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Therapy for non-small-cell lung cancer patients with brain metastasis

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Abstract Brain metastasis is a major cause of poor prognosis and high mortality for non-small cell lung cancer patients. The prognosis of non-small-cell lung cancer (NSCLC) patients with brain metastasis is generally poor and more effective treatment is required to improve their prognosis. Whole-brain radiotherapy, surgery, stereotactic radiosurgery, chemotherapy and targeted therapy are the main treatment for brain metastasis. This review focuses on the five therapeutic strategy and in particular, on targeted therapy.

Key words non-small-cell lung cancer (NSCLC); brain metastasis; whole-brain radiotherapy; surgery; stereotactic radiotherapy; chemotherapy; targeted therapy

Lung cancer is the leading cause of cancer-related mortality, non-small-cell lung cancer (NSCLC) accounts for approximately 80% of primary lung cancer, approximately two-thirds of such patients are diagnosed at an advanced stage [1]. Efficiency of radiotherapy and chemotherapy for advanced NSCLC is only 20% –40%, the 5-year survival rate is only 8%–12% [2]. The main reason for the poor prognosis of patients with lung cancer is local recurrence or distant metastasis [3]. Although exact data are unavailable, the incidence of brain metastasis (BM) in NSCLC patients is 30%–50%, patients with non-squamous NSCLC had a significantly higher risk of BM compared to patients with squamous cell NSCLC [4]. The prognosis of NSCLC with BM is poor and the natural median survival is only 1–2 months [5]. And retrospective analyses reported that the median survival time (MST) of such patients is 3–6 months [6–8] and the 1- and 2-year survival rates were 14% and 7.6%, respectively [9]. In addition, neurologically symptomatic patients exhibited significantly shorter survival compared to asymptomatic patients, with an MST of 4.0 and 7.5 months, respectively ($P = 0.02$) [9].

Currently, radiotherapy, surgery, chemotherapy and targeted therapy are still the main treatment for NSCLC patients with BM, these therapeutic approaches should be selected appropriately, based on each patient's clinical, histological and molecular condition. In this review, we aim to summarize the currently available treatment options and present a therapeutic strategy for NSCLC patients with BM.

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Whole-brain radiotherapy (WBRT)

WBRT is generally considered to be the standard therapy in clinical trials, which is particularly suitable for patients with poor performance status (PS), multiple BM, old patients and patients in poor condition. The schedule of 10 fractions of 3-Gy over 2 weeks (total dose of 30 Gy) is most commonly used, and combined with glucocorticoids and efficient radiation sensitizer, the short-term efficacy of WBRT can be increased. WBRT can effectively relieve neurological symptoms and improve patients' quality of life (QOL), but due to poor tolerance to therapy, tumor recurrence and the primary lesion not controlled, the overall response rate (ORR) was 60% –80% with a MST (MST) of only 3 to 6 months [10–11]. A meta-analysis from Tsao including eight randomized controlled trials found that, compared the standard dose schedule with altered dose schedules on patients with BM from various primary cancers, including NSCLC, there was no significant difference in overall survival (OS) and symptom control rate [12]. Major toxicities of WBRT is brain cell edema, resulting in increased intracranial pressure. Patients with long-term survival may appear delayed brain cell damage, manifested as intractable headache, mental decline, cognitive dysfunction, while despite these adverse effects, benefit of WBRT is still greater than the toxicity [13–15]. Prophylactic cranial irradiation can only effectively reduce BM rate in locally advanced NSCLC, with no significant im-

provement in OS and progression-free survival (PFS), in addition to the toxicity and negative impact of WBRT on the QOL of patients, there is still controversy [16–18].

Surgery

Surgery is often selected for patients with a single BM. Surgical resection of intracranial metastasis can quickly relieve or alleviate patients' intracranial pressure, relieve clinical symptoms, prolong survival time, improve QOL, and also can obtain pathological specimens. For patients with BM, there is a growing trend of surgery therapy, especially for patients with high KPS score and can tolerate surgery, or primary tumor has been resected or there is no local recurrence after radiotherapy or chemotherapy, superficial tumor location or tumor in the non-critical functional areas [19].

Postoperative residual tumor recurrence, new metastasis, primary tumor progression can not be controlled and other issues are more likely to occur with surgery alone. Research data support that surgery combined WBRT, stereotactic radiosurgery (SRS) or chemotherapy treatment is more effective, and among them, the role of surgery plus WBRT treatment model has been established. Patchell *et al* found that surgery plus WBRT can significantly reduce the frequency of BM recurrence compared to WBRT alone (52 vs. 20%, respectively, $P < 0.02$), and get a better OS (MST, 40 vs. 15 weeks, respectively; $P < 0.01$) [20]. Vecht *et al* got a similar conclusion and they also found that in patients with stable extracranial disease the survival advantage was prominent (MST, 12 vs. 7 months), whereas in patients with progressive extracranial disease the MST was the same, 5 months for both groups [21]. Thus surgery followed by WBRT is recommended for NSCLC patients with a single BM when extracranial disease is controlled.

For multiple BM, there is no prospective study of surgery in patients with multiple BM, the role of surgery for multiple BM remains uncertain. A retrospective study from Bindal RK showed multiple BM patients with all the BM surgically resected achieved survival times similar to those of patients with a single BM who underwent surgery. However, patients with multiple BM who did not have all the BM completely resected exhibited significantly shorter survival times [22]. But surgery is still not generally recommended for patients with multiple BM in current clinical work.

Radiosurgery

In recent years SRS has become an effective treatment for the NSCLC with BM. SRS has the characteristics of positioning accuracy, dose centralized, so that it is less invasive and allows more than one lesion to be treated, including those in areas not surgically accessible [23]. A report from Mariya also prove that SRS can be reused in the same patient [24]. However, SRS is limited to tumor diameter (< 3 cm), the number of metastasis (< 5), can not get the pathological diagnosis, normal brain tissue necrosis and other factors, it still can not completely replace WBRT and surgery. Currently, SRS is recommended in combination with WBRT. Data from Andrews et al showed that WBRT plus SRS can not improve the OS of NSCLC patients with BM, however, the combination of WBRT and SRS provided a survival advantage in patients with a single BM (MST, 6.5 vs. 4.9 months, respectively; $P = 0.0393$), and patients in the WBRT plus SRS group were more likely to have stable or improved PS at 6-month follow-up, compared to patients in the WBRT alone group [25]. Aoyama et al got a similar result in OS and what's more, they found for patients with ≤ 4 BM WBRT plus SRS can reduce the brain tumor recurrence rate at 1 year (46.8 vs.. 76.4%, $P < 0.001$) and the 1-year actual rate of developing new BM [26]. So for NSCLC patients with ≤ 4 BM the combination of WBRT and SRS is considerable. While for patients with a single BM, there is no direct comparison between surgery and SRS, the actual situation of patient needs to be considered to make a choice.

Chemotherapy

Chemotherapy agent is traditionally considered to be little effect for BM because of the blood-brain barrier (BBB) protecting the brain from exposure to toxins, limiting the delivery of chemotherapeutic agents to the brain [27–28]. However, recent studies [29–30] showed that in the process of tumor metastasis to the brain the BBB has been damaged, in addition, WBRT and use of dehydration can also make BBB open to varying degrees, so chemotherapy drugs can smoothly go through BBB into the central nervous system (CNS) to kill tumor cells. However, which should be kept in mind is, for the choice of chemotherapy drugs for patients with BM, the fundamental basis is the always the tumor chemosensitivity (pathology, driver mutation), effective chemotherapy results in good systemic RR, as well as good intracerebral RR, and a number of prospective trials have demonstrated this point [31–38].

WBRT is the standard treatment for lung cancer with BM. However, chemotherapy agent (carboplatin, cisplatin, topotecan, vinorelbine, etc.) in combination with WBRT did not find a better RR or OS for patients with BM [36, 39–40]. Efficacy of temozolomide for BM has been highly anticipated, but the current study result remains debated is still controversial [41–43].

Sequence of radiotherapy and chemotherapy for patients with multiple BM is also an issue of concern. Concurrent WBRT and chemotherapy result in a higher brain toxicity, and with poor tolerance [44–45]. Sequential

treatment is thus more widely used in patients suitable for both treatment modalities. Lee *et al* compared chemotherapy (vinorelbine/gemcitabine) followed by WBRT with WBRT followed by chemotherapy and found there was no significant differences in RR or survival [46]. A phase III trial also suggested that the timing of WBRT does not influence survival of NSCLC patients with BM, which compared early concurrent versus delayed WBRT in patients receiving cisplatin-based chemotherapy [47].

Targeted therapy

EGFR-tyrosine kinase inhibitors (TKI)

From standard chemotherapy, the field of advanced NSCLC treatment has experienced a paradigm shift to targeted therapy. The most famous EGFR TKI, have now been included in standard NSCLC treatments. Treatment of patients with EGFR activating and sensitizing mutation-driven NSCLC with EGFR TKIs results in an unprecedented RR of 60-80%, a median PFS of 8–13 months, as well as an improved QOL compared with chemotherapy [48–49]. Targeted therapies have been initially employed in primary cancers, based on the identification of molecular targets critical for tumor growth. More recently, the increased amount of information on new molecular compounds and the advances in understanding the molecular pathways that mediate brain colonization have led to a new interest in both preclinical and clinical investigations in the field of BM. In recent years, several authors have reported a growing number of cases of response in BM patients treated with EGFR TKIs. For unselected patients, RR after TKIs could be 38 to 86% with a MST of 9.9–19.1 months [50–53], while for patients with NSCLC harboring EGFR mutations RR reaches 60–100%, with a rate of complete response as high as 40%, the MST are in the range of 15–20 months, and PFS in the brain reaches 6.6–11.7 months [54–59], which is significantly longer than in EGFR wild-type tumors [60].

There are reports that erlotinib reaches higher serum and cerebrospinal fluid (CSF) concentrations than gefitinib [61–63] and some cases also show that erlotinib could be an effective treatment in patients who develop CNS metastasis after initial extracranial response to gefitinib [64], but no available data favor one EGFR TKI over another.

Some case reports show that brain progression on TKI treatment in EGFR mutated NSCLC seems to occur with no identifiable resistance mechanism in the brain lesion, BM may remain sensitive to EGFR TKI therapy but require higher CSF concentrations [65–68].

In addition, EGFR inhibitors can be safely administered concurrently with WBRT [69–70].

Anaplastic lymphoma kinase (ALK)

About 4% NSCLC patients have ALK rearrangement. Crizotinib is an oral selective inhibitor of activated ALK, and can lead to objective response or stabilization in most patients harboring this molecular alteration [71].

There are no definitive conclusions on the activity of crizotinib in patients with BM so far [72–74]. While BM are frequent in ALK rearranged NSCLC, and CNS is the most frequent site of progression on crizotinib therapy, even in systemic responders [75–77]. Reasonable explanation may bethat a poor penetration of the agent into the brain limited the potential efficacy [78]. Clinical trial about whether high-dose crizotinib after CNS progression on standard-dose crizotinib could be effective has been described [79]. Several second generation ALK inhibitors show inhibitory activity *in vitro* even with the gatekeeper mutant tumor with acquired resistance to crizotinib, and the efficacy for BM need to be tested.

Bevacizumab

Efficacy of bevacizumab has been confirmed when combined with paclitaxel and carboplatin in patients with non-squamous NSCLC [80–81]. Patient with BM have been excluded from clinical trials of bevacizumab, for fear of the intracranial hemorrhage (ICH) [82–83], while PASSPORT study showed bevacizumab was safely administered to patients with BM [84], and the subsequent brain study assessed safety of bevacizumab combined with carboplatin and paclitaxel, only one ICH, grade 1, occurred, and an intracranial RR of 61.2% and a RR in extracranial lesions of 64.2% in the first line cohort, and 20.8% and 12.5% in the second-line cohort, was observed respectively [85].

Conclusion

Systemic therapy still plays a major role in the treatment of BM in NSCLC. First-line combination platinum based chemotherapy in advanced NSCLC or EGFR TKI therapy in EGFR mutated lung cancer should be used in first intention in patients with asymptomatic BM because of their high RRs. WBRT is still an essential and standard treatment, especially for patients with neurological symptoms. Combined with systemic therapy can improve survival and provide better QOL for patients. Local treatment (surgery or SRS) should switch to a second systemic treatment line when extracerebral disease is controlled, and should consider the number, location, etc of of brain tumors. For patients with ALK-rearranged NSCLC radiotherapy should be considered first, due to poor penetration of crizotinib to the CNS. More information about the treatment mode selection and the exact efficacy is still the answer in the future.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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