

Combination treatment stymies breast cancer growth in mice

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Baylor College of Medicine News Release:

Combination treatment stymies breast cancer growth
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Combination treatment stymies breast cancer growth

HOUSTON -- (May 1, 2007) -- A combination of three different drugs that block the HER-2 receptor, a critical cellular growth signal for some breast cancers, eradicated aggressive breast tumors in mice and could point the way toward developing better treatments in patients, said researchers from the Breast Center at Baylor College of Medicine in a report that appears today in the Journal of the National Cancer Institute.

"For the first time, we were able to cure mice of a very aggressive human breast tumor," said Dr. Rachel Schiff, assistant professor in the Breast Center at Baylor College of Medicine and senior author of the report.

In prior such studies, treatment only slowed or delayed the growth of tumors, she said. In this case, the tumors disappear and do not come back, even when treatment is stopped.

The treatment involved is a new approach known as "targeted" therapy because the protein (in this case, HER-2) driving a tumor to grow is first identified in a patient's tumor and then specific drugs are used to block that particular growth pathway in the cells, said Dr. C. Kent Osborne, director of the Breast Center and the Dan L. Duncan Cancer Center at BCM. He is also an investigator on the study.

"When you go after a specific target in a patient's tumor, the treatment is likely to be more effective and less toxic," said Schiff.

The tumors in question ? nearly 25 percent of all breast cancers ? have high levels of HER-2. While the HER-2 makes the tumors

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more aggressive, it also provides a target against which new drugs can act.

Previously, treatment for patients with HER-2 positive tumors was less effective.

"Now we have effective treatment, and survival is markedly improved," said Dr. Grazia Arpino, lead investigator of the study and a postdoctoral fellow at BCM.

"These tumors are initially highly sensitive to a drug known as trastuzumab or Herceptin, one of the drugs used in combination in the mouse study and which is approved by the FDA (U.S. Food and Drug Administration) for treatment," said Schiff.

However, the tumor is wily and can sometimes escape the drug's effects, resulting in resistance. Adding two other experimental drugs — gefitinib and pertuzumab — that inhibit HER-2 in different ways can more completely block the growth signals in the tumor, causing it to die.

In one of the tumors studied in this report, blocking the stimulatory effects of estrogen on the tumor was also necessary for optimal treatment, said Schiff. Completely blocking the HER pathway is critical, she said. Leaving out just one of the three drugs was much less effective.

A clinical study using drug combinations in newly diagnosed patients with HER-2 positive breast cancer will start soon under the direction of physicians at BCM's Breast Center, said Osborne.

"We are very excited to see if our laboratory results can be translated to patients with the more aggressive types of breast cancer," he said.

Others who participated in the research include Carolina Gutierrez, Heidi Weiss and Mothaffar Rimawi of BCM, Suleiman Massarweh, now of the University of Kentucky, Lavina Bharwani now of Johns Hopkins Singapore International Medical Center in China, and Sabino De Placido of Universita di Napoli Federico of Naples, Italy.

Funding for this research comes from the National Institutes of Health, The Jacqueline Seroussi Memorial Foundation for Cancer Research and the Susan G. Komen for the Cure (previously Susan G. Komen Breast Cancer) Foundation.

The reference for the study is

Arpino G, Gutierrez C, Weiss H, Rimawi M, Massarweh S, Bharwani L, De

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Placido S, Osborne CK, Schiff R.

Treatment of human epidermal growth factor receptor 2–overexpressing breast cancer xenografts with multiagent HER–targeted therapy.

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PMID: 17470737 [PubMed – in process]

<<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17470737>>

<<http://jnci.oxfordjournals.org/cgi/content/full/99/9/694>> (free full text)

Abstract:

"BACKGROUND: Human epidermal growth factor receptor 2 (HER2) is a member of the HER signaling pathway. HER inhibitors partially block HER signaling and tumor growth in preclinical breast cancer models. We investigated whether blockade of all HER homo– and heterodimer pairs by combined treatment with several inhibitors could more effectively inhibit tumor growth in such models. METHODS: Mice carrying xenograft tumors of HER2–overexpressing MCF7/HER2–18 (HER2–transfected) or BT474 (HER2–amplified) cells were treated with estrogen supplementation or estrogen withdrawal, alone or combined with tamoxifen. One to three HER inhibitors (pertuzumab, trastuzumab, or gefitinib) could also be added (n > or = 8 mice per group). Tumor volumes, HER signaling, and tumor cell proliferation and apoptosis were assessed. Results were analyzed with the t test or Wilcoxon rank sum test and survival analysis methods. All statistical tests were two–sided. RESULTS: Median time to tumor progression was 21 days for mice receiving estrogen and 28 days for mice receiving estrogen and pertuzumab (difference = 7 days; P = .001; hazard ratio [HR] of progression in mice receiving estrogen and pertuzumab versus mice receiving estrogen = 0.27, 95% confidence interval [CI] = 0.09 to 0.77). Addition of gefitinib and trastuzumab to estrogen and pertuzumab increased this time to 49 days (difference = 21 days; P = .004; HR of progression = 0.28, 95% CI = 0.10 to 0.76). MCF7/HER2–18 tumors disappeared completely and did not progress (for > or = 189 days) after combination treatment with pertuzumab, trastuzumab, and gefitinib plus tamoxifen (19 of 20 mice) or plus estrogen withdrawal (14 of 15 mice). Both combination treatments induced apoptosis and blocked HER signaling and proliferation in tumor cells better than any single agent or dual combination. All BT474 tumors treated with pertuzumab, trastuzumab, and gefitinib disappeared rapidly, regardless of endocrine therapy, and no tumor progression was observed for 232 days. CONCLUSION: Combined treatment with gefitinib, trastuzumab, and pertuzumab to block signals from all HER homo– and heterodimers inhibited growth of HER2–overexpressing xenografts statistically significantly better than single agents and dual combinations."

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