ALK+ lung cancer and the Blood-Brain Barrier (BBB)

A concise guide
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Section 1: Lung cancer and ALK+ NSCLC

Lung cancer

Lung cancer is the most common type of cancer worldwide. There are more than 1.8 million new cases of lung cancer each year, which equates to 13% of total cancer cases. It is also more deadly than any other cancer, having resulted in 1.59 million deaths in 2012.

There are two main types of lung cancer – small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC is relatively uncommon, occurring in about 15% of lung cancer patients, while NSCLC occurs in the majority of the remaining lung cancer cases. Within NSCLC, there are several further subtypes driven by different receptors and genetic mutations, including anaplastic lymphoma kinase-positive (ALK+) NSCLC.

Worldwide, approximately 90,000 new cases of ALK+ NSCLC are diagnosed each year, which amounts to more than 5% of the total new lung cancer cases. The anaplastic lymphoma kinase (ALK) gene plays an important role in the cells of the nervous system and its expression is normally under strict genetic control. ALK+ NSCLC is caused by ‘activating mutations’ in the ALK gene, which cause it to fuse with another gene (most often EML4) to create an ALK-fusion protein. Unlike other forms of lung cancer, ALK+ NSCLC is most commonly diagnosed in younger people with a light or non-smoking history.

FACT 1: More people die of lung cancer worldwide than of breast, prostate and colorectal cancers combined

FACT 2: Researchers have identified 15 unique mutations and biomarkers that are responsible for tumour growth in NSCLC

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Section 2: The Blood-Brain Barrier (BBB): What and why?

Blood-Brain Barrier (BBB) and lung cancer

Patients with this distinct form of lung cancer are at high risk of developing brain metastases. As many as 60% of anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALK+ NSCLC) patients who are treated with the current standard of care see their tumours spread to the brain within a year. This means that treatments for the disease need to be able to reach tumours in both the lungs and the brain.

The ability to effectively treat brain metastases is extremely important, as tumours that spread to the brain are particularly devastating to patients. They can result in the loss of vital functions such as vision or movement, impact mental performance or cause changes in personality and behaviour. Furthermore, compared to other sites, brain metastases are associated with a significant reduction in quality of life and life expectancy.

Structure of the Blood-Brain Barrier (BBB)

The BBB is a tightly-joined network of cells lining the blood vessels in the brain and spinal cord, which protects the brain and Central Nervous System by preventing the entry of certain harmful molecules.

Brain metastases can be difficult to treat because most anaplastic lymphoma kinase (ALK) inhibitors are able to cross the BBB, but are pumped out by active efflux so the concentration is low in the brain.
Section 3:
Behind the Blood-Brain Barrier (BBB): The function of the barrier

FACT 5: The total length of all the blood vessels in the BBB is 600 km. That’s the equivalent of 2000 stacked Eiffel Towers!

How the Blood-Brain Barrier (BBB) works
The BBB controls which molecules can enter the brain from the blood, for example, according to their size. The BBB stops some molecules entering the brain entirely.

There are a few different ways a molecule can cross the BBB, for example:
• By diffusion
• Through the tight gaps between the BBB cells (for smaller molecules)
• By carrier proteins (for larger molecules)

The active efflux system
Even if a drug is able to cross the BBB, it may be pumped out of the brain and wider Central Nervous System by a mechanism called active efflux. Active efflux occurs when special proteins recognise some of the molecules that have crossed the BBB and transport them back into the blood.

Only the molecules that can both cross the BBB and avoid the active efflux system are able to treat brain metastases.

FACT 6: More than 90% of cancer morbidity (poor quality of life, pain, impaired organ function) and cancer deaths are directly related to metastasis.
References


6. Roche data on file.


10. Molecular Profiling of Lung Cancer [Available at: http://www.mycancergenome.org/content/disease/lung-cancer Last accessed 07.05.15].


