

Beneath the Blood Brain Barrier: The Challenge of Diagnosis and Management of Central Nervous System Involvement in ALK-Positive Lung Cancer

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Involvement of the central nervous system (CNS) in non-small cell lung cancer (NSCLC) patients is frequent and usually presents a diagnostic and therapeutic challenge. In a large cohort of NSCLC patients analyzed according to diagnosis-specific graded prognostic score, median survival from diagnosis of brain metastases was 7 months.¹ Other series reported shorter survival, usually in the range of 3 to 6 months, depending on institutional profiles and patient selection criteria. Patients with CNS involvement typically present with headache, seizures, and a range of neurological deficits. Change in mental status, signs of depression, or psychosis may occasionally call for psychiatric assistance. Complications from CNS involvement are frequently devastating, leading to poor quality of life, and physical and emotional suffering. Patients with CNS involvement are typically excluded from clinical trials, and this severely limits our knowledge on their optimal management. This limitation is currently recognized by many national health authorities, and researchers are encouraged to include in clinical trials separate cohorts of patients with CNS involvement.

Careful clinical examination and magnetic resonance imaging most often results in appropriate diagnosis. Lumbar puncture and examination of cerebrospinal fluid (CSF) should be part of diagnostic work up in cases of suspected leptomeningeal carcinomatosis. Although increased risk of early brain dissemination has long been attributed to adenocarcinoma histology, the molecular basis of this phenomenon is poorly understood. CNS involvement may be more common in patients with ALK rearranged NSCLC. Approximately 35% of patients enrolled in the PROFILE 1007, a phase III second-line study comparing ALK inhibitor crizotinib to chemotherapy, presented with brain metastases at screening.² The putative involvement of ALK in the CNS dissemination is not surprising, given its biological role as a tyrosine kinase receptor involved in the brain development.³

In this issue of the *Journal of Thoracic Oncology*, Dr. Gainor and colleagues⁴ report on two series of uncommon forms of CNS involvement in patients with ALK-rearranged NSCLC: intramedullary spinal cord metastases (ISCM) and leptomeningeal carcinomatosis (LC). Of note, most of these patients developed ISCM or LC while on therapy with crizotinib, often with continuous extracranial response. Thus, poor penetration of crizotinib to the brain (“pharmacokinetic relapse”) rather than cellular resistance is suspected as the mechanism of ALK inhibitor failure. Presented cases add to the current knowledge on limited activity of crizotinib in the CNS, most probably due its low penetration through the blood brain barrier.⁵ Although clinical presentations described by Dr. Gainor and colleagues are relatively uncommon, they should call for attention in ALK-positive NSCLC patients treated with crizotinib, now increasingly used worldwide. Therapeutic options in patients with “pharmacokinetic relapses” in the CNS include radiotherapy (be it conventionally fractionated or stereotactic), surgery in very selected patients, and systemic treatment: a continuation of crizotinib “beyond CNS progression”, chemotherapy, or experimental

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agents such as second generation ALK inhibitors or hsp90 inhibitors.

Due to often prolonged systemic benefit from ALK inhibition, local therapies appear to be particularly important in this group of patients. Whole brain radiotherapy, if not administered previously, may additionally disrupt the blood brain barrier, potentially increasing CSF concentration of crizotinib, as exemplified by our own experience. One of our patients, who progressed in the brain during continued response in the chest, achieved a response after whole brain radiotherapy (WBRT), with successful re-exposure to crizotinib given in the recommended dose of 250 mg twice daily, lasting for more than 2 years. Several other patients are currently managed with this approach. Another promising crizotinib retreatment strategy, published in the case reports section of this issue of the *Journal of Thoracic Oncology*, includes administration of 500 mg of crizotinib once daily, with a possible advantage of its increased peak concentration leading to better penetration to the brain.⁶ Several novel ALK inhibitors (LDK378, CH5424802, AP26113, TSR-011) appear to better penetrate through the blood brain barrier, which will hopefully translate into fewer CNS relapses and continued successful ALK inhibition in patients with isolated failures in the CNS while on crizotinib therapy.

The reports by Dr. Gainor and Dr. Peled emphasize the importance of a phenomenon of CNS as a sanctuary site in ALK positive NSCLC, and pose new questions to be addressed in this increasingly recognized group of patients. Is active surveillance by imaging useful to detect and treat CNS metastases before they become symptomatic, often leading

to dramatic neurological sequelae? Is it safe to administer WBRT concomitantly with crizotinib? To what extent and for how long WBRT disrupts the blood brain barrier and what crizotinib concentrations are expected in the CSF after radiotherapy with different crizotinib administration schedules? Will CNS remain a sanctuary site for new generation of ALK inhibitors?

With these questions in mind, authors of both papers should be congratulated for careful evaluation of their patients. Their work may stimulate further research which will translate into prolonged symptom-free survival of ALK-rearranged lung cancer patients with CNS involvement.

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