Leptomeningeal metastasis in lung cancer

Leptomeningeal metastasis is the spread of cancer cells to the membranes surrounding the brain and spinal cord as well as the cerebrospinal fluid (CSF). This occurs in 3-5% of patients with non-small cell lung cancer (NSCLC), the most common type of lung cancer. Since many conventional therapeutic agents either cannot penetrate the blood brain barrier or reach high enough therapeutic concentrations, it is challenging to treat. We reviewed current techniques in diagnosing this debilitating disease and the latest treatment options currently available.

Patients with leptomeningeal metastasis can present with a variety of neurological complaints ranging from worsening fatigue to seizures. Diagnosis requires a complete neurological exam, magnetic resonance imaging (MRI) and analysis of the CSF for cancer cells (cytology). A liquid biopsy can now be used to perform genetic analysis on the fluid to evaluate for specific lung cancer mutations in genes for which molecularly targeted therapy are currently available. The fluid can also be analyzed to assess for resistance mechanisms and response to treatment.

Since Leptomeningeal metastasis signifies advanced disease, the goal of treatment is to improve quality of life, increase survival and reduce neurological symptoms. Treatment options include radiotherapy, systemic cytotoxic chemotherapy, immunotherapy molecularly targeted drugs and directly infusing chemotherapy into the spinal canal or subarachnoid space (intrathecal chemotherapy).

There are no systemic cytotoxic option that is agreed upon as the standard of care in NSCLC to treat leptomeningeal disease. Intrathecal chemotherapy has been effective but the agent and dose to be administered is not standardized. Local radiotherapy can be useful to ease symptoms, reduce bulky disease and to correct CSF flow. Whole craniospinal radiotherapy is rarely used as there is substantial toxicity.

A subset of patients have specific mutations in molecular drivers of cancers such as *EGFR*, *ROS* and *ALK*. DNA from CSF can be directly sequenced for specific mutations to tailor treatment effectively. Interestingly, there have been differences in resistance mutations between analysis from the CSF and the primary tumor. EGFR is an oncogenic driver that is found in 10-15% of patients with NSCLC. Currently, oral drugs called EGFR Tyrosine kinase inhibitors are used to treat patients with these mutations. Several strategies such as increased dose and drugs that have improved penetrability of the blood brain barrier have been developed and studied to improve effectiveness of these therapies. Of these, osimertinib and AZD3579 show promise in overcoming some of the resistance mechanisms. In the phase I BLOOM study, high dose osimertinib had good activity in patients with leptomeningeal metastasis. In the same study, AZD3579 had good penetration and clinical activity without significant side effects.

Another common molecular subtype in NSCLC are ALK rearrangements, for which drugs such as Crizotinib, Ceritinib and Alectinib are used. Of these, the second generation Alectinib has

impressive systemic and CNS efficacy and produced both durable radiological and neurological improvement in case reports.

Immunotherapy has transformed the landscape of lung cancer treatment. Although they cannot easily penetrate the brain due to their large size, they may exert activity through immunomodulation. Currently, the data in its use to treat leptomeningeal metastasis is limited to a few promising case reports.

Over the past few years, significant progress has been made in the characterization of genetic profiles using liquid biopsies and the development of novel agents with better CNS penetrations. The studies in patients with EGFR-mutant and ALK-rearranged leptomeningeal metastasis are promising. However, many more studies are required to standardize care in patients without actionable mutations. Moreover, the role of immunotherapy in the treatment of leptomeningeal metastasis is still awaiting development.

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