Combination treatment may improve survival of breast cancer patients with brain metastases

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Adding an angiogenesis inhibitor to treatment with a HER2-inhibiting drug could improve outcomes for patients with HER2-positive breast cancer who develop brain metastases. In their report published online in *PNAS* Plus, Massachusetts General Hospital (MGH) investigators report the first preclinical study combining antiangiogenic and anti-HER2 drugs in an animal model of brain metastatic breast cancer.

"We have shown dramatic improvement in survival by slowing the growth of brain metastatic, HER2-amplified breast cancer," says Rakesh Jain, PhD, director of the Steele Laboratory for Tumor Biology at MGH, Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School and senior author of the study. "This is particularly important because patients with this type of breast cancer have an increased risk of brain metastases, which have not responded to current therapies."

A quarter of breast cancers are driven by overexpression of the growth factor HER2, making them particularly aggressive. Treatment with drugs that block the pathway controlled by HER2 – trastuzumab (Herceptin) and lapatinib (Tykerb) – suppresses the growth of these tumors and extends patient survival. But these patients are at increased risk of developing brain metastases, which have resisted anti-HER2 treatment. Angiogenesis is also known to have an important role in breast cancer, and although previous studies combining chemotherapy with the

antiangiogenesis drug bevacizumab (Avastin) delayed disease progression, they have not extended overall survival.

In addition to directly blocking the HER2-controlled growth pathway, anti-HER2 drugs also contribute to suppression of tumor-associated blood vessels. Previous studies in Jain's lab suggested that the proangiogenic factor VEGF may overcome the antiangiogenic effects of anti-HER2 drugs. This observation led the researchers to investigate whether blocking the VEGF pathway would improve the results of anti-HER2 treatment. Their study used a new mouse model in which the proliferation of HER2-amplified breast cancer cells implanted into brain tissue could be monitored over time. The researchers first confirmed that, as in human patients, treatment with a single anti-HER2 drug suppressed tumor growth in breast tissue but not within the brain.

While treatment with DC101, an antibody that blocks the VEGF pathway in mice, improved survival compared with either anti-HER2 drug, combining DC101 with one anti-HER2 drugs produced even greater survival improvement, including the death of tumor cells through significant reduction in tumor-associated angiogenesis. A triple combination of DC101 with both anti-HER2 drugs had the most dramatic effects. Animals receiving a single anti-HER2 drug along with DC101 lived more than three times as long as control animals, while those receiving all three drugs lived five times as long.

Jeffrey Engelman, MD, PhD, of the MGH Cancer Center, co-corresponding author of the PNAS Plus report, notes that a clinical trial now underway combining chemotherapy with bevacizumab in breast cancer addsanti-HER2 treatment for those participants whose tumors are HER2-amplified. The results of the current MGH study suggest that investigating a triple combination may be particularly beneficial. "With targeted therapies like anti-HER2 drugs suppressing the growth of tumors outside the central nervous system, brain metastasis is becoming

a more common cause of treatment failure."

Co-corresponding author Dai Fukumura, MD, PhD, of the Steele Lab adds, "A clinical trial of this sort of triple combination will be an important next step. And in the meantime, we will continue to investigate the mechanisms of resistance to the effects of both double and triple combinations." Fukumura is an associate professor of Radiation Oncology and Engelman an associate professor of Medicine at Harvard Medical School.

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