Review Article

Brain metastases in oncogene-driven non-small cell lung cancer

Makoto Nishino[1], Kenzo Soejima[2], Tetsuya Mitsudomi[3]

[1]Division of Pulmonary Medicine, Department of Medicine, Keiyu Hospital, 3-7-3 Minatomirai, Nishi-ku, Yokohama, Japan; [2]Clinical and Translational Research Center, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan; [3]Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka, Japan

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Correspondence to: Tetsuya Mitsudomi, MD. Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Email: mitsudom@med.kindai.ac.jp.

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

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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) (1,2). However, the prognosis is not yet satisfactory. One of the most significant causes for poor prognosis and quality of life (QOL) in advanced NSCLC is brain metastases (3). According to the literature, the major prognostic factors affecting the treatment outcome in patients with metastatic NSCLC include age, time from diagnosis, and the location and extension of the intracranial disease (4-7).

About 40–50% of the brain metastases originate from systemic lung cancers. Conversely, approximately 10–20% of NSCLC patients present with brain metastases at diagnosis (8,9). NSCLC with brain metastases has a poor overall survival (OS) (10). Two-thirds of brain metastases present with multiple lesions while remaining one-third present with solitary lesions. Major sites of NSCLC brain metastases are the cerebrum (80%), cerebellum (15%), and

the brain stem (5%) (11). NSCLC patients with EGFR/ALK mutations appear to have a higher incidence (50–60%) of brain metastasis (12-15). In contrast, NSCLC with ROS1 translocations is reported to have a lower incidence (33%) of brain metastasis compared to that with EGFR/ALK (16).

The efficacy of platinum doublet chemotherapy (carboplatin and paclitaxel) which is the conventional treatment option is generally low (20%) (17). However, newer agents such as cisplatin + pemetrexed or carboplatin, paclitaxel plus bevacizumab showed better intracranial response rate [42% (18) and 61% (19), respectively] in the phase 2 trials. The standard of care for the treatment of NSCLC patients with a limited number of brain metastases has been local therapy either by surgical resection, whole-brain irradiation, and stereotactic radiosurgery (SRS). However, the newly developed tyrosine kinase inhibitors (TKIs) such as osimertinib or alectinib that can efficiently penetrate the blood-brain barrier (BBB) have demonstrated remarkable intracranial activity. Furthermore, the overall improvement of survival outcome for NSCLC patients increases the chances of developing cognitive dysfunctions induced by radiation. This further emphasizes the advantage of systemic treatment with targeted therapies over radiation therapies (12,13).

While developing new strategies to improve patient care in NSCLC, it is important to understand why oncogene-driven NSCLC have a high incidence of brain metastases. Further, the molecular mechanisms that lead to the development of brain metastases need to be identified. In addition, it is important to develop a treatment strategy that utilizes an ideal balance of targeted therapeutics that cannot penetrate the BBB and those that can cross the BBB for providing the best possible management of the disease without the risk of developing new brain lesions.

In this review, we describe the epidemiology and molecular background of brain metastases in driver-oncogene positive NSCLC. We also discuss what we have learned from the first-generation TKIs and how this has helped us develop the second and third-generation TKIs with improved BBB penetration capabilities for the management of brain metastases.

Mechanisms underlying brain metastasis

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 (20). 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/PI3K 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

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

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

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; CSF, cerebrospinal fluid.

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 nor 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

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

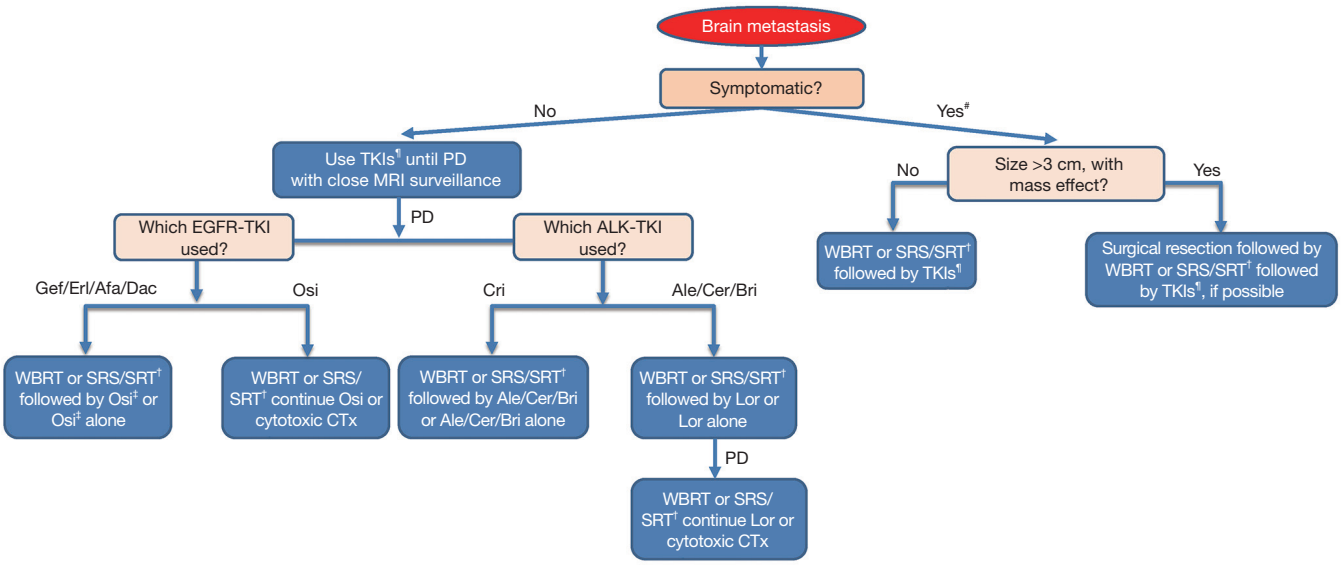

Figure 1 Flow chart for management of brain metastasis in the oncogene-driven NCSLC. This flow chart is according to JLCS, ESMO, NCCN guidelines. Detection of T790M mutation is mandatory to use osimertinib in the case of *EGFR* mutation-positive NSCLC. #, Dexamethasone or equivalent corticosteroid is 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.

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.

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Footnote

Conflicts of Interest: M Nishino has received lecture fees from AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Pfizer Japan Inc., and Taiho Pharmaceutical Co. Ltd. K Soejima has received personal fees as honoraria from AstraZeneca K.K., Chugai Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Japan, MSD Oncology, Eli Lilly Japan K.K. and Novartis Pharma K.K and has received research funding from Boehringer Ingelheim Japan Inc. and Taiho Pharmaceutical Co. Ltd. T Mitsudomi has received lecture fees from AstraZeneca K.K., Pfizer Japan Inc., Chugai Pharmaceutical Co. Ltd., Boehringer Ingelheim Japan Inc., MSD K.K., Ono Pharmaceutical Co. Ltd., Bristol Myers Squibb, Eli Lilly Japan K.K., and Taiho Pharmaceutical Co. Ltd.; research funding from Boehringer Ingelheim Japan Inc., Chugai Pharmaceutical Co. Ltd., Pfizer Japan Inc., Ono Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd.; as well as advisory fees from AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol Myers Squibb, MSD K.K., Chugai Pharmaceutical Co. Ltd., Pfizer Japan Inc., Ono Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd.

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