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Early Detection of Brain Mets in ALK-positive Lung Cancer Patients

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Why should ALK-positive lung cancer patients who take Crizotinib (Xalkori) get a brain MRI when they have no symptoms?

Brain metastasis (brain mets or BM) is very common in non-small cell lung cancer patients (about 10% of lung cancer patients will present initially and about 24%[1] to 40%[2] of ALK-positive lung cancer patients present initially, and 25-40% of patients will develop BM after initial diagnosis). BM complicates treatment modalities because it normally requires a change in medications, radiation therapy, or other invasive treatments to get BM under control.

There are some Anaplastic Lymphoma Kinase (ALK) specific Tyrosine Kinase Inhibitors (TKIs) that have little or no Blood Brain Barrier (BBB) penetration in most patients, leaving the Central Nervous System (CNS) unprotected. Crizotinib[3] is one of those ALK TKIs and is routinely prescribed as the first line drug to treat ALK-positive lung cancer patients, even though there are second generation TKIs with a smaller molecule that has superior penetration of the BBB, approved for first line use in the United States such as Alectinib[4] . Other countries may still require the use of Crizotinib as first-line treatment for ALK-positive lung cancer patients. A patient may show dramatic response to Crizotinib, but most will progress after about a year into treatment and progression is typically in the cranial space via BM for 70% of those who have BM and 20% of those who have not had previous BM[5].

[1] The Emerging Role of Targeted Therapy and Immunotherapy in the Management of Brain Metastases in Non-Small Cell Lung Cancer, April 5, 2017 via online at NCBI

[2] Patterns of Metastatic Spread and Mechanisms of Resistance to Crizotinib in ROS1-Positive Non–Small-Cell Lung Cancer, online via ASCO Pubs.

[3] Crizotinib was developed by Pfizer, Inc. and sold under the trade name Xalkori

[4] Alectinib was developed by Chugai Pharmaceutical Co. Japan, which is part of the Hoffmann-La Roche group and sold under the trade name Alecensa

[5] Alectinib for the management of ALK-positive non-small cell lung cancer brain metastases, February 5, 2017 via online at NCBI

Former treatment modalities were to wait for symptoms of BM, most likely due to cost and accuracy of imaging, and frankly, BM historically came with a very grim prognosis for the patient. Therefore many oncologists preferred to perform an initial baseline MRI at diagnosis and then wait for symptoms before subsequent MRIs were performed. If you've never had a baseline brain MRI be sure to demand this from your oncologist as it is advised for stages II and III and very important for stage IV[6]. Best results would be achieved having the brain MRI with and without contrast.

There has been a shift in attitude by many top ALK lung cancer doctors in recent years where routine, or regular, brain MRIs are performed to ensure early detection of any BM for patients taking Crizotinib. These scans are being done absent of any symptoms because the quality of life can be greatly affected by BM whether it be from symptoms or the treatment required to achieve a desired response. ALK patient survivability is continuing to increase and keeping a close watch for BM can improve not only the quality of life through early detection and intervention, but also provide numerous treatment options due early detection. There are newer generation TKIs coming to market and even newer medications available via drug trials that can address BM without the harsh effects of radiation or surgery.

Many treatment facilities are limited in their treatment options when a patient presents with innumerable brain mets whether the mets are tiny, or one large single metastasis. Through early detection you may have options like switching to another TKI that has superior penetration of the BBB and resolves the brain mets. Another option could be to use radiation therapy such as Gamma Knife (GK), which uses a halo type frame, or Cyberknife (CK) which uses a face mask to "spot treat" brain mets. Some facilities can treat numerous tiny brain mets, and others cannot. For the facilities that cannot treat numerous brain mets you may be required to undergo Whole Brain Radiation (WBR) treatment. This is the least desired treatment option because the necrosis that is being experienced by some longtime ALK-positive lung cancer survivors has presented some debilitating effects.

As you can see, taking a "wait and see" approach to BM can lead to some serious issues in ALK-positive lung cancer patients. It is in your best interest to talk with your care team and demand brain MRI's to allow early detection of BM and minimize the chances of having symptoms which could indicate innumerable BM or very large BM that may require more invasive treatments.

[6] National Cancer Compendium Network (NCCN) Guidelines, 2018

A new approach in this line of treatment is to be on a regular brain MRI schedule. Most recommend every three months, but not more than six months while taking Crizotinib. If you develop brain mets it is recommended you get a brain MRI at least every three months if not more often, especially if you have active brain mets, consider changing to a second or third generation TKI, if available, and have next generation sequencing (NGS) performed to determine mechanism of resistance, such as a secondary mutation or sub mutation.

One more point to make is that not all MRI machines are created equally. Many MRI machines typically scan in five millimeter slices on all three planes, or views (sagittal, axial, and coronal). Some may scan one plane in one millimeter slices while the other two planes are at five millimeter. Newer machines can scan in one millimeter slices for all three planes. Be sure to ask this question as having at least one view that is at 1mm slices can detect 1mm or larger brain mets. The reason you want a one millimeter slice is that a four millimeter BM can hide between five millimeter slices.