

CANCER CARE
CHRONICLES

Patients with Brain Metastases Deserve Better—A Hard-Won Perspective

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It has been observed that “the development of brain metastases is one of the most feared complications of cancer due to the substantial neurocognitive morbidity and a grim prognosis.”¹ In my own case, when I learned that my lung cancer had metastasized to my brain in 2016, I shared that fear. I remember that my husband and I took special pains to sit down with our 2 sons to explain the situation, knowing, as we did, that when people at their elementary school learned of my new medical situation, our boys would likely see the dire nature of things in other people’s faces.

Cancer in the brain is frequently used to justify arguments in favor of legalizing euthanasia. Cancer in the brain is seen as “the end of the road.” And yet, I’ve been living with brain metastases since 2016 thanks to advances in scientific research to combat this very common turn in lung cancer. I’ve traveled internationally and cross-country with my family. I’ve been a lung cancer advocate at the state, federal, and international levels. Here, I hope to convince you that we should be prioritizing cancer research, specifically lung cancer research involving brain metastases. Unfortunately, the fear of brain metastases is fully justified. Progression of intracranial disease is the cause of death in 50% of cancer patients.¹

Patients with lung cancer have particular reason to worry. They have a 1:2 chance of developing brain metastases at some point, and certain types of lung cancer are even more likely to spread the disease to the brain.² Indeed, patients with lung cancer are the most frequent of all cancer patients to experience progression to the brain.³

If we can expect that lung cancer will progress to the brain half the time, why has research and care lagged so far behind? I believe that the reasons for this lag can be categorized into 3 areas: poor research, poor care, and poor treatment options.

Poor Research

It is generally agreed that there are no good preclinical models to understand lung cancer with brain metastases, which means that there is not even a foundation on which to build the needed research in this area. Researchers are also identifying a microenvironment in the brain, further complicating studies.

When clinical trials do study lung cancer, they typically exclude patients with active metastatic disease in the brain. Excluding those with brain metastases from clinical trials may make the research less complicated, but it in no way reflects the lived experience of patients and clinicians battling this disease. And, even if trials include people with brain metastases, there are often no specialized trial arms, which limits their usefulness in analyzing outcomes.

Poor Care

Presently, there is no standard of care for monitoring either the existence or progression of brain metastases. In my own case, I was allowed to go 15 months after my initial treatments and my surgical lobectomy without magnetic resonance imaging of my brain under the assumption that my cancer would reappear in my chest before it appeared in my brain. That assumption was wrong. I had more than 12 tumors that were all advanced in size and causing observable symptoms in my brain without any new cancer activity in my chest.

Although people with brain metastases have special needs, there is no consistent care for them. I have a thoracic oncologist, brain radiation oncologist, neuro-oncologist, and neurosurgeon with whom I consult regularly. Most don’t get this kind of complete care.

Metastases in the brain are *not* the same as metastases in other parts of the body, and yet they are often treated that way. Brain surgery, radiotherapy, and systemic therapy cause other adverse effects like seizures, headaches, memory loss, cognitive loss, speech changes, paralysis, radiation necrosis, and balance issues. Patients are often left to negotiate these changes in their health without proper medical support.

Poor Treatment Options

Simply stated, the blood-brain barrier is a major complication in the treatment of patients with brain metastases. Systemic treatments often fail to cross the barrier. When they do, they are known to have a reduced effectiveness after being filtered by the blood-brain barrier.

Those treatment options that are known to enter and act in the brain more effectively—lorlatinib, for instance—are associated with increased neurocognitive adverse effects and deficits, which are even more common and pronounced in those who have had brain metastasis, stereotactic radiosurgery, and/or brain surgery.⁴

Those facing disease progression in the brain confront the challenge of discerning the cause or causes of the progression. A brain biopsy is invasive and dangerous, so patients and clinicians are often forced to make treatment decisions blindly. Liquid biopsies of the brain are ineffective, and studying cerebrospinal fluid is not much better for brain-only progression.

Increasingly, as patients with lung cancer and brain metastases live longer and as more and more see their cancer develop into leptomeningeal disease, the prognosis is even worse, because leptomeningeal disease is even more difficult to track and treat.

My story illustrates much of the argument in favor of increased attention to brain metastases. I was diag-

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nosed with stage IIIA lung cancer in 2015. It was 2016 when we discovered that the cancer had metastasized to my brain. I was fortunate that alectinib had been approved by the US Food and Drug Administration (FDA) as a second-line therapy and that my physicians were forward-looking enough to prescribe alectinib even though it had not been approved as a first-line therapy at the time.

My survival, over 6 years later, has come at a high price. I have had more than 20 different therapeutic interventions involving my brain since 2016. I have increased and decreased doses. Capmatinib was added to alectinib in 2019, and I became the first person in the world to receive this combination. And, most recently, alectinib was replaced with lorlatinib.

During this time, I have had brain radiotherapy by stereotactic radiosurgery 5 times to combat numerous brain lesions. One lesion was irradiated twice. I have had to be in Boston for these treatments for multiple weeks, including 11 days this past fall. What's more, I have had 5 brain operations, 2 of them on the same day in April 2022. Once, an external ventricular drain brought me out of a life-threatening coma.

Even today, the most recent round of radiotherapy has left me with a bald spot in my hair and considerable right hand numbness. The hair will grow back. My hand....

My most difficult battle has involved the drug lorlatinib. This drug is known to get into the brain more effectively than others, but it

can have (and has, in my case) serious and significant consequences to cognitive functioning and mood. I've seriously contemplated stopping all treatment. Fortunately, I found that a reduced dose of only 25 mg/d is somewhat tolerable. I see a speech therapist regularly to help me account for and manage the impairments the drug causes even at that minimal dosage. Patients deserve better.

Brain metastasis needs much more attention. There need to be ample preclinical models and studies; drugs that address these unique challenges, including the cognitive issues that often come with drugs like lorlatinib; and better tests for those who have and/or are likely to get brain metastases.

Brain metastases present something of an oncological paradox. They are at once very common even as they present unique challenges for clinicians and patients. For far too long, brain metastases have been overlooked either because they rendered trials too complex or because of a sense that they rendered a patient's case hopeless. The truth is that patients like me are now living with brain metastases, and we are suffering for want of better care options. It is past time we started to acknowledge this and to push for positive change.

Patients with brain metastases deserve better.

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