Editorial Commentary

Anaplastic lymphoma kinase inhibitor development: enhanced delivery to the central nervous system

Toyoaki Hida^

Lung Cancer Center, Central Japan International Medical Center, Minokamo, Gifu, Japan

Correspondence to: Toyoaki Hida, MD, PhD. Lung Cancer Center, Central Japan International Medical Center, Kenkonomachi, Minokamo, Gifu 505-8510, Japan. Email: t-hida@cjimc-hp.jp.

Comment on: Chow LQM, Barlesi F, Bertino EM, *et al.* ASCEND-7: Efficacy and Safety of Ceritinib Treatment in Patients with ALK-Positive Non-Small Cell Lung Cancer Metastatic to the Brain and/or Leptomeninges. Clin Cancer Res 2022;28:2506-16.

Keywords: Lung cancer; anaplastic lymphoma kinase inhibitor (ALK I); blood-brain barrier (BBB); brain metastasis; cerebrospinal fluid (CSF)

Submitted Jan 24, 2023. Accepted for publication Jul 17, 2023. Published online Jul 31, 2023.
doi: 10.21037/tlcr-23-43
View this article at: https://dx.doi.org/10.21037/tlcr-23-43

Anaplastic lymphoma kinase (ALK) gene rearrangement is a potent oncogenic driver in non-small cell lung cancer (NSCLC) and occurs in about 5% of patients with NSCLC (1). ALK-positive NSCLC is associated with a high risk of central nervous system (CNS) dissemination, and CNS metastases coexist in approximately 30% of patients with ALK-positive NSCLC at the time of diagnosis (2). Brain metastasis management aims to enhance survival and quality of life, with a maximum preference for neurocognitive function maintenance. Therefore, it is crucial to properly treat CNS and systemic lesions.

Brain cells are segregated from the entire body by several barriers, including the blood-brain barrier (BBB), blood-cerebrospinal fluid (CSF) barrier, blood-retinal barrier, and blood-spinal barrier (3,4). The BBB assists CNS homeostasis by preserving the CNS from poisonous substances (5). BBB active drug efflux transporters of the adenosine triphosphate (ATP)-binding cassette gene family, including the P-glycoprotein (P-gp), the multidrug resistance protein, and the breast cancer resistance protein (BCRP), are crucial for pharmacokinetics and effects of drugs (6-8). The effects of ATP-binding cassette (ABC) efflux transporters in the BBB include reducing the appearance of the neurotoxic adverse effects of drugs. In contrast, ABC efflux transporters may also restrict the central accumulation of drugs that are effective for treating CNS metastasis (5). The BBB is localized at the endothelial cells comprising the brain microvessels. In opposition to the peripheral endothelial cells, the BBB endothelial cells possess tight junctions. Because the existence of a tight junction among adjoining endothelial cells obstructs the paracellular space at the BBB, the permeability of small molecular drugs depends on their transcellular transport across the BBB, which is mainly brought about by passive transport. Several key physicochemical parameters, including molecular weight, lipophilicity, polar surface area, hydrogen bonding, and charge, request optimization to enhance BBB permeability by passive transport (9).

Today, five ALK inhibitors, including crizotinib, ceritinib, brigatinib, alectinib, and lorlatinib, are available for clinical use. Ceritinib, brigatinib, alectinib, and lorlatinib have been designed to overcome the failure of crizotinib at the brain site. Second- and third-generation ALK tyrosine kinase inhibitors (TKIs) are used for ALK positive patients with brain metastases instead of chemotherapy and first-generation TKI (10). The second- and third-generation ALK inhibitors are ingeniously designed to cross BBB more efficiently than crizotinib and to achieve higher concentrations in the CSF, thus providing a superior ability to control the CNS extension. The effect was achieved by reducing their molecular weight, increasing lipophilicity, and changing the number of available hydrogen bond donors.

^ ORCID: 0000-0003-3537-0020.

Table 1 Intracranial response in patients with measurable brain metastasis as per investigator assessment

Study arm	Intracranial metastasis and previously treatments	Intracranial overall response rate (95% CI)
Arm 1 (n=28)	Brain RT (+)/ALK I (+)	39.3 (21.5–59.4)
Arm 2 (n=29)	Brain RT (–)/ALK I (+)	27.6 (12.7–47.2)
Arm 3 (n=7)	Brain RT (+)/ALK I (–)	28.6 (3.7–71.0)
Arm 4 (n=33)	Brain RT (–)/ALK I (–)	51.5 (33.5–69.2)
Arm 5 (n=8)	Leptomeningeal meta	12.5 (0.3–52.7)

RT, radiotherapy; ALK I, anaplastic lymphoma kinase inhibitor; CI, confidence interval.

Table 2 Blood-brain barrier penetration

ALK inhibitor	Concentration ratio	CSF concentration (ng/mL)
CSF to unbound (free) plasma		
Ceritinib	13–35% (14)	2.31–12.4
Alectinib	86% (20)	1.396
Lorlatinib	75–77% (21,22)	2.64–125
CSF to serum/plasma		
Crizotinib	0.06–0.26% (23,24)	0.35–0.616
Brigatinib	1.27% (25)	13.23

ALK, anaplastic lymphoma kinase; CSF, cerebrospinal fluid.

Ceritinib is a second-generation ALK TKI, and in a murine experiment, the blood-to-brain transition ratio of ceritinib reached 15% (11). In the phase I trial (ASCEND-1), ceritinib showed overall intracranial response rates of 36% and 63% with and without ALK TKI pretreatment, respectively (12). In the ASCEND-2 study, the intracranial response rate reached almost 40%, and the intracranial disease control rate was 85% (11). The phase 3 ASCEND-4 trial compared ceritinib with chemotherapy as a first-line treatment, and in patients with CNS metastases, the mean progression-free survival was 10.7 months in the ceritinib group and 6.7 months in the chemotherapy group (13). The ASCEND-7 study was conducted to further assess ceritinib efficacy and safety in ALK-positive patients having brain and leptomeningeal metastases. In the issue of *Clinical Cancer Research*, Chow *et al.* (14) reported the phase 2 ASCEND-7 trial results. The trial investigated patients with ALK-positive NSCLC examined by the FDA-approved Vysis ALK Break Apart FISH Probe Kit test. ASCEND-7 was one of the prospective trials designed to use uniform eligibility criteria and assessments to investigate intra/extracranial effects of an ALK-targeted drug, although ASCEND-7 included a relatively small number of patients. Patients with active brain metastases were allocated to study arms 1–4 according to prior brain radiation and/or prior exposure to an ALK inhibitor (arm 1: prior radiotherapy/ALK inhibitor-pretreated; arm 2: no radiotherapy/ALK inhibitor-pretreated; arm 3: prior radiotherapy/no ALK inhibitor; arm 4: no radiotherapy/no ALK inhibitor). Patients with leptomeningeal carcinomatosis were evaluated in arm 5. Intracranial overall response rates per investigator assessment were 39.3% [95% confidence interval (CI), 21.5–59.4] in arm 1, 27.6% (95% CI, 12.7–47.2) in arm 2, 28.6% (95% CI, 3.7–71.0) in arm 3, and 51.5% (95% CI, 33.5–69.2) in arm 4. In arm 5, the intracranial response was 12.5% (95% CI, 0.3–52.7) (*Table 1*). Paired CSF and plasma sampling showed that ceritinib passed through the human BBB. Paired samples from 3 patients showed that ceritinib passed through the human BBB with a CSF-to-plasma concentration ratio of 13–35% (14). In a recent study, Katayama *et al.* (15) reported that ceritinib is a P-gp substrate, and P-gp inhibition reverses ceritinib and crizotinib resistance. Furthermore, Kort *et al.* (16) reported that P-gp and BCRP limit brain accumulation of ceritinib.

In brain metastases, the BBB is impaired and is shown to be different from the normal healthy BBB (17-19). The extent of BBB impairment is a key factor that affects the entry of drugs into the CNS. Effective therapy requires attaining targetable drug concentrations in the CNS. So, effective therapy of brain lesions requires efficient drug delivery across the BBB. Some clinical studies have reported on brain and CNS penetration of ALK inhibitors, although the conclusions from the small number of cases must be interpreted with caution. Usually, surrogate endpoints such as CSF-to-plasma ratios are substituted to consider whether a drug can be transported into the CNS and pass through the BBB (*Table 2*). Paired samples showed that ceritinib passed through the human BBB with a CSF-to-plasma concentration ratio of 13–35% (14). Another second-generation tyrosine kinase inhibitor, alectinib, showed a penetration rate of 86% into the CSF (20). Lorlatinib is a highly potent, selective, third-generation ALK inhibitor specifically developed to pass through the BBB and has broad ALK mutational coverage. This was confirmed in clinical trial, where the mean CSF-to-plasma ratio (unbound) was 0.75 in four patients with matched specimens available (21). Additionally, Sun *et al.*

reported that the regression analysis based on a sample of 5 patients with available CSF and estimated unbound plasma concentration data indicated a CSF-to-free plasma concentration ratio of 0.77 (22). Although the many CNS adverse events of lorlatinib, including mood, cognitive, speech, and psychotic effects, resolved without intervention or with lorlatinib dose modification and/or concomitant medication, the toxicity profile of lorlatinib may make the physicians hesitant providing it as first-line therapy.

Next-generation ALK inhibitors which are effective for brain metastases should be considered first-line therapy for patients with asymptomatic brain metastases. Radiotherapy or surgical resection may be considered in patients with symptomatic brain metastases. It is encountering a paradigm evolution from cranial radiotherapy to the use of more potent and central nervous system-penetrating ALK inhibitors. Our goal of treatment is to avert or postpone radiation therapy and its cognitive sequelae in ALK patients. The intracranial effects of novel TKIs may also potentially turn patients from requiring whole-brain radiotherapy to stereotactic radiosurgery with lighter side effects. A network meta-analysis demonstrated that lorlatinib had superior efficacy for patients with brain lesions but exhibited unique side effects. However, alectinib showed superior efficacy and lower toxicity in patients with ALK-positive NSCLC. On the other hand, ALTA trials demonstrated up to 70% response of ALK patients with brain metastasis, so brigatinib might be able to reverse the activation of a greater percentage of brain-related metastasis effectors despite relatively lower blood-brain barrier penetration (26). Treatment with second-generation ALK inhibitors, such as alectinib, brigatinib, ceritinib, and ensartinib, significantly improved overall survival compared with crizotinib (13). Much remains to optimize outcomes for patients with ALK CNS diseases. According to the concept of using the most effective drug first, the choice of the first line treatment for advanced ALK-positive NSCLC with CNS involvement is still under debate, and ceritinib's place in the landscape of ALK-positive NSCLC will need to be defined.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-43/coif). TH has received lecture fees from Pfizer, Novartis, Chugai Pharmaceutical, and Takeda Pharmaceutical. TH serves as the unpaid editorial board member of *Translational Lung Cancer Research* from January 2020 to December 2023. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res 2013;19:4273-81.
2. Johung KL, Yeh N, Desai NB, et al. Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis. J Clin Oncol 2016;34:123-9.
3. Abbott NJ, Patabendige AA, Dolman DE, et al. Structure and function of the blood-brain barrier. Neurobiol Dis 2010;37:13-25.
4. Francisco DMF, Marchetti L, Rodríguez-Lorenzo S, et al. Advancing brain barriers RNA sequencing: guidelines from experimental design to publication. Fluids Barriers CNS 2020;17:51.
5. Löscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. NeuroRx 2005;2:86-98.
6. Silverman JA. Multidrug-resistance transporters. Pharm Biotechnol 1999;12:353-86.

7. Fromm MF. P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. Int J Clin Pharmacol Ther 2000;38:69-74.
8. Schinkel AH, Jonker JW. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. Adv Drug Deliv Rev 2003;55:3-29.
9. Lipinski CA, Lombardo F, Dominy BW, et al. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 2001;46:3-26.
10. Jiang J, Zhao C, Zhang F, et al. ALK inhibitors in ALK-rearranged non-small cell lung cancer with and without brain metastases: systematic review and network me-ta-analysis. BMJ Open 2022;12:e060782.
11. Felip E, Crino L, Kim DW, et al. Whole body and intracranial efficacy of ceritinib in patients (pts) with crizotinib (CRZ) pretreated, ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) and baseline brain metastases (BM): results from ASCEND-1 and ASCEND-2 trials. J Thorac Oncol 2016;11:S118-9.
12. Kim DW, Mehra R, Tan DSW, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452-63.
13. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017;389:917-29. Erratum in: Lancet 2017;389:908.
14. Chow LQM, Barlesi F, Bertino EM, et al. ASCEND-7: Efficacy and Safety of Ceritinib Treatment in Patients with ALK-Positive Non-Small Cell Lung Cancer Metastatic to the Brain and/or Leptomeninges. Clin Cancer Res 2022;28:2506-16.
15. Katayama R, Sakashita T, Yanagitani N, et al. P-glycoprotein Mediates Ceritinib Resistance in Anaplastic Lymphoma Kinase-rearranged Non-small Cell Lung Cancer. EBioMedicine 2015;3:54-66.
16. Kort A, Sparidans RW, Wagenaar E, et al. Brain accumulation of the EML4-ALK inhibitor ceritinib is restricted by P-glycoprotein (P-GP/ABCB1) and breast cancer resistance protein (BCRP/ABCG2). Pharmacol Res 2015;102:200-7.
17. Ningaraj NS, Rao M, Hashizume K, et al. Regulation of blood-brain tumor barrier permeability by calcium-activated potassium channels. J Pharmacol Exp Ther 2002;301:838-51.
18. Percy DB, Ribot EJ, Chen Y, et al. In vivo characterization of changing blood-tumor barrier permeability in a mouse model of breast cancer metastasis: a complementary mag-netic resonance imaging approach. Invest Radiol 2011;46:718-25.
19. Daneman R. The blood-brain barrier in health and disease. Ann Neurol 2012;72:648-72.
20. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119-28.
21. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017;18:1590-9.
22. Sun S, Pithavala YK, Martini J-F, et al: Evaluation of lorlatinib cerebrospinal fluid concentrations in relation to target concentrations for Anaplastic Lymphoma Kinase (ALK) inhibition. J Clin Pharmacol 2022;62:1170-6.
23. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 2011;29:e443-5.
24. Metro G, Lunardi G, Floridi P, et al. CSF Concentration of Crizotinib in Two ALK-Positive Non-Small-Cell Lung Cancer Patients with CNS Metastases Deriving Clinical Benefit from Treatment. J Thorac Oncol 2015;10:e26-7.
25. Hiya S, Fujiwara S, Nakagawa A, et al. Isolated progression of miliary brain metasta-sis in a patient with stable lung adenocarcinoma successfully treated with whole-brain ra-diotherapy: A case report. eNeurologicalSci 2021;25:100366.
26. Carcereny E, Fernández-Nistal A, López A, et al. Head to head evaluation of second generation ALK inhibitors brigatinib and alectinib as first-line treatment for ALK+ NSCLC using an in silico systems biology-based approach. Oncotarget 2021;12:316-32.

Cite this article as: Hida T. Anaplastic lymphoma kinase inhibitor development: enhanced delivery to the central nervous system. Transl Lung Cancer Res 2023. doi: 10.21037/tlcr-23-43