Introduction

Molecular targeted therapy against mutated driver oncogenes such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) dramatically improved the outcome of patients with non-small cell lung cancer (NSCLC) harboring driver gene mutations such as receptor (EGFR) or anaplastic lymphoma kinase (ALK). However, the brain is a frequent site of recurrence, and it significantly deteriorates the prognosis of these patients. Treatment strategies include surgical resection, whole-brain radiation therapy, stereotactic radiotherapy, and drug therapy depending on patient condition. First-generation EGFR/ALK tyrosine kinase inhibitors (TKI) demonstrates only limited efficacy for intracranial lesions probably because of low penetration through the blood-brain barrier (BBB). However, newly developed TKIs with improved penetration such as osimertinib for EGFR and alectinib, ceritinib, brigatinib, or lorlatinib for ALK have demonstrated significant intracranial activity that should contribute to improved overall survival. Whole-brain radiation therapy used to be a standard of care that confers alleviation of symptom and modest survival benefit. However, it potentially causes neurological and cognitive deficits as a chronic toxicity. With the prolonged survival owing to newer generation drugs, this toxicity is becoming more relevant. Stereotactic radiotherapy is considered when there are three or fewer lesions, and the lesions are <3 cm as local control of tumor is excellent, and neurotoxicity is less. In this review, we discuss the various aspects of brain metastases occurring in NSCLC patients with driver gene mutations. We also propose a treatment algorithm for these patients.

Keywords: Brain metastases; driver mutations; non-small cell lung cancer (NSCLC); targeted therapy

Abstract: Molecular targeted therapies have significantly improved the treatment outcome of patients with non-small cell lung cancer (NSCLC) harboring driver gene mutations such as receptor (EGFR) or anaplastic lymphoma kinase (ALK). However, the brain is a frequent site of recurrence, and it significantly deteriorates the prognosis of these patients. Treatment strategies include surgical resection, whole-brain radiation therapy, stereotactic radiotherapy, and drug therapy depending on patient condition. First-generation EGFR/ALK tyrosine kinase inhibitors (TKI) demonstrates only limited efficacy for intracranial lesions probably because of low penetration through the blood-brain barrier (BBB). However, newly developed TKIs with improved penetration such as osimertinib for EGFR and alectinib, ceritinib, brigatinib, or lorlatinib for ALK have demonstrated significant intracranial activity that should contribute to improved overall survival. Whole-brain radiation therapy used to be a standard of care that confers alleviation of symptom and modest survival benefit. However, it potentially causes neurological and cognitive deficits as a chronic toxicity. With the prolonged survival owing to newer generation drugs, this toxicity is becoming more relevant. Stereotactic radiotherapy is considered when there are three or fewer lesions, and the lesions are <3 cm as local control of tumor is excellent, and neurotoxicity is less. In this review, we discuss the various aspects of brain metastases occurring in NSCLC patients with driver gene mutations. We also propose a treatment algorithm for these patients.

Keywords: Brain metastases; driver mutations; non-small cell lung cancer (NSCLC); targeted therapy

Submitted May 06, 2019. Accepted for publication May 21, 2019.
doi: 10.21037/tlcr.2019.05.15
View this article at: http://dx.doi.org/10.21037/tlcr.2019.05.15
Development of clinical cancer metastases is a multistep process starting from an asymptomatic micrometastases initiating from single cancer cell colonization followed by invasion or extravasation leading to the development of symptomatic macro-metastases through proliferation, angiogenesis, and interaction with the microenvironment. Metastasis to the brain, unlike metastasis to other distal organ sites, involves the breach of the BBB, which is a physical, metabolic, and chemical separation of the blood and the cerebrospinal fluid in the central nervous system (CNS). The BBB is made up of endothelial cells connected via tight junctions, the basement membrane, pericytes, astrocytic foot process, and the transporter systems. The transporter systems consist of proteins, such as the ATP-binding cassette efflux-transporters (ABC-transporter), including the breast cancer resistance protein (BRCP) and the multidrug-resistant proteins [MDR; MDR-1 also known as P glycoprotein (P-gp)] (21-29). The BBB restricts the diffusion of microorganisms, pathogens, and toxins, as it obstructs the entry of particles which are over 500 Daltons. Interestingly, some cancer cells can cross the BBB through specific mediators.

In most brain metastases, the BBB is disrupted and appears to be different from the normal healthy BBB (30-33). The extent of BBB disruption is a key factor that affects the entry of anti-cancer agents into the CNS. Efficient treatment requires attaining targetable drug concentrations in the CNS. Therefore, effective control of brain lesions requires efficient drug delivery across the BBB.

Two main strategies used for efficient drug delivery across the BBB are chemical modifications of drugs to inhibit efflux-transporters and allow BBB penetration. It was reported that an mTOR/P13K inhibitor (GNE-317) modified to bypass P-gp and BRCP activation improved treatment outcome in brain metastasis. In addition, it was also shown that agents that can penetrate the BBB controlled brain dormant cancer cells, other distal metastases, and brain lesions, while agents that cannot penetrate the BBB were not able to control brain lesions (34-37).

**EGFR-driven NSCLCs**

EGFR is a receptor tyrosine kinase receptor that normally activates several downstream pathways upon binding to the ligands such as EGF, or TGF-α. In NSCLC with mutated EGFR, the pathway is activated without ligand binding, and this activation facilitates survival and proliferation of cancer cells (38). Based on the results from the IPASS trial and several other clinical trials that selected patients based on the presence of EGFR mutations such as NEJ002 or WJTOG3405 (39-41), EGFR-TKI monotherapy has been established as the standard first-line treatment for these
patients. However, life-time incidence of brain metastases in NSCLC patients with EGFR mutation is reported to be higher compared to those with wild-type EGFR (70% in EGFR+, 38% in EGFR-) (42). It is also noteworthy that 1 out of 3 EGFR+ NSCLC patients develops brain metastasis during their clinical course (43). The secondary mutation of the EGFR gene resulting in the substitution of threonine 790 to methionine (T790M) that has lower affinity to gefitinib/erlotinib and higher affinity to ATP (44) is responsible for acquired resistance in about 50% of the cases. However, brain metastases usually do not harbor T790M, and the emergence of the cancer cells in the CNS is due to an insufficient concentration of EGFR-TKI, often referred to as pharmacokinetic resistance.

Among the 1st generation EGFR-TKIs, erlotinib has relatively better BBB penetration capabilities compared to gefitinib (Table 1) (14,43-51). In some patients who develop brain metastases/leptomeningeal disease after gefitinib treatment, switching to erlotinib results in intracranial tumor shrinkage or symptom alleviation. However, the effect is usually transient (52-60). Pulsatile high-dosing and dose-escalation of erlotinib were also shown to achieve more effective control of brain metastases (59), with limited efficacy.

In contrast, the third-generation EGFR-TKI, osimertinib much more efficiently penetrated the BBB (58) (Table 1). A subset analysis of the results from the FLAURA trials that compared osimertinib with gefitinib or erlotinib as the first-line treatment of EGFR+ patients showed that CNS progression-free survival with osimertinib was significantly better [hazard ratio (HR) 0.48; 95% CI: 0.26–0.86] with manageable adverse effects (59,60).

### ALK fusion-positive NSCLC

Patients with gene rearrangement in the ALK gene are also known to have a higher risk of brain metastases—23.8% at initial evaluation. The cumulative incidence of brain metastasis after diagnosis will sum up to 58.4% 3 years later (61).

Currently, there are five ALK-TKIs that are approved by the FDA for ALK-positive NSCLC, namely crizotinib (1st generation), alectinib, ceritinib, brigatinib (2nd generation), and lorlatinib (3rd generation). It is noteworthy that up to 74% of those who were treated with crizotinib develop brain metastases (62). The 2nd generation TKIs have a better ability to penetrate the BBB and control brain metastases compared to crizotinib (Table 1). The ALEX trial revealed alectinib had 81% of intracranial response toward previously untreated brain metastases, while the response rate of crizotinib was 50%. High intracranial responses were also obtained either with ceritinib (45%) (63) and brigatinib (42–67%) (61,64), in patients with recurrence after first-line treatment with crizotinib. Among the TKIs, the 2nd generation ALK-TKIs showed better survival at the front-line compared to crizotinib (65-67). The 2nd generation ALK-TKI intracranial ORR was also reported to be almost 2 to 3 times higher than that of the 1st generation TKI, crizotinib (68) and are now positioned as front-line drugs in NSCLC with brain metastases. Similar to that with the erlotinib, alectinib dose-escalation therapy achieved ALK inhibition and is awaiting clinical approval (69). The 3rd generation ALK-TKI, lorlatinib also demonstrated 42–48% intracranial response in patients with recurrence after first-line crizotinib (51). The sequence in which ALK-TKIs are to be used for effective disease control needs further evaluation. Further studies on the effectiveness of the ALK-TKIs in controlling oligo-recurrence or oligo-progression (one or a few lesions) in the brain should be conducted.

### ROS1 and beyond

For NSCLC patients with ROS1-rearrangement (1–2% of

---

**Table 1** Blood-brain barrier (BBB) penetration capabilities of EGFR- and ALK-TKIs in human

<table>
<thead>
<tr>
<th>TKIs</th>
<th>Penetration (CSF/blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR-TKIs</strong></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>1.1% (43)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2.8% (43)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>1.7% (44)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td></td>
</tr>
<tr>
<td>160 mg</td>
<td>16% (45)</td>
</tr>
<tr>
<td>80 mg</td>
<td>2.0% (46)</td>
</tr>
<tr>
<td><strong>ALK-TKIs</strong></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>0.26% (47)</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>No human data [animal model: 15% (48)]</td>
</tr>
<tr>
<td>Alectinib</td>
<td>No human data [animal model: 63–94% (49)]</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>No human nor animal data</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>75% (50)</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; CSF, cerebrospinal fluid.
all NSCLC), the standard first-line treatment is crizotinib (70-72). As the pivotal trial did not capture CNS metastasis in the database, there is no separate analysis of intracranial-overall response rate. Several early phase studies have suggested the potentially improved intracranial activity of next-generation ROS1-targeted therapies, including ceritinib, entrectinib, and lorlatinib, although only a small number of patients were included because of the rarity of this type of NSCLC. Among these TKIs, lorlatinib appears to have the most promising treatment effects in both crizotinib-naïve and -resistant ROS1-positive patients (73,74).

BRAF mutation and NTRK fusion are emerging molecular targets in NSCLC. The combination of dabrafenib, BRAF inhibitor, and trametinib, a MEK inhibitor, was approved for the treatment of NSCLC with BRAF mutations and larotrectinib, a TRK inhibitor, was approved for use in NSCLC with NTRK fusion. However, information about brain metastases in these tumors is lacking because of the rarity of these tumors (75-77).

Radiotherapy

Irradiation to tumor cell triggers mitotic cell death, apoptosis, autophagy, and senescence (78,79). Brain metastases are traditionally treated by whole-brain radiation therapy (WBRT) (a total dose of 30 Gy in 10 daily fractions of 3 Gy). WBRT may improve neurological symptoms from brain metastasis (with approximately 70–90%), and its intracranial control rate is known to be approximately 40–60%. There is a continuing discussion on whether WBRT improves QOL, and survival (80-83). On the other hand, SRS or stereotactic radiotherapy (SRT) use scattered γ rays or high-energy X-ray, respectively, converging on the target to effectively kill tumor cells, induce apoptosis of endothelial cells and lead to tumor radio-sensitization, maximizing the protection of tumor peripheral tissues to increase local control and microscopic tumor infiltration, while reducing the risks of neurocognitive side effects compared to WBRT. Radionecrosis is still a challenging complication to manage (19,84,85). SRS/SRT is now considered as a standard treatment for patients with brain metastasis when the total volume is low enough, and the number is limited (86). Combination of WBRT and SRS/SRT is not recommended because it does not improve survival benefits but increases neurocognitive deficits (87-89). In order to prevent and reduce neurocognitive decline, the use of memantine (90,91) and Hippocampal-sparing radiation (92) is under investigation.

A meta-analysis on 12 observational studies that evaluated CNS response rate and 2-year OS in patients with EGFR mutation-positive NSCLC with brain metastases revealed that radiotherapy (SRS and WBRT) improved the OS by 2 years. Furthermore, it showed similar CNS response rate as that of the 1st generation EGFR-TKIs for the initial intervention but also resulted in more frequent adverse effects (93). On the other hand, a couple of retrospective studies have suggested that postponing radiotherapy for brain metastasis in EGFR mutation-positive NSCLC results in a poor outcome (94,95). In cases with disease progression in CNS after treatment with 1st or 2nd generation EGFR-TKIs, consider switching to osimertinib if T790M mutation is detected in any other site or lesion. If there are no extracranial progressive lesions for re-biopsy to prove T790M mutation, and if there is no need for neurosurgical intervention, local radiation therapy by SRS/SRT or WBRT for oligo or multiple metastases, respectively, to control brain metastases (holding TKI until radiation is completed) with continued treatment with EGFR-TKIs is recommended (Figure 1). Moreover, EGFR-TKIs and concurrent WBRT seems to have good tumor control ability (96) but increase the risk of potential cognitive complications (97).

Neurosurgical resection of NSCLC brain metastases

Surgical resection of the metastatic brain tumors has been another effective local treatment. Surgery is especially indicated when the brain lesion is large, and a patient is symptomatic due to elevated intracranial hypertension, and the tumor is preferably located in a non-functional region. Postoperative WBRT has shown to prolong OS from 16 to 19 months and is usually recommended (98,99).

Conclusions: general principles of current management of brain metastases

For those NSCLC patients with driver-oncogene mutations, including EGFR and ALK mutations, systemic therapy with the newest targeted therapy is preferred as the initial intervention rather than old generation TKIs. This is because the new-generation TKIs, such as osimertinib and alectinib, are designed to penetrate the BBB, and possess significantly higher intracranial activities compared to other
chemotherapies. Local radiotherapy followed by TKI is generally preferred, except when brain metastases have the risk of herniation or possess severe mass effect that needs neurosurgical intervention.

Acknowledgments
None.

Footnote

References

Figure 1 Flow chart for management of brain metastasis in the oncogene-driven NCSLC. This flow chart is according to JLCS, ESMO, NCCN guidelines. Detection of T790M mutation is mandatory to use osimertinib in the case of EGFR mutation-positive NSCLC. Dexamethasone or equivalent corticosteroid is recommended for most patients with symptomatic brain metastasis; Osimertinib as EGFR-TKI, alectinib, ceritinib and brigatinib as ALK-TKIs, is preferred; SRS is preferred when the total tumor volume is lower than 15 mL and the number of lesions is 10 or less; Detection of T790M mutation is mandatory to use osimertinib in case of EGFR mutation-positive NSCLC. NSCLC, non-small cell lung cancer; JLCS, Japan Lung Cancer Society; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network; EGFR, epidermal growth factor receptor; WBRT, whole brain radiation therapy; SRS/SRT, stereotactic radiosurgery/stereotactic radiotherapy; Gef, gefitinib; Erl, erlotinib; Afa, afatinib; Dac, dacomitinib; Osi, osimertinib; Cri, crizotinib; Ale, alectinib; Cer, ceritinib; Bri, brigatinib; Lor, lorlatinib.
63. Mok T, Spigel D, Felip E, et al. ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). J Clin Oncol 2015;33:abstr 8059.
76. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung


