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# Herceptin Combinations Improve Survival, Lessen Heart Toxicity

BY LAURA BEIL

Two studies presented Saturday offer hope of enhancing both the effectiveness and safety of Herceptin (trastuzumab), the drug that helped introduce the era of targeted therapy a decade ago. Although Herceptin has been shown to reduce the risk of recurrence by half when combined with chemotherapy, researchers are still working to improve its track record and reduce the risk of side effects.

One experimental combination is Herceptin and Tykerb (lapatanib)—two drugs that target the same protein overproduced in many breast tumors. Data presented Saturday in San Antonio suggest the combination may help women with advanced breast cancer live longer. It is one of the few studies to report a regimen that has the ability to prolong survival among women with metastatic disease.

In describing the results, Kimberly Blackwell, MD, of Duke University Medical Center, reported that women who received the two-drug combination lived an average of about 14 months, while women who took Tykerb alone lived about 9.5 months. She noted that the study took place among women whose disease had progressed despite an average of three prior chemotherapy regimens; some women had tried as many as six.

“These were patients for whom there were not a lot of good options,” she said. After taking the combination—which did not include a new round of chemotherapy—“fifteen more out of 100 women were alive a year later,” she said.

Herceptin works by targeting a gene known as HER2, which plays a role in about 25 percent of breast cancers. HER2-driven tumors tend to grow faster and carry a greater risk of recurrence than HER2-negative cancers. In 1998, the FDA first approved Herceptin for metastatic breast cancer, and in 2006, it was approved for early-stage disease when combined with chemotherapy. Tykerb targets HER2 and a related gene, HER1. But the drugs work on different fronts: Herceptin targets HER2 from the outside of the cell, and Tykerb interferes with the cellular machinery inside. The hope is that the combination might give the tumor a double whammy.

The question of whether to use Herceptin, Tykerb, or a combination of the two in women with early-stage breast cancer will be answered with results of another study underway, called ALTTO, which will examine these two drugs in about 8,000 women. That study is expected to produce its first results in approximately two years.

Researchers are also trying to determine which drug makes the best chemotherapy platform to use with Herceptin. Scientists have sought to reduce Herceptin's most serious side effect—a dangerous toxicity to the heart—while still preserving its tumor-fighting effectiveness. One of the largest ongoing studies of Herceptin is named BCIRG 006; results of this study were first presented during the San Antonio Breast Cancer Symposium in 2005, and it reported a risk of heart damage from Herceptin, especially when used in combination with anthracyclines, some of the most widely used chemotherapy drugs. But the study is still ongoing, as researchers try to determine whether using non-anthracycline drugs might reduce the cardiac danger from Herceptin. The BCIRG 006 trial compares three approaches, with about 1,000 women in each group: standard anthracycline-based chemotherapy without Herceptin, anthracycline-based chemotherapy with Herceptin, and Taxotere-based (non-anthracycline) chemotherapy with Herceptin.

Consistent with research presented previously, the longest results so far indicate that using newer drugs as a chemotherapy base—in this case Taxotere (docetaxel)—can make Herceptin safer for the heart. After five years of follow-up, four patients with the Taxotere-based Herceptin therapy experienced heart failure, compared with 21 who took Herceptin with an anthracycline regimen. “The damage we’re doing to the heart is not transient,” said Dennis Slamon, MD, PhD, of the UCLA Women’s Cancer Research Program. In addition, his data suggested a greater risk of developing leukemia as a result of treatment. Based on the study results so far, he prefers that most women receive treatment with Taxotere-based chemotherapy cocktails.

Not all doctors agree. “We cannot conclude that this is a better regimen,” said Edith Perez, MD, director of the breast program at the Mayo Clinic in Florida, of the Taxotere-based regimen. She pointed out that women who received Herceptin with the anthracycline regimen were less likely to die than women who received either chemotherapy alone or Taxotere-based Herceptin treatment. No woman in any treatment group so far has died from heart disease. In all, 94 women on the anthracycline/Herceptin combination have died from any cause, compared with 113 women on the Taxotere/Herceptin treatment and 141 who received standard chemotherapy without Herceptin. “We can all agree that Herceptin adds to chemotherapy,” Perez said. Given the new results, she said she will continue to recommend anthracycline-based chemotherapy with Herceptin. “At the same time,” she said, “I am open to alternatives.”

*This article is a part of CURE's 2009 San Antonio Breast Cancer Symposium coverage. To read more articles from SABCS 2009, visit [sabcs2009.curetoday.com](http://sabcs2009.curetoday.com).*