Systemic therapies for breast cancer brain metastasis are largely unsuccessful. Mouse models of brain metastasis show significant heterogeneity in uptake of paclitaxel and doxorubicin, with average levels more than those seen in normal brain tissue, but significantly less than in metastases to other organs. Clinical Cancer Research. 2010;16(23):5605-7. ©2010 AACR.

Brain metastasis may be the most devastating, and is certainly the most feared, consequence of breast cancer. It not only robs the patient of her life, it has the potential to rob her of her self, of her essence as a human being. It is also poorly studied. In the clinic, this dearth of research has been a function of the difficulty of obtaining tissue in those who suffer from it, and the lack of dedicated trials. In the laboratory, researchers have lacked model systems that allow them to dissect the mechanisms and effects of brain metastasis. This situation is now changing, as shown in the report by Lockman and colleagues in the current issue of Clinical Cancer Research (1).

What we know about brain metastasis in breast cancer is easily summarized. Although not the most frequent of clinical presentations, numerous autopsy studies have shown that occult brain metastases are exceptionally common (2). As many as 15% of patients with advanced breast cancer will have asymptomatic brain metastases visible on screening MRI or computer assisted tomography (CAT) scans (2).

Brain metastasis occurs relatively more commonly in patients with HER2-positive and triple-negative (basal) breast cancers than in patients with estrogen receptor-positive breast cancers (3, 4). Among patients with HER2-positive tumors, the frequency of brain metastasis may have increased recently as a function of the use of trastuzumab, of which the inability to penetrate the central nervous system, even as it controls other metastases, allows them to dissect the mechanisms and effects of brain metastasis. This situation is now changing, as shown in the report by Lockman and colleagues in the current issue of Clinical Cancer Research (1).

Brain metastasis occurs relatively more commonly in patients with HER2-positive and triple-negative (basal) breast cancers than in patients with estrogen receptor-positive breast cancers (3, 4). Among patients with HER2-positive tumors, the frequency of brain metastasis may have increased recently as a function of the use of trastuzumab, of which the inability to penetrate the central nervous system, even as it controls other metastases, allows clinical brain metastases time to emerge (4).

Therapy for brain metastases has been divided into local control measures (both surgery and radiation therapy) and systemic therapy. Local control measures are palliative and generally ineffective, with median survivals following diagnosis generally fewer than 12 months (5, 6). More targeted radiation techniques (e.g., stereotactic radiation) have improved palliation and (in combination with whole brain radiation for patients with few lesions) modestly improved survival (6). Systemic therapies [both chemotherapy, hormonal therapy, and more recently HER2-targeted therapy with the small molecule receptor tyrosine kinase (RTK) inhibitor lapatinib] produce occasional responses of short duration (7, 8). All told, it is a gloomy story.

Why have we failed so miserably? Part of the failure, of course, represents our larger failure to cure metastatic breast cancer, a failure rooted in the development of drug resistance to all existing systemic therapy modalities. But there has always been a sense that brain metastasis poses specific challenges, rooted in normal neurophysiology, which must be addressed if we are to improve outcome. The existence of the blood-brain barrier, with efflux pumps in brain endothelium capable of preventing the penetration of many therapeutic agents (especially natural products such as anthracyclines and taxanes), has long been recognized, but also debated as a cause of therapeutic failure, given its disruption in the setting of brain metastasis (9). One recent clinical report has suggested that disruption of the blood-brain barrier is common in triple-negative breast cancers but rare in HER2-positive brain metastases (10).

It is in this context that we should view the contribution of Lockman and colleagues to the brain metastasis literature. This report represents the combination of separate technology approaches to the study of brain metastasis, and it is worth devoting some space to the examination of these techniques.

First, the authors used relatively newly developed murine models of breast cancer metastasis to the brain (11–13). These models (using the human xenograft MDA-MB-231 human breast cancer cell line and the murine 4T1 breast cancer cell line) involve the intracardiac injection of cells that have been serially passed through the brain to produce brain-tropic cell lines (Fig. 1). Such model systems are necessarily artificial, and the degree to which they are representative of the processes by which human brain metastasis occurs is open to question. But, they are undoubtedly an efficient means of producing brain metastases in rapid fashion, and this useful attribute provides the basis for this report.

This metastasis model, in turn, has been married to novel quantitative imaging techniques allowing analysis of blood-tumor barrier (BTB) permeability of both size.
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Fig. 1. Intracardiac injection of breast cancer cells with brain-seeking ability leads to development of brain metastasis. Mice are injected with radioactive 14C-paclitaxel and radioactive drug uptake and apoptosis are measured. Brain metastases, A and B, vary in permeability for paclitaxel by up to 200 fold. A, the drug does not accumulate in low uptake metastases, which, as a result, exhibit no cell death, whereas more permeable metastases capable of higher drug uptake (B), undergo significant apoptosis.

References


Heading in a New Direction: Drug Permeability in Breast Cancer Brain Metastasis

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