

Editorial

Targeting HER2 in Brain Metastases from Breast Cancer

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For many types of cancers, therapy aimed at a specific molecular target remains in the realm of clinical research. However, for breast cancer, rational therapeutics is routinely practiced in the clinic. For many years, oncologists have used tamoxifen to selectively treat women with estrogen receptor-positive breast cancer. Clinicians now screen breast cancer for HER2 overexpression, which occurs in approximately a quarter of all breast cancers (1). The optimal way to classify breast cancers for HER2 (also called HER-2/*neu* or *c-erbB-2*) expression has been debated (2). In clinical practice, HER2 is usually analyzed in tumor specimens by immunohistochemistry for HER2 protein expression or by fluorescence *in situ* hybridization for HER2 gene amplification. When appropriate quality controls are followed, breast cancers appear to be reliably classified as HER2 overexpressed either by 3+ protein overexpression using immunohistochemistry or by HER2 gene amplification via fluorescence *in situ* hybridization (2).

Several studies have shown that HER2 analysis provides prognostic information: patients with breast cancer that overexpress HER2 have a worse overall survival (1, 3). Reports focusing on the response of HER2-overexpressing breast cancers to either hormonal therapy or chemotherapy are conflicting (reviewed in Ref. 2), with some studies suggesting that these tumors have a decreased response to tamoxifen and an increased response to anthracycline-containing chemotherapy. However, these results have not been uniformly observed in all studies. Interestingly, breast cancers without HER2 overexpression tend to metastasize to bone, whereas HER2-overexpressing breast cancers are more likely to spread to visceral organs, such as lung, liver, and brain (4).

In addition to providing prognostic information, HER2 can be targeted for cancer therapy. HER2 is a transmembrane growth factor receptor that resides at the cell surface. An extracellular domain of HER2 is recognized by trastuzumab (Herceptin), a humanized monoclonal antibody. When it is delivered together with chemotherapy, Trastuzumab improves survival for patients with metastatic breast cancer that overexpress HER2 (5). However, when patients with metastatic breast cancer

are treated with trastuzumab, the breast cancer frequently progresses in the CNS.³

A recent retrospective review of 122 women with metastatic breast cancer treated with trastuzumab found that one-third developed CNS metastases at a median time of 6 months after starting trastuzumab therapy (6). Remarkably, at the time that brain metastases were identified, in half of the patients other systemic disease was either stable or responding to trastuzumab-based therapy. Moreover, 50% of the women who developed CNS disease died from neurological decline.

CNS disease progression during trastuzumab therapy does not result from a loss of HER2 overexpression in the brain metastasis. The correlation between HER2 overexpression of primary breast cancers and subsequent brain metastases is 97% (7). Instead, progressive CNS disease probably results from poor penetration of trastuzumab into the brain. Trastuzumab is a relatively large protein with a molecular weight of 148,000. Therefore, it would not be expected to cross the blood-brain barrier. The clinically important obstacle of delivering trastuzumab to an intracerebral metastasis is addressed by Grossi *et al.* (8) in this issue of *Clinical Cancer Research*.

These investigators modeled HER2-overexpressing brain metastases in athymic rats. They implanted a human breast cancer cell line that overexpressed HER2 into the brain by intracerebral injection. The rats were treated with trastuzumab or a control, isotype-matched antibody using a microinfusion technique that utilizes bulk flow current (convection) to deliver large proteins into the brain (9). Trastuzumab or the control antibody was administered regionally via an intracerebral cannula directly into the tumor for 7 days. Animals treated with intracerebral microinfusion of trastuzumab had significantly improved survival compared with controls. However, systemic administration of trastuzumab via i.p. microinfusion failed to deliver the drug to the brain and did not significantly affect survival.

These results demonstrate that HER2-overexpressing breast cancer, which is growing in the brain, can be targeted with HER2-directed therapy if the drug penetrates the CNS. This preclinical study may serve as the basis for future clinical trials. Patients with brain metastases from HER2-overexpressing breast cancer that have progressed through conventional therapy (neurosurgical resection, radiation therapy, and chemotherapy) may benefit from intracerebral microinfusion of trastuzumab.

Just as HER2-overexpressing breast cancer metastases at other sites have a limited response to trastuzumab therapy alone (10), the efficacy of intracerebral microinfusion of trastuzumab for CNS metastases in patients may not be as impressive as this animal model suggests. However, for HER2-overexpressing metastatic breast cancer, the response to trastuzumab is improved with concurrent chemotherapy in animal models and patients (5, 11). Therefore, improved CNS disease control may

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³ The abbreviation used is: CNS, central nervous system.

result from combining intracerebral microinfusion of trastuzumab with concurrent radiation therapy or chemotherapy that crosses the blood-brain barrier, such as temozolamide or high-dose methotrexate.

Although intracerebral microinfusion may prove to be an effective way to treat brain metastases in patients, this therapy would require placement of an intracerebral cannula and continuous infusion of trastuzumab for several days. Therefore, this approach may be supplanted by other drugs that are administered systemically and target HER2 but are small enough to cross the blood-brain barrier. Because the oncogenic activity of HER2 appears to function through its intracellular tyrosine kinase domain, small molecules that cross the blood-brain barrier and inhibit HER2 tyrosine kinase activity are attractive drugs to treat brain metastases from HER2-overexpressing breast cancer. One example of an irreversible inhibitor of HER2 tyrosine kinase activity, which may cross the blood-brain barrier, is CI-1033. In addition to inhibiting HER2 (erbB-2), CI-1033 also inhibits the other three members of the epidermal growth factor receptor family (erbB-1, erbB-3, and erbB-4). CI-1033 has already completed a Phase I clinical trial, which demonstrated acceptable side effects at doses that modulated target tyrosine kinase activity (12). Another small molecule inhibitor of HER2 is GW572016. The ability of GW572016 to reversibly inhibit the tyrosine kinase activity of HER2 and the epidermal growth factor receptor has been demonstrated in preclinical animal models (13).

Regardless of whether intracerebral microinfusion of trastuzumab enters routine clinical practice in the future, the work by Grossi *et al.* (8) has demonstrated that HER2-overexpressing brain metastases are susceptible to HER2-targeted therapy. With the increasing use of i.v. trastuzumab for HER2-overexpressing breast cancer, more patients will present with progressive disease only in the CNS. To maximally control this CNS disease, clinicians will need to overcome the challenge of delivering HER2-directed therapies across the blood-brain barrier, whether by intracerebral microinfusion or by other means, to effectively treat brain metastases.

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