

From Fear to Hope: Research on Brain Metastases in Breast Cancer

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If you ask women living with metastatic breast cancer what they fear most, brain metastases are high on the list. "I was terrified of possible brain mets," says Claudia Feigner, diagnosed with a single brain metastasis, then months later with another. "I thought it would mean that my death would be almost immediate, although death would be preferable to me than 'losing my mind' and living."

Claudia is one of an increasing number of women with HER2-positive breast cancer whose metastatic disease is controlled outside the brain by the drug Herceptin (trastuzumab) but whose central nervous system remains vulnerable to the disease. Studies estimate incidence of brain metastases in women with HER2+ metastatic breast cancer to be 25-50% over the course of the disease. Because the Herceptin molecule is large, it cannot penetrate the protective blood-brain barrier formed by the closely-linked cells lining the brain's circulatory system. These "tight junctions" between cells, as well as efficient pumps that remove toxins from cells, prevent most breast cancer treatments that work elsewhere in the body from entering brain tissue. Most recent advances in drug treatments that have prolonged these women's lives do not work well in the brain. Radiation treatments (and, less frequently, surgery) are still the mainstays for treating brain metastases. While offering some control of the disease in the short term, the longer-term cognitive effects of radiation may be problematic, and the maximum dose is quickly reached in treating recurrences.

Drug treatment for brain metastases has been a stab in the dark because so little is known about the permeability of drugs into the brain, according to molecular biologist Patricia Steeg, Chief, Women's Cancers Section of the National Cancer Institute, who has been researching metastases for 20 years. "We knew nothing," says Steeg, in reference to brain metastasis research. "We had no resources. We had no mouse models, and we certainly had no tissues." Without tissues for gene expression analysis, and animal models (usually mice) that are experimentally given brain metastases in the lab to study and test treatments on, drug development is impossible.

Steeg determined to change all this by creating the research infrastructure that was lacking, then working on developing new treatment strategies. Since May, 2006, under her direction, an interdisciplinary team of 23 scientists, physicians and advocates with diverse

expertise has been working as a collaborative research group. Funded as a Center of Excellence, under a five-year \$17 million grant from the Department of Defense Breast Cancer Research Program, are molecular biologists who analyze tissue for gene expression and study mouse models for brain metastases, experts in blood-brain barrier permeability and tumor dormancy, and oncologists, neurologists and neurosurgeons who examine new and existing treatments.

Much has already been accomplished in the team's first year and a half. Paul Lockman and Quentin Smith, experts on the blood-brain barrier from the Texas Tech University School of Pharmacy, have adapted a mouse model system developed in the Steeg lab at NCI to reliably determine drug levels in metastases. Ann Chambers, of the London Regional Cancer Centre in Ontario, has, Steeg says, "identified what we think are dormant cancer cells in the brain, which opens up another whole new area of thinking." When cancer spreads, what causes some cancer cells to remain "asleep" in the brain, while others "awaken" to form life-threatening brain metastases?

Working with an oral tyrosine kinase inhibitor of HER2 small enough to cross the blood-brain barrier, Steeg and others in her lab at NCI have "preclinically validated lapatinib (Tykerb) as having preventative ability against metastatic colonization in the brain." Neurosurgeon Robert Weil is working with oncologists David Peereboom of the Cleveland Clinic and Andrew Seidman of Memorial Sloan Kettering Cancer Center on a pre-surgical trial that will shed light on how drugs are actually absorbed by tumors in the brain.

At the 2007 San Antonio Breast Cancer Symposium, advocates working with the scientists and physicians of the Center of Excellence, Musa Mayer and Helen Schiff, launched BrainMetsBC.org, a consumer website for women with breast cancer and caregivers dealing with brain metastases, featuring patients sharing their own experiences.

Two years after her diagnosis with brain metastases, Claudia reports that she is still doing well. She offers encouraging words to women experiencing what she once so feared, grounded in her own experience: "There is much hope for successful treatment of brain mets and prolonged meaningful quality of life." The Center of Excellence is laying the groundwork to make Claudia's experience with brain metastases the rule, rather than the exception.

