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Efficacy of Lorlatinib on Cerebral Metastases in the Management of Alk-Positive Lung Adenocarcinoma, Case Report

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Abstract **Case Report**

Bronchial cancers are the leading cause of brain metastases and, in the absence of treatment, the median survival time for patients with bronchial cancer complicated by symptomatic brain metastases is approximately one month. Genetic sequencing has radically changed the management of non-small cell lung cancer over the last few decades. Anaplastic lymphoma kinase (ALK) rearrangements are responsible for 3-7% of non-small cell lung cancers. Patients with *ALK-positive* non-small cell lung cancer have a particular phenotype compared with other non-small cell lung cancers: they are younger, non-smokers and more frequently present with brain metastases. Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI) are the standard recommended first-line treatment for patients with *ALK-positive* in non-small cell lung cancer. Lorlatinib is a third-generation brain-penetrant ALK TKI that has greater coverage of ALK resistance mutations than second-generation ALK inhibitors. ***Conclusion*:** Brain metastases are a poor prognostic factor and are common in non-small cell lung cancer. Lorlatinib is a potent third-generation ALK tyrosine kinase inhibitor that has improved penetration of the central nervous system across the blood-brain barrier, resulting in higher intracranial response rates and preventing brain metastases.

Keywords: Non-Small Cell Lung Cancer, Brain Metastases, Anaplastic Lymphoma Kinase (ALK), Tyrosine Kinase Inhibitors (TKIs), Lorlatinib.

INTRODUCTION

With around 2.20 million new cases and 1.79 million deaths a year, lung cancer is the most common cancer diagnosis in the world and remains the leading cause of cancer-related death. It is the second most common cancer in men, after prostate cancer, and the second most common cancer in women, after breast cancer [1]. Bronchial cancers are the leading cause of brain metastases and, in the absence of treatment, the median survival time for patients with bronchial cancer complicated by symptomatic brain metastases is approximately one month [2].

The discovery of tumour-specific alterations in oncogenes capable of stimulating cancer growth and survival has revolutionised the approach to cancer treatment. Genetic sequencing has radically changed the management of non-small cell lung cancer over the last few decades. Rapid advances in next-generation sequencing (NGS) and a better understanding of cancer biology have provided the opportunity to characterise human cancer genomes, including NSCLC, leading to the identification of several exploitable driver alterations implicated in aetiopathogenesis and the subsequent development of targeted therapies [3].

Anaplastic lymphoma kinase (ALK) rearrangements are responsible for 3-7% of non-squamous non-small cell lung cancers, mutually exclusive of other driving mutations. Patients with an ALK rearrangement have the following clinicopathological features: young age at diagnosis (median 50 years), female gender, non-smoker or light smoker, adenocarcinoma histology with distinctive morphological patterns such as the sieve ring and solid ring, expression of thyroid transcription factor 1, tendency to metastasise to the pleura or pericardium, and in particular to the central nervous system [4].

Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) are the standard recommended first-line treatment for patients with ALK-positive non-

small cell lung cancer [5]. Lorlatinib is a third-generation brain-penetrant ALK TKI that has greater coverage of ALK resistance mutations than second-generation ALK inhibitors [6, 7].

PATIENT AND OBSERVATION

A 31-year-old female patient presented with intense occipital headaches that were not relieved by Level 2 analgesics, vomiting that was not accompanied by meals and the onset of generalised tonic-clonic seizures.

Cerebral CT and MRI scans revealed multiple secondary lesions above and below the tentorial surface with signs of intracranial hypertension (FIG 1). In the search for the primary sitea thoracic-abdominopelvic scan revealed a pulmonary lesion which was biopsied. The histological study revealed a non-small cell bronchial carcinoma and the immunohistochemical profile was in favour of a pulmonary bronchial adenocarcinoma. Next-generation sequencing (NGS) was positive for anaplastic lymphoma kinase (ALK) fusion, PDLl was 0%.

To control the symptoms associated with the brain metastases, we carried out five sessions encephalic radiotherapy totalling 20 grays, as the neurosurgeons felt that the patient could not be operated on, and put her on high-dose corticosteroids (methylprednisolone hemisuccinate 240mg per day) plus an anti-epileptic (sodium valproate 1500mg per day).

In conclusion, this is a young patient aged 31 with no previous history of lung adenocarcinoma metastatic to the brain and an ALK gene rearrangement.

The decision of the medical oncology multidisciplinary consultation meeting (RCP) was to start the patient on a third-generation tyrosine kinase inhibitor: lorlatinib 100mg per day. After two months of treatment, a brain scan showed a clear regression of the brain metastases. (FIG2)

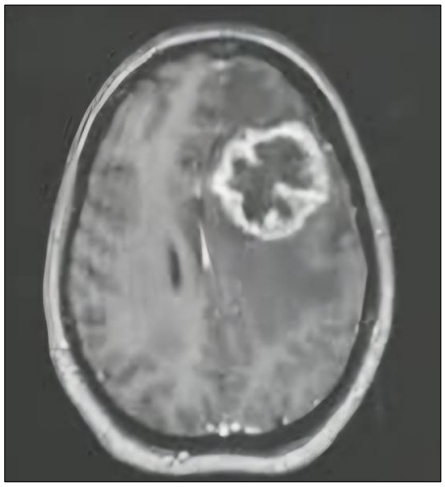

Figure 1: Cerebral scan; cerebral locations above and below the tentorial

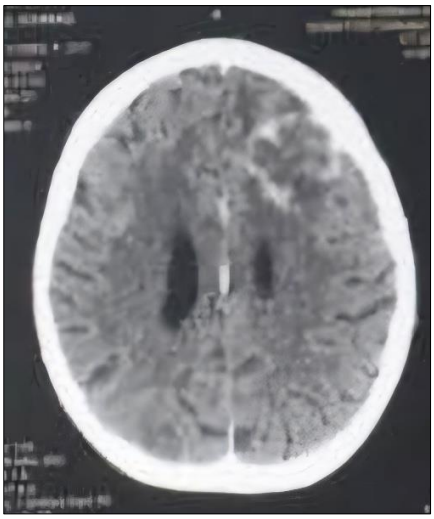

Figure 2: CT scan image showing partial regression of target lesions in the brain

DISCUSSION

Lung cancer is the most common cause of brain metastases, accounting for up to 50%, compared with 17% for breast cancer and 10% for melanoma [8]. The incidence of brain metastases at diagnosis is higher in the presence of certain genomic alterations: 24% in the case of EGFR mutation [9], and up to 48% in the case of ALK translocation [10]. When metastases are not present at diagnosis, they appear during follow-up in 40-50% of cases of non-small cell lung cancer, with a median time to onset of 11 months [11]. The management of brain metastases is therefore a major challenge, not only because of their incidence but also because of their seriousness. They are symptomatic in 80% of cases and are directly responsible for death in 50% of cases [12]. The therapeutic arsenal for the treatment of these metastases has been considerably expanded and made more sophisticated, including radiotherapy in stereotactic conditions, irradiation of the entire brain, microsurgical resection, laser therapy, systemic chemotherapy, targeted therapies and immune checkpoint inhibitors [13].

Since our patient was not considered for surgery, we underwent total cephalic radiotherapy and symptomatic treatment with high-dose corticosteroids, analgesics and anti-epileptics, which considerably improved her symptoms of intracranial hypertension (nausea, vomiting, headaches and epileptiform seizures).

The ALK gene encodes a receptor with tyrosine kinase activity from the insulin receptor superfamily, expressed physiologically in nervous tissue during development. Rearrangements of this gene, first identified in 1994 in anaplastic lymphomas, are observed in various cancers and ultimately lead to the juxtaposition of an N-terminal "heterologous" domain to the C-terminal ALK kinase domain. Many partner genes are involved in these rearrangements, which determine the subcellular localisation of the chimeric protein produced, particularly in anaplastic lymphomas [14]. Patients with *ALK-positive* non-small cell lung cancer have a particular phenotype compared with other non-small cell lung cancers: they are younger, non-smokers and more frequently have brain metastases [15].

Crizotinib, the first-in-class ALK tyrosine kinase inhibitor (TKI) [16], improved outcomes (Progression-Free Survival, and quality of life) over platinum-based chemotherapy for the initial treatment of patients with newly diagnosed *ALK-positive* non-small cell lung cancer in the phase III PROFILE 1014 trial [17], establishing first-line ALK-TKIs as the standard of care. Ceritinib, a second-generation ALK-KI, has also been shown to be superior to first-line chemotherapy [18]. However, new-generation TKI-ALKs have been shown in phase III trials to be superior to crizotinib as first-line therapy, including alectinib [19], brigatinib [20], ensartinib (not approved by the EMA) [21], and lorlatinib [22]. Alectinib, brigatinib and lorlatinib are preferred for initial treatment [23]. For reasons of accessibility, we prescribed lorlatinib for our patient at a dose of 100mg per day after a multidisciplinary consultation meeting.

It should be noted that no direct comparison has been made between the new generation TKI-ALKs. The choice of drug will be influenced by factors such as the extent of CNS disease, patient preference and the need to manage the different toxicity profiles seen with these drugs [23].

In the CROWN phase III trial (N=296), lorlatinib resulted in significantly longer progression-free survival (PFS) than crizotinib (not reached (NR)) (9.3 months; HR 0.28, 95% CI 0.19-0.41) [24]. The overall intracranial response rate and time to intracranial progression were superior for lorlatinib. The cerebral efficacy of lorlatinib is well known and demonstrated by several clinical data. For example, on lorlatinib, brain disease control rates were 82% in treatment-naïve patients and 63% in treatment-experienced patients [24, 25]. Lorlatinib was designed to penetrate the blood-brain barrier, thanks in particular to a macrocyclic ring and a more lipophilic character than crizotinib. A study conducted in rats exposed to lorlatinib showed greater permeability of the blood-brain barrier [26], with lorlatinib inhibiting the expression of the SPP1 gene in cells of the blood-brain barrier, leading to a reduction in the production of VEGF and TGF-β and an increase in the expression of EGR-1. In addition, the SSP1 gene enables the production of osteopontin, a neuroprotective glycoprotein that plays an important role in the structure of the blood-brain barrier. All these mechanisms induced by lorlatinib ultimately lead to the destruction of the tight junctions between the endothelial cells of the blood-brain barrier, and to increased permeability of the blood-brain barrier in rats. The intracranial availability of lorlatinib is estimated at 21% in rats without brain damage [27]. The intracerebral activity of lorlatinib was demonstrated in a pre-clinical trial using a mouse xenograft model of a tumour with an EML4-ALK rearrangement associated or not with an ALK L1196M [28]. In primates, a radioisotope of lorlatinib showed significant and rapid cerebral diffusion on positron emission tomography, particularly in the cerebellum, frontal cortex and thalamus [29, 30]. Finally, in 4 patients in the phase 1 trial of lorlatinib who had undergone lumbar puncture, the mean concentrations of lorlatinib in cerebrospinal fluid corresponded to 75% of plasma concentrations, confirming the excellent bioavailability in the brain [31]. Overall, lorlatinib has a high intracranial penetration rate and does not appear to be subject to the resistance phenomenon associated with the P-glycoprotein (P-gp) efflux pump system [27].

This intracerebral activity of lorlatinib was demonstrated in our patient who, after just two months of treatment, showed a significant regression of more

than 40% of her brain lesions on CT scan and a complete reduction in the symptoms associated with brain metastases.

The most common adverse events of any grade with lorlatinib were hyperlipidaemia, oedema, weight gain, peripheral neuropathy and cognitive effects. Lorlatinib was associated with more grade 3-4 adverse events (mainly altered lipid levels) than crizotinib (72% versus 56%) [23].

Our patient's follow-up was marked by minor lipid disturbances, namely hyperlipidaemia, which was managed by prescribing a statin with the involvement of the endocrinology department. These lipid disorders did not necessitate a reduction in dose or discontinuation of our treatment.

CONCLUSION

Brain metastases are a poor prognostic factor and are common in non-small cell lung cancer. Treatment options for patients with ALK-rearranged NSCLC have advanced considerably over the past decade. Lorlatinib is a potent third-generation ALK tyrosine kinase inhibitor that has improved penetration of the central nervous system across the blood-brain barrier, resulting in higher intracranial response rates and preventing brain metastases.

REFERENCES

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *71*(3), 209-249.
2. Downey, R. J., Ng, K. K., Kris, M. G., Bains, M. S., Miller, V. A., Heelan, R., ... & Rusch, V. W. (2002). A phase II trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis. *Lung Cancer*, *38*(2), 193-197.
3. Rodak, O., Peris-Díaz, M. D., Olbromski, M., Podhorska-Okołów, M., & Dzięgiel, P. (2021). Current landscape of non-small cell lung cancer: epidemiology, histological classification, targeted therapies, and immunotherapy. *Cancers*, *13*(18), 4705.
4. Lei, Y., Lei, Y., Shi, X., & Wang, J. (2022). EML4-ALK fusion gene in non-small cell lung cancer. *Oncology letters*, *24*(2), 1-6.
5. Planchard, D., Popat, S. T., Kerr, K., Novello, S., Smit, E. F., Faivre-Finn, C., ... & Peters, S. (2018). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *29*, iv192-iv237.
6. Johnson, T. W., Richardson, P. F., Bailey, S., Brooun, A., Burke, B. J., Collins, M. R., ... & Edwards, M. P. (2014). Discovery of (10 R)-7-Amino-12-fluoro-2, 10, 16-trimethyl-15-oxo-10, 15, 16, 17-tetrahydro-2H-8, 4-(metheno) pyrazolo [4, 3-h][2, 5, 11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *Journal of medicinal chemistry*, *57*(11), 4720-4744.
7. Shaw, A. T., Felip, E., Bauer, T. M., Besse, B., Navarro, A., Postel-Vinay, S., ... & Solomon, B. J. (2017). 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. *The Lancet Oncology*, *18*(12), 1590-1599.
8. Rangachari, D., Yamaguchi, N., VanderLaan, P. A., Folch, E., Mahadevan, A., Floyd, S. R., ... & Costa, D. B. (2015). Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung cancer*, *88*(1), 108-111.
9. Bajard, A., Westeel, V., Dubiez, A., Jacoulet, P., Pernet, D., Dalphin, J. C., & Depierre, A. (2004). Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer*, *45*(3), 317-323.
10. Gaspar, L, (1997). Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials *Int J Radiat Oncol Biol Phys*, *37*(4), 745-751.
11. Sperduto, P. W., Yang, T. J., Beal, K., Pan, H., Brown, P. D., Bangdiwala, A., ... & Mehta, M. P. (2016). The effect of gene alterations and tyrosine kinase inhibition on survival and cause of death in patients with adenocarcinoma of the lung and brain metastases. *International Journal of Radiation Oncology* Biology* Physics*, *96*(2), 406-413.
12. Kiesel, B., Prihoda, R., Borkovec, M., Mercea, P. A., Steindl, A., Berghoff, A. S., ... & Widhalm, G. (2020). Postoperative magnetic resonance imaging after surgery of brain metastases: analysis of extent of resection and potential risk factors for incomplete resection. *World Neurosurgery*, *143*, e365-e373.
13. Chua, T. H., See, A. A. Q., Ang, B. T., & King, N. K. K. (2018). Awake craniotomy for resection of brain metastases: a systematic review. *World Neurosurgery*, *120*, e1128-e1135.
14. Kruczynski, A., Delsol, G., Laurent, C., Brousset, P., & Lamant, L. (2012). Anaplastic lymphoma kinase as a therapeutic target. *Expert opinion on therapeutic targets*, *16*(11), 1127-1138.
15. Lange, M., Joly, F., Vardy, J., Ahles, T., Dubois, M., Tron, L., ... & Castel, H. (2019). Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Annals of Oncology*, *30*(12), 1925-1940.
16. Kwak, E. L., Bang, Y. J., Camidge, D. R., Shaw, A. T., Solomon, B., Maki, R. G., ... & Iafrate, A. J. (2010). Anaplastic lymphoma kinase inhibition in

non–small-cell lung cancer. *New England Journal of Medicine*, *363*(18), 1693-1703.
17. Solomon, B. J., Mok, T., Kim, D. W., Wu, Y. L., Nakagawa, K., Mekhail, T., ... & Blackhall, F. (2014). First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *New England Journal of Medicine*, *371*(23), 2167-2177.
18. Soria, J. C., Tan, D. S., Chiari, R., Wu, Y. L., Paz-Ares, L., Wolf, J., ... & de Castro, G. (2017). 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. *The Lancet*, *389*(10072), 917-929.
19. Peters, S., Camidge, D. R., Shaw, A. T., Gadgeel, S., Ahn, J. S., Kim, D. W., ... & Mok, T. (2017). Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. *New England Journal of Medicine*, *377*(9), 829-838.
20. Camidge, D. R., Kim, H. R., & Ahn, M. J. (2021). Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of the ALTA-1L phase 3 trial, *J Thorac Oncol*, *16*, 2091-2108.
21. Horn, L., Wang, Z., Wu, G., Poddubskaya, E., Mok, T., Reck, M., ... & Wu, Y. L. (2021). Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase− positive non–small cell lung cancer: a randomized clinical trial. *JAMA oncology*, *7*(11), 1617-1625.
22. Shaw, A. T., Bauer, T. M., de Marinis, F., Felip, E., Goto, Y., Liu, G., ... & Solomon, B. J. (2020). First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *New England Journal of Medicine*, *383*(21), 2018-2029.
23. Hendriks, L. E., Kerr, K. M., Menis, J., Mok, T. S., Nestlé, U., Passaro, A., Peters, S., Planchard, D., Smit , E. F., Salomon, B. J., Véronèse, G., & Reck, M. (2023). Oncogene-dependent metastatic non-small cell lung cancer: *ESMO clinical practice guideline for diagnosis, treatment and follow-up*, *34*(4), 339-357.
24. Shaw, A. T., Bauer, T. M., de Marinis, F., Felip, E., Goto, Y., Liu, G., ... & Solomon, B. J. (2020). First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *New England Journal of Medicine*, *383*(21), 2018-2029.
25. Solomon, B. J., Besse, B., Bauer, T. M., Felip, E., Soo, R. A., Camidge, D. R., ... & Shaw, A. T. (2018). Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *The Lancet Oncology*, *19*(12), 1654-1667.
26. Chen, W., Jin, D., Shi, Y., Zhang, Y., Zhou, H., & Li, G. (2020). The underlying mechanisms of lorlatinib penetration across the blood-brain barrier and the distribution characteristics of lorlatinib in the brain. *Cancer Medicine*, *9*(12), 4350-4359.
27. Johnson, T. W., Richardson, P. F., Bailey, S., Brooun, A., Burke, B. J., Collins, M. R., ... & Edwards, M. P. (2014). Discovery of (10 R)-7-Amino-12-fluoro-2, 10, 16-trimethyl-15-oxo-10, 15, 16, 17-tetrahydro-2H-8, 4-(metheno) pyrazolo [4, 3-h][2, 5, 11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *Journal of medicinal chemistry*, *57*(11), 4720-4744.
28. Zou, H. Y., Friboulet, L., Kodack, D. P., Engstrom, L. D., Li, Q., West, M., ... & Smeal, T. (2015). PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. *Cancer cell*, *28*(1), 70-81.
29. Collier, T. L., Maresca, K. P., Normandin, M. D., Richardson, P., McCarthy, T. J., Liang, S. H., ... & Vasdev, N. (2017). Brain penetration of the ROS1/ALK inhibitor lorlatinib confirmed by PET. *Molecular Imaging*, *16*, 1536012117736669.
30. Collier, T. L., Normandin, M. D., Stephenson, N. A., Livni, E., Liang, S. H., Wooten, D. W., ... & Vasdev, N. (2017). Synthesis and preliminary PET imaging of 11C and 18F isotopologues of the ROS1/ALK inhibitor lorlatinib. *Nature communications*, *8*(1), 15761.
31. Shaw, A. T., Felip, E., Bauer, T. M., Besse, B., Navarro, A., Postel-Vinay, S., ... & Solomon, B. J. (2017). 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. *The Lancet Oncology*, *18*(12), 1590-1599.