monotherapy | 160 | Intracranial PFS | Recruiting | China |
| NCT02162537 (METAL2)    | 2014 | Non-squamous NSCLC | 1st            | Pemetrexed + cisplatin + bevacizumab + cerebral radiotherapy | 95 | PFS | Terminated | France |
| NCT022844900            | 2014 | Adenocarcinoma | NA            | Pemetrexed               | 25                  | PFS                              | Unknown         | China |
| NCT03507244             | 2018 | Solid tumors | 1st            | Intrathecal pemetrexed + involved-field radiotherapy | 34 | Adverse events | Completed | China |
| ChiCTR1800016615       | 2018 | NSCLC      | After multi-line failures | Intrathecal pemetrexed | 20 | OS | Recruiting | China |
| NCT03526900 (ATEZO-BRAIN) | 2018 | Non-squamous NSCLC | 1st            | Pemetrexed + carboplatin + atezolizumab | 40 | PFS | Recruiting | Spain |
| NCT04211090             | 2019 | Non-squamous NSCLC | 1st            | Pemetrexed + carboplatin + camidanizumab | 64 | ORR of brain metastasis | Recruiting | China |
| ChiCTR2000028936       | 2020 | NSCLC      | NA            | Intrathecal pemetrexed via an Ommaya reservoir | 25 | ORR, PFS | Recruiting | China |

CNS = central nervous system, DCR = disease control rate, DFS = disease-free survival, NA = not available, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, SCLC = small-cell lung cancer.
A retrospective analysis of NSCLC patients with BM and EGFR mutation showed that the concurrent EGFR-TKI and whole-brain radiotherapy improved the oncological benefits without additional adverse events. Nonetheless, emerging data revealed that the whole-brain radiotherapy is associated with high incidences of neurotoxicity; therefore, despite the improvements in targeted therapy and immunotherapy, new agents that target the genetic mutations enriched in BM are still urgently needed. Besides the intracranial activity of immuno-therapy, there is growing evidence indicating that TKIs used in patients with identified targetable genetic mutations or rearrangements could be effective in the central nervous system. It is reported that the number of BM does not impact the oncological prognosis in the EGFR/ALK mutated NSCLC patients; in addition, the number of BM independently affect the survival in driver gene wild-type BM patients. The ALK inhibitors including alectinib, ceritinib, brigatinib, lorlatinib have been designed to cross the blood-brain barrier more efficiently than crizotinib and achieve higher concentration in the CSE. A pooled analysis of 2 trials confirmed the safety and efficacy of second-line bevacizumab and pemetrexed in NSCLC patients with BM.

We searched PubMed, Web of Science, Scopus, Embase, Europe PMC, Cochrane Library, and Google Scholar for similar studies regarding pemetrexed and targeted therapy for advanced NSCLC with BM up to February 2020. Keywords and MeSH terms in title or abstract including “TKI” or “pemetrexed” or “targeted therapy” and “pulmonary” or “lung” and “cancer” and “brain metastasis” or “cranial metastasis” were used. No restriction was made regarding the publication languages. Finally a total of 17 reports involving 369 patients were summarized and listed in Table 1, which demonstrated the efficacy of combination therapeutic regimen in lung cancer with BM. Specifically, Yu et al. reported that first-line pemetrexed-based chemotherapy provided a median OS and intracranial PFS of 21.0 months and 9.5 months respectively in 138 NSCLC patients with BM. Furthermore, a retrospective cohort study showed that the overall cumulative incidence of BM was significantly higher in the targeted therapy group than those in the cytotoxic chemotherapy group, whereas the younger age, female, and first-line targeted therapy were significant risk factors of subsequent BM.

However, a pooled analysis or meta-analysis was not applicable because most of the survival data of the patients were not available from these articles. Considering the generally low quality of evidence from the retrieved studies, more trials are warranted. The registered trials regarding anlotinib (AL3818) or pemetrexed for the treatment of lung cancer with BM was listed in Table 2 and Table 3, respectively. Accordingly, an updated guideline or consensus recommendation using targeted therapy plus pemetrexed for the treatment of lung cancer with BM might be provided based on the ongoing evidence.

4. Conclusions
Pemetrexed/carboplatin plus anlotinib could be considered for patients with EGFR wild-type, ALK-negative lung adenocarcinoma, and BM. Further well-designed trials are warranted.

Author contributions
Conceptualization: Chu Zhang, Feng-Wei Kong, Xiang Wang.
Data curation: Guang-Mao Yu.

Funding acquisition: Chu Zhang, Miao Zhang.
Methodology: Yuan-Yuan Liu.
Resources: Xiang Wang, Wen-Bin Wu.
Writing – original draft: Feng-Wei Kong, Wen-Bin Wu, Xiang Wang.
Writing – review & editing: Chu Zhang, Feng-Wei Kong, Yuan-Yuan Liu.

References
[1] Syed YY. Anlotinib: first global approval. Drugs 2018;78:1057–62.
[2] Zhou M, Chen X, Zhang H, et al. China National Medical Products Administration approval summary: anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. Cancer Commun (Lond) 2019;39:36.
[3] Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol 2016;9:105.
[4] Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol 2018;11:120.
[5] Ettenger DR, Wood DE, Aggarwal C, et al. NCCN guidelines insights: non-small cell lung cancer, version 1.2020. J Natl Compr Canc Netw 2019;17:1464–72.
[6] Lancia A, Merizzoli E, Filippi AR. The 8th UICC/AJCC TNM edition for non-small cell lung cancer staging: getting off to a flying start? Ann Transl Med 2019;7(Suppl 6):S205.
[7] Chukwueke UN, Brastianos PK. Precision medical approaches to the diagnoses and management of brain metastases. Curr Treat Options Oncol 2019;20:49.
[8] Abdollahi SM, Wong A. Brain metastases in non-small-cell lung cancer: are tyrosine kinase inhibitors and checkpoint inhibitors now viable options? Curr Oncol 2018;25(Suppl 1):S103–14.
[9] Niranjana A, Lunsford LD, Ahluwalia MS. Targeted therapies for brain metastases. Prog Neurol Surg 2019;34:125–37.
[10] Dai H, Chen Y, Elmqust WF. Distribution of the novel antifolate pemetrexed to the brain. J Pharmacol Exp Ther 2005;315:222–9.
[11] Kunthekar P, Grimm SA, Avram MJ, et al. Pharmacokinetics and efficacy of pemetrexed in patients with brain or leptomeningeal metastases. J Neurooncol 2013;112:247–53.
[12] Boire A, Brastianos PK, Garzia L, et al. Brain metastasis. Nat Rev Cancer 2020;20:4–11.
[13] Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer 2020;20:26–41.
[14] Chen H, Wu A, Tao H, et al. Concurrent versus sequential whole brain radiotherapy and TKI in EGFR-mutated NSCLC patients with brain metastasis: a single institution retrospective analysis. Medicine (Baltimore) 2018;97:e13014.
[15] Brastianos P, Davies MA, Margolin K, et al. Modern management of central nervous system metastases in the era of targeted therapy and immune oncology. Am Soc Clin Oncol Educ Book 2019;39:e59–69.
[16] Balasubramanian SK, Sharma M, Venur VA, et al. Impact of EGFR mutation and ALK rearrangement on the outcomes of non-small cell lung cancer patients with brain metastasis. Neuro Oncol 2020;22:267–77.
[17] Wrona A. Management of CNS disease in ALK-positive non-small cell lung cancer: is whole brain radiotherapy still needed? Cancer Radiother 2019;23:432–8.
[18] Gubens MA, Chuzhang JC, Akerley W, et al. A pooled analysis of advanced nonsquamous non-small cell lung cancer patients with stable treated brain metastases in two phase II trials receiving bevacizumab and pemetrexed as second-line therapy. J Thorac Dis 2018;10:219–27.
[19] Omlin A, D’addario G, Gillessen S, et al. Activity of pemetrexed against brain metastases in a patient with adenocarcinoma of the lung. Lung Cancer 2009;65:383–4.
[20] Bearz A, Garassino I, Tiseo M, et al. Activity of pemetrexed on brain metastases from non-small cell lung cancer. Lung Cancer 2016;98:264–8.
[21] Barlesi F, Gervais R, Lena H, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01). Ann Oncol 2011;22:2466–70.
[22] Bailon O, Chouahnia K, Augier A, et al. Upfront association of carboplatin plus pemetrexed in patients with brain metastases of lung adenocarcinoma. Neuro Oncol 2012;14:491–5.
[23] Ito S, Ogawa Y, Harada H, et al. Long-term survival of patient with brain metastases from lung cancer treated by pemetrexed monotherapy. Gan To Kagaku Ryoho 2012;39:793–6.
[24] Yuan Y, Tan C, Li M, et al. Activity of pemetrexed and high-dose gefitinib in an EGFR-mutated lung adenocarcinoma with brain and leptomeningeal metastasis after response to gefitinib. World J Surg Oncol 2012;10:235.
[25] Liang J, Liu X, Yin B, et al. Efficacy assessment of pemetrexed treatment of an NSCLC case with brain metastasis. Oncol Lett 2012;4:1119–21.
[26] Ochi N, Yamane H, Yamagishi T, et al. Continuous pemetrexed treatment for brain metastasis in non-small cell lung cancer—a report of two cases. Lung Cancer 2013;80:111–3.
[27] Zhang Y, Yang H, Yang X, et al. Erlotinib with pemetrexed/cisplatin for patients with EGFR wild-type lung adenocarcinoma with brain metastases. Mol Clin Oncol 2014;2:449–53.
[28] Zhu W, Roe OD, Wu C, et al. Activity of pemetrexed-based regimen as first-line chemotherapy for advanced non-small cell lung cancer with asymptomatic inoperable brain metastasis: a retrospective study. J Chemother 2015;27:221–6.
[29] Zhang J, Wu QY, Li XF, et al. Efficacy of pemetrexed in a patient with brain metastases during crizotinib treatment. Per Med 2015;12:549–53.
[30] He Y, Sun W, Wang Y, et al. Comparison of erlotinib and pemetrexed as second-/third-line treatment for lung adenocarcinoma patients with asymptomatic brain metastases. Onco Targets Ther 2016;9:2409–14.
[31] He G, Xiao X, Zou M, et al. Pemetrexed/cisplatin as first-line chemotherapy for advanced lung cancer with brain metastases: a case report and literature review. Medicine (Baltimore) 2016;95:e4401.
[32] Stefanou D, Stamatopoulou S, Sakellaropoulou A, et al. Bevacizumab, pemetrexed and carboplatin in first-line treatment of non-small cell lung cancer patients: focus on patients with brain metastases. Onco Lett 2016;12:4635–42.
[33] Tian Y, Zhai X, Tian H, et al. Bevacizumab in combination with pemetrexed and platinum significantly improved the clinical outcome of patients with advanced adenocarcinoma NSCLC and brain metastases. Cancer Manag Res 2019;11:10083–92.
[34] Yu X, Fan Y. Effect of pemetrexed on brain metastases from nonsmall cell lung cancer with wild-type and unknown EGFR status. Medicine (Baltimore) 2019;98:e14110.
[35] Lee JS, Hong JH, Sun S, et al. The impact of systemic treatment on brain metastasis in patients with non-small-cell lung cancer: a retrospective nationwide population-based cohort study. Sci Rep 2019;9:18689.