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REVIEW ARTICLE

Updates in the management of brain (leptomeningeal) metastasis of lung cancer

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Abstract

Brain (leptomeningeal) metastasis is one of the most common and severe complications of lung cancer. This article interprets expert consensus on the treatment advice for brain (leptomeningeal) metastasis of lung cancer, expounding on its epidemiology, diagnostic standards, efficacy assessment, treatment advice, and other aspects.

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In 2012, there were approximately 1.24 million new cases of lung cancer and 1.1 million related deaths worldwide; in 2016, a total of 220 000 new patients were diagnosed with lung cancer in the U.S. alone, and over 158 000 of them died from the disease. One of the most common and severe complications of lung cancer is brain metastasis (BM). Although there has not been any census of the actual global or national incidence rate of BM, a conservative estimate reveals that 10%–30% of lung cancer patients will experience BM. In the past, the survival rate after BM used to be low, and treatments were often futile. Nevertheless, with the emergence of molecular targeted therapy and immunotherapy, the survival rate of lung cancer has been rising continuously. Consequently, patients also suffer from a greater risk of developing sequelae like BM at the later stages of lung cancer [1]. In the U.S., BM is the most prevalent tumor in the central nervous system (CNS). It may emerge as an initial symptom of cancer before cancer diagnosis or appear within a few years or decades after the confirmatory diagnosis of primary cancer. The incidence rate of BM differs significantly depending on the location of the primary cancer; the main primary cancers related to BM are lung cancer, breast cancer, and melanoma. BM is difficult to treat, and to most individuals, the diagnosis of BM is usually a sign of poor prognosis [2]. Among all patients of solid tumors, the incidence rate of leptomeningeal metastasis (LM) ranges from 1% to 9.1%; over the last decade, lung cancer and breast cancer were the most common primary solid tumors associated with LM [3]. The incidence rate of LM is 3.8% in patients with non-small cell lung cancer (NSCLC), most of whom are females and non-smokers and have adenocarcinoma; one third of the patients already have BM at the time of diagnosis of LM [4].

Diagnosis and classification

LM refers to the multifocal seeding of cancer cells in the leptomeninges [5]. Malignant cells can reach the leptomeninges in several ways: hematogenous spread through arterial or venous circulation, lymphatic spread around blood vessels, dissemination along or around nerves, direct spread of metastatic lesions from the bones or the part of the brain near the arachnoid or interventricular space, as well as from choroid plexus and subependymal metastases. LM is divided into 2 types: diffuse and nodular. The former involves free-floating and non-adherent cancer cells, whereas the latter is characterized by contrast-enhancing leptomeningeal tumor nodules [5].

The diagnosis of LM entails three key elements that are universally recognized: neurological symptom assessment, neuroimaging evaluation, and cerebrospinal

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fluid (CSF) cytology or flow cytometry (FC). The Response Assessment in Neuro-Oncology (RANO) LM working group recommended that all patients enrolled in LM clinical trials should undergo a complete standardized neurological examination, CSF analysis (including cytology for all cancers and FC for hematological cancers), enhanced magnetic resonance imaging (MRI) of the brain and spine, and radioisotope CSF flow studies (only in patients treated with intra-CSF therapy). Most randomized controlled trials related to LM have already adopted a combination of neurological examination and CSF cytology to assess therapeutic efficacy.

Neurological symptom assessment

The initial clinical manifestations may not be typical, and may include cauda equina syndrome, cranial nerve defects, headache, back pain, visual impairment, diplopia, hearing loss, and symptoms of neurocognitive disorders . Symptoms related to increased intracranial pressure may arise at a later stage [6].

Neuroimaging evaluation

Brain and spine MRI is the gold standard in LM imaging evaluation. Brain involvement is observed in 40%–75% of LM cases, whereas spine involvement is seen in 15%–25% of cases. The sensitivity and specificity of MRI for detecting LMs of solid tumors are expected to be 70%–87% and 75%–94%, respectively [7]. Gadolinium-enhanced MRI can increase sensitivity, especially in LMs that are mainly or solely manifested in the cranial nerve.

Any stimulus to the leptomeninges, such as surgery or puncture, can induce local MRI enhancement . Therefore, MRI examinations should be conducted before such operations. It is worth noting that normal MRI results cannot exclude the probability of LM because such results are found in up to 20% of LM cases.

CSF cytology/FC examination

CSF cytological analysis remains the gold standard for LM diagnosis. First-time CSF examination yields a sensitivity of 45%–50%. Usually, two consecutive CSF samples are required for an adequate cytological evaluation [8]. Yet, up to 30% of LM cases produce negative CSF cytology results; their diagnosis is assisted by MRI [9].

There are several ways to increase the sensitivity of cytological analysis, including using tumor marker-immunostaining fluorescence *in situ* hybridization (TM-iFISH), CellSearch, and FC [10]. Direct DNA sequencing of the CSF of NSCLC patients with LM can identify sensitizing and resistant epidermal growth factor receptor (EGFR) mutations and detect the same EGFR mutation subtype as that in the primary tumor despite the absence of malignant cells in the CSF [11].

The diagnosis-specific graded prognostic assessment (DS-GPA) was initially based on four factors found in 1833 cases of NSCLC and BMs from 1985–2005: patient's age, Karnofsky performance score (KPS), presence of extracranial metastases, and number of BMs; the median survival of patients who were surveyed for the development of the DS-GPA from the beginning of BM treatment was 7 months. To design a newer version of the DS-GPA, the Lung-molGPA , data from 2186 patients with NSCLC and newly-diagnosed BM (1521 cases of adenocarcinoma and 665 cases of non-adenocarcinoma) from 2006–2014 were analyzed by researchers; significant prognostic factors included the original four factors used in the DS-GPA index, and the addition of two new factors: EGFR and ALK alterations in adenocarcinoma patients (mutation status was not routinely tested for in non-adenocarcinoma patients). The overall median survival for the cohort in that study was 12 months, and patients with NSCLC-adenocarcinoma and Lung-molGPA scores of 3.5–4.0 had a median survival of nearly 4 years. Patient's age, KPS, presence of extracranial metastases, and number of BMs were once again confirmed as prognostic factors. Positive EGFR and ALK results were also independent prognostic factors and were added to the Lung-molGPA. The more significant factors were scored up to 1.0; the higher the score, the better the prognosis. These factors included a KPS of 90–100 [hazard ratio (HR), 0.6 vs KPS ≤ 70], absence of extracranial metastases (HR, 0.5), EGFR or ALK positive (HR, 0.5 vs negative or unknown EGFR and ALK results). The remaining two factors – patient's age and number of BMs – had a less significant impact (HR, 0.7 and 0.8, respectively), and were scored up to 0.5. Therefore, 4.0 remained as the highest possible score. Table 1 describes the new Lung-molGPA parameters in detail [1].

Efficacy assessment

The metastasis of solid tumors to the CNS, be it BM or LM, differs according to histology and molecular subtypes. Under the action of the blood-brain barrier, anti-cancer therapy with systemic activity at the standard dose may fail to reach the same drug concentration in the CNS. Such differences may exert insignificant effects on certain types of drugs; for instance, although immunomodulatory

Table 1 Summary of the new Lung-molGPA parameters [1]

Prognostic factor	GPA (graded prognostic assessment)		
	0	0.5	1
EGFR/ALK	–	NA	+
Age	≥ 70	< 70	NA
KPS	< 70	70–80	90–100
Extracranial metastases	Present	NA	Absent
Number of brain metastases	> 4	1–4	NA

antibodies cannot pass through the blood-brain barrier, expanding and activated peripheral lymphocytes can enter the CNS. However, this issue may lower the activity of some other drugs in the CNS. During the clinical development of a new drug, if the drug lacks CNS activity and is inappropriately included in the clinical trial design or used to assess CNS metastatic diseases, the common efficacy endpoints may be substantially diminished due to early CNS progression. Conversely, if the drug indeed has CNS activity and is inappropriately excluded from the clinical trial design or used to assess CNS diseases, the collection of data about the benefits for the CNS may be hindered.

It is unreasonable to completely exclude BM patients from the clinical trials for diseases such as NSCLC, breast cancer (HER2 positive or triple negative), and melanoma because that can mean excluding half to two thirds of all patients with stage IV cancers. According to a recent systematic study of 413 trials on systemic medications against advanced NSCLC, 14%–19% of the clinical trials excluded all patients with a history of LM or BM, and 41% of them allowed the enrollment of BM patients who had been treated and were in stable condition. Since many BM patients are often excluded from clinical trials, the existing trials are unable to demonstrate efficacy for the treatment of BM [12].

A measurable disease is defined by the presence of contrast-enhanced lesions that can be accurately measured in at least one dimension. The longest diameter in the plane of measurement is to be recorded, and the corresponding perpendicular diameter should also be at least 5 mm long. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least two times the slice thickness. When determining the minimum size of the measurable lesion at baseline, the presence of inter-slice gaps should also be taken into consideration.

Non-measurable lesions include: those with a longest diameter of less than 10 mm, those with boundaries that are not repeatedly measurable, dural metastases, skull metastases, cystic lesions, and LMs.

It was recommended that the CNS and the non-CNS compartments should be evaluated separately. CNS and non-CNS progression should be assessed based on the RANO-BM and RECIST 1.1 criteria, respectively. The definition and assessment of BM and LM survival involve: the overall bio-compartmental progression-free survival (PFS) for local CNS lesions, remote CNS lesions, and extracranial non-CNS lesions; CNS PFS for local and remote CNS lesions; extracranial non-CNS PFS; and CNSlocal PFS only for local CNS lesions [13].

Treatments

For driver gene-positive tumors

A retrospective study found that, patients with EGFR mutations had a higher incidence of LM than those with wild-type EGFR (9.4% vs 1.7%; $P < 0.001$); the time interval from the diagnosis of metastatic lung cancer to the occurrence of LM was 13.3 months [3]. This study also showed that patients receiving tyrosine kinase inhibitor (TKI) therapy had longer overall survival (OS) than those who were not (10 months vs 3.3 months; $P < 0.001$) [3]. A combined regimen of TKI and whole brain radiotherapy (WBRT) failed to achieve further survival benefits. On the other hand, it was also found that the Eastern Cooperative Oncology Group (ECOG) score is a survival indicator of poor prognosis (< 2 vs ≥ 2; HR, 3.657; $P < 0.001$) [3]. Another study also discovered that patients with NSCLC and EGFR mutations had a similar incidence of LM (9%) and a median survival of 3.1 months [14]. At the time of LM diagnosis, patients with an ECOG score of 0–1 showed longer survival than those with a score ≥ 2. Another retrospective study also showed that the use of EGFR-TKI therapy is an independent predictor of increased post-diagnosis survival rates in NSCLC patients with LM and EGFR mutations [4].

Erlotinib and gefitinib are first-generation EGFR-TKIs. The former is able to reach a higher concentration in the CSF (66.9 nM vs. 8.2 nM; $P = 0.0008$) and has a higher penetration rate than the latter (2.8% vs 1.13%) [15]. A retrospective study comprising 25 cases of LM indicated that erlotinib might be more effective than gefitinib in the treatment of LM and that it had a higher cytologic conversion rate in the CSF than the latter (64.3% vs 9.1%; $P = 0.012$) [16]. Another retrospective study compared the therapeutic efficacy of high-dose erlotinib (200 or 300 mg every 2 days, 300 or 450 mg every 3 days, or 600 mg every 4 days) with that of standard-dose erlotinib or gefitinib in patients with EGFR-mutant lung cancer and refractory LM after they had developed resistance against standard-dose erlotinib or gefitinib [17]. The results showed that the two groups had similar median survival (6.2 months for the high-dose group vs 5.9 months for the standard-dose group; $P = 0.94$). According to yet another retrospective study, high-dose EGFR-TKI failed to prolong the survival of LM patients (2.4 months for the high-dose group vs 3.1 months for the standard-dose group; $P = 0.863$) [14]. Despite the use of EGFR-TKI at a standard dose, nine patients with EGFR-mutant NSCLC were still experiencing refractory CNS metastases. A retrospective study on high-dose, pulsatile erlotinib therapy (at the median dose of 1500 mg once a week) revealed that three patients had isolated LM, whereas one had isolated BM, and five had both types of lesions [18]. Among these nine patients (including two with isolated LM), six (67%)

displayed radiological improvement and had a median OS of 12 months. The patients demonstrated satisfactory tolerance to treatments, and no severe toxicity (grade 3 or above) was observed. After pulsatile therapy, the drug concentration in the CSF was 130 nM, which was higher than the IC50 of erlotinib [19].

Afatinib is a second-generation EGFR-TKI. Tamiya *et al* reported the therapeutic efficacy and CSF concentration of afatinib in 11 patients with EGFR-mutant NSCLC and LM. Afatinib had a median penetration rate of 1.65% and a median concentration of 1.4 ng/mL (2.9 nM) in the CSF, which was higher than the previously reported concentration of 1 nM [20]. There was a patient response rate of 27.3%, median OS of 3.8 months, and median PFS of 2 months.

Osimertinib is a third-generation EGFR-TKI. With its excellent efficacy against systemic and CNS metastatic tumors, it is considered a standard regimen for EGFR Thr790Met mutation-positive metastatic NSCLC [21]. Studies have also been conducted on osimertinib as a treatment for LM. In a prospective study, Nanjo *et al* examined the therapeutic efficacy of standard-dose osimertinib (80 mg per day) by observing 13 cases of patients with Thr790Met-positive NSCLC after the treatment failure of standard-dose erlotinib, gefitinib, or afatinib [22]. Among them, five patients were cytologically diagnosed as having LM, whereas eight had suspected LM. The median PFS among all 13 patients was 7.2 months, and the osimertinib penetration rate into the CSF was 2.5%. A study published in New England compared the efficacy of osimertinib with that of the combination chemotherapy of platinum therapy plus pemetrexed in advanced NSCLC; the median PFS of the osimertinib group was significantly longer than that of the platinum–pemetrexed group [10.1 months vs. 4.4 months; HR, 0.30; 95% confidence interval (CI), 0.23–0.41; $P < 0.001$]. The objective response rate (ORR) of osimertinib (71%; 95% CI, 65–76) was significantly better than that of the platinum-pemetrexed group (31%; 95% CI, 24–40; ORR, 5.39; 95% CI, 3.47–8.48; $P < 0.001$). Among 144 patients with CNS metastases, those receiving osimertinib therapy had a longer median PFS than those in the platinum-pemetrexed group (8.5 months vs. 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). The proportion of patients with adverse events of grade 3 or higher was significantly lower with osimertinib (23%) than with the regimen of platinum therapy plus pemetrexed (47%) [21].

Crizotinib is an ATP-competitive inhibitor against ALK/MET/ROS1. It is also the first targeted drug for ALK-positive NSCLC approved by the U.S. Food and Drug Administration. Despite its low penetration rate into the CNS, studies have shown that it can better control CNS diseases than standard chemotherapy [23–24]. Regardless, the CNS is a common site of cancer recurrence in patients who have received crizotinib therapy. There are very few reports about its efficacy against LM.

Ceritinib is a second-generation ALK/ROS1 inhibitor that is more effective than crizotinib. It has higher permeability across the blood-brain barrier and is used for treatment after the development of crizotinib resistance in patients. After treatment failure of standard-dose crizotinib and WBRT in ALK-positive NSCLC patients, the sequential therapy of administering pulse-dose crizotinib (500 mg per day) followed by standard-dose ceritinib (750 mg per day) was found to be able to keep BMs (LMs) under control [25]. Another case report indicated that ceritinib was able to control BM and LM for over 5 months among ALK-positive NSCLC patients receiving chemotherapy and crizotinib therapy [26].

For NSCLC patients carrying EGFR mutations, the response rate to EGFR-TKI therapy for BM (gefitinib, erlotinib, and afatinib) was up to 60%–80%, whereas the complete response rate was up to 40%. The median OS was 15–20 months, and the PFS for patients with intracranial lesions was 6.6–11.7 months, both of which were significantly longer than those of patients with wild-type EGFR tumors.

Surgical resection, stereotactic radiosurgery (SRS), and WBRT have long been the main treatment methods for BM. Recently, a phase II clinical trial reported that using erlotinib alone to treat BM patients yielded a median OS of 15.9–22.9 months and a median PFS of 5.8–14.5 months; the ORR of the patients was 55%–89% [27].

Although many phase II clinical trials studied the efficacy of early application of EGFR-TKI therapy in BM treatment, none of them have compared the efficacy of using TKI before radiotherapy and using radiotherapy before TKI. Therefore, William *et al* conducted a multi-institutional analysis to determine the optimal management of patients with EGFR-mutant NSCLC who had developed brain metastases and had not received EGFR-TKI therapy yet. The conclusion was that postponing BM radiotherapy would lower the patients' OS and that SRS followed by EGFR-TKI could result in the longest OS [27]. Another study demonstrated that the WBRT of patients with EGFR mutations or ALK-positive NSCLC and BM could be safely postponed using highly effective targeted therapy, in order to minimize toxic effects that will decrease the patients' quality of life.

The time from the initial diagnosis to the onset of LM ranges from 7 to 17 months [28–29], accompanied with a generally poor prognosis and a median OS of approximately 3–6 months [29–30]. Before the introduction of EGFR-TKI therapy, the treatment regimen for LM included intrathecal chemotherapy (ITC), WBRT, and ventriculoperitoneal (VP) shunting; but the therapeutic efficacy remained poor [31]. A retrospective study reported the treatment results and prognostic factors of NSCLC LM

patients. In a large-scale retrospective study on NSCLC patients with cytologically diagnosed LM, a few favorable prognostic factors were brought to attention, including patients having received WBRT, ITC, EGFR-TKI, and VP shunt; on the other hand, unfavorable prognostic factors included low PFS score, high CSF protein level, and high CSF white cell count, all of which hinted at a heavier disease burden. Interestingly, the median OS of patients receiving traditional treatment was merely 14 weeks, while the median OS of patients receiving EGFR-TKI therapy was 38 weeks [29]. It was also observed in other retrospective studies that patients receiving EGFR-TKI therapy had a longer OS [32]. However, it is still unclear whether such changes in OS were caused by EGFR mutation status, the use of EGFR-TKI therapy, or both. It is worth noting that most of these small-scale studies selected East Asian patients with a higher EGFR mutation incidence as their main research targets.

Overall, the sources of data related to LM treatment were restricted to single-institutional retrospective studies. Favorable prognostic factors were associated with lower disease burden (such as low intracranial pressure and low white cell count in the CSF). In patients receiving EGFR-TKI therapy, better physical strength and prolonged survival were observed [33].

For driver gene-negative tumors

Fenske *et al* summarized the median OS of NSCLC BM patients treated by different methods across seven countries. In the U.S., NSCLC BM patients treated with systemic chemotherapy had the longest median OS – 11.8 months – compared with those treated with other methods. Yet, in Japan and Italy, patients treated with radiotherapy had a median OS of 13.4 months and 10.5 months respectively, compared with those receiving systemic therapy and surgery. In three countries, surgery resulted in the longest OS – 13.2 months in France, 6.05 months in the U.K., and 5 months in Spain. When the treatment method was taken out of consideration, patients in Japan had the longest median OS of 13.1 months, followed by those in the U.S. and Italy, both of which had a median OS of 10 months. The median OS was 8 months in the U.K., 6.7 months in France, and 5 months in Spain. The German studies did not report the median OS of patients. The U.S. and Japan had a higher median OS than the countries in the European Union. When nationality was put aside, radiotherapy resulted in the longest median OS of 10 months, followed by systemic chemotherapy and surgery, which led to a median OS of 9.15 months and 8.5 months respectively [34].

Anti-angiogenic therapy

Bevacizumab is a recombinant humanized monoclonal antibody. It can selectively bind with VEGF and prevent it from reacting with its receptors. The combined use of bevacizumab and platinum-containing chemotherapy has been authorized as the first-line treatment for advanced, metastatic, or recurrent and non-squamous NSCLC.

The phase II prospective, non-comparative BRAIN study (NCT00800202) examined asymptomatic and untreated patients with stage IV non-squamous NSCLC and BM who received first-line bevacizumab (15 mg/kg) plus carboplatin (area under the curve = 6) and paclitaxel (200 mg/m^2) every 3 weeks (B + CP) or second-line bevacizumab plus erlotinib (150 mg/d; B + E) therapy. The safety and efficacy of using bevacizumab to treat asymptomatic and untreated NSCLC BM patients were observed. The results showed that, in the first-line B + CP group (n = 67), the 6-month PFS rate was 56.5%, whereas the median PFS was 6.7 months, and the median OS was 16.0 months. The investigator-assessed ORR was 62.7%; the intracranial lesion incidence was 61.2%, and the extracranial lesion incidence was 64.2%. Due to the low enrollment rate (n = 24), the efficacy results for the second-line B + E group were merely exploratory – the 6-month PFS rate was 57.2%, whereas the median PFS was 6.3 months, and the median OS was 12.0 months; the ORR was 12.5%. The adverse events were comparable to those in previous bevacizumab trials. Grade 1 intracranial hemorrhage occurred and was resolved with no sequelae. This study verified the efficacy and safety of using first-line bevacizumab with paclitaxel and carboplatin for treating asymptomatic and untreated NSCLC BM patients [35].

Traditional chemotherapy

A post-hoc analysis was conducted on the BM patients observed in a large-scale, prospective, and observational study on the first-line treatment of NSCLC – the European FRAME study. It aimed to describe the baseline characteristics of NSCLC BM patients, understand their first-line treatment, and report real-life treatment outcomes. BM patients and the overall cohort had a median OS of 7.2 months and 10.3 months respectively; the median PFS was 3.6 months and 5.6 months respectively, whereas the 1-year survival rates were 30% and 45% respectively. Patients treated with pemetrexed plus platinum had a median OS of 9.3 months (95% CI, 6.2–11.9), whereas those treated with gemcitabine plus platinum had a median OS of 5.6 months (95% CI, 4.1–8.4). The results were in line with those of the recently published retrospective analysis on a database of 1833 cases of NSCLC BM, which reported a median OS of 7.0 months (95% CI, 6.5–7.5) while highlighting the significant heterogeneity in the results. On the other hand, a retrospective cohort study on all new lung cancer cases in institutions in Canada between July 2005 and June 2007 showed that the median OS among 91 NSCLC BM patients was 7.8 months [36].

Despite some recent improvements in radiotherapy

technologies, such as surgical resection of single brain lesions and SRS for oligometastases, WBRT remains the fundamental treatment for BM, whereas systemic chemotherapy remains the basic treatment for disseminated NSCLC. Recent data revealed that pemetrexed plus platinum-based chemotherapy could be a sensible option for asymptomatic BM patients and could prevent such patients from receiving early radiotherapy to the head. The pemetrexed cohort was the largest treatment group in the study on BM patients and had a 1-year survival rate of 39% (95% CI, 29–48). Due to the possibility of selection bias, the results were not directly comparable between cohorts. Therefore, these descriptive data should be interpreted with caution. The OS reported in that study could merely represent some NSCLC BM patients receiving platinum-containing combination chemotherapy [36].

Immunotherapy

Check-point inhibitors that are currently available include atezolizumab, nivolumab, and pembrolizumab. The sample of CNS metastasis patients treated with single-agent immune-oncology (IO) therapy is small, and treatment is restricted by tight constraints. Based on the existing data, atezolizumab is, at present, the only IO drug observed to have evident survival benefits to BM patients; nivolumab has been observed to have the same therapeutic efficacy in both CNS and non-CNS metastasis patients. A prospective, small-sample study preliminarily confirmed that pembrolizumab is effective in treating patients with CNS metastasis.

Conclusion

BMs (LMs) should be scored and rated; a recommended tool for doing so is the GPA. The three key elements of LM diagnosis include clinical evaluation of CNS functions, imaging manifestations, and CSF cytological examination. The genetic profile of CSF mutations in LM is different from that of the primary tumor and blood-based circulating tumor DNA; mutated genes can be detected in the CSF. Hence, next-generation sequencing of the CSF is recommended for eligible individuals.

Clinical trials should include BM patients as much as possible to ensure the universality of the trial results; a combination of RECIST 1.1 and RANO-BM was recommended as the standard for efficacy assessment. The endpoints of clinical trials should include indicators of efficacy assessment for BM and LM; both separate and comprehensive assessments should be performed.

TKI was recommended as the top treatment option for NSCLC with BMs (LMs) and positivity for EGFR, ALK, or any other driver genes; as for recurrent LM, high-dose, pulsatile TKI therapy can be considered (gefitinib 500–1000 mg orally every other day for 14 days or erlotinib 1500 mg orally once a week +/– bevacizumab 10 mg intravenously once every 2 weeks); clinical trials on sequential therapy of TKIs or combination therapy of TKIs and WBRT for multiple BM were also recommended. Radiotherapy, systemic chemotherapy, and ITC remain as the main treatment methods for driver gene-negative multiple BMs (LMs). The optimal chemotherapy regimen has yet to be determined, but pemetrexed appears to offer better survival benefits to patients with adenocarcinoma BM. Anti-angiogenic therapy is shown to have promising prospects due to its anti-BM (LM) efficacy. The therapeutic activity of check-point inhibitors has been demonstrated in small-scale trials.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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