Herceptin and Tykerb effective against a subset of gastric cancers

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A combination of two targeted therapies already shown to be effective in breast cancer packs an effective one-two punch against a subset of gastric cancers that have a specific genetic mutation, a study at UCLA's Jonsson Comprehensive Cancer Center has found.

The drugs Herceptin and Tykerb when given together proved to significantly inhibit tumor growth in gastric cancers that had amplified levels of HER2, a mutation that results in an aggressive form of the disease, causing the cancers to grow and spread faster. The work was done both on cell lines and in animal models with human HER2-amplified gastric cancers.

Between 18 and 27 percent of gastric cancers exhibit HER2 amplification, so the finding - if confirmed in humans - could provide a new, more effective and less toxic treatment option for tens of thousands of patients diagnosed every year worldwide with gastric cancers that carry the mutation, said Dr. Zev Wainberg, a Jonsson Cancer Center researcher and first author of the study.

"This study adds further support to the concept that if you target a specific gene in gastric cancer, a more tailored treatment approach can be considered," said Wainberg, an assistant professor of hematology/oncology. "This study also provides further proof to what we already know - that is that gastric cancer is ripe for the development of targeted therapies."

The study appears in the March 1, 2010 issue of the journal *Clinical Cancer Research*.

Herceptin, developed based on basic and clinical research done in Jonsson Cancer Center laboratories, has been combined with chemotherapy with great success to treat first women with HER2 amplified metastatic breast cancer and, later, women with earlier stages of disease. Tykerb was approved in 2007 for use in breast cancer. The two drugs also have been tested together in breast cancer, and the combination has recently been shown to be better than Herceptin alone in women who had previously progressed while on the single drug.

Tykerb was tested at UCLA for use in gastric cancers, first in cell lines and animal models, and was shown to be effective in cancers with HER2 amplification. A randomized Phase III clinical trial testing Tykerb with chemotherapy in HER2 amplified gastric cancer patients opened recently and is currently enrolling patients.

Herceptin also has been successfully tested in HER2 amplified gastric cancer patients, Wainberg said, and is expected to be approved for that use by the U.S. Food & Drug Administration within the next six months.

Wainberg said this is the first time that Herceptin and Tykerb have been paired to fight this subset of gastric cancers.

"In our animal models, the mice that received both Herceptin and Tykerb had their tumors shrink down to virtually nothing," Wainberg said. "This suggests that in those tumors that are dependent on HER2 for growth, this combination may be a very effective treatment. The combination of therapies was much better than either Herceptin or Tykerb alone."

The dual blockade works using two mechanisms, blocking cell signaling

from inside the cell as well as on the cell's surface. Herceptin, an antibody, blocks growth signals sitting on the surface of the cancer cell, while Tykerb, a tyrosine kinase inhibitor, works from inside the cell to block the signaling that results in out of control growth of the cancer cells.

If just one therapy is used, the cancer cells often can find ways to get around the single blockade, Wainberg said. Using the combination provides a double whammy, and makes it much more difficult for the cancer to circumvent treatment. Herceptin is administered by intravenous infusion, while Tykerb is taken in pill form.

The Jonsson Cancer Center study offers further proof that molecularly targeted therapies - those that hone in on what is broken in the cancer cell and leave the healthy tissue unharmed - can be used to treat cancers more effectively with fewer side effects. It also supports the widespread theory that cancers should not be treated based on their organ of origin, but by the genetic mutations driving their growth.

"We have known for many years that not all breast cancers should be treated alike and the same is proving to be true in gastric cancers," Wainberg said.

The same test that is used to detect HER2 amplification in breast cancer, fluorescence in situ hybridization or FISH, is used to find the subset of gastric patients with the same mutation.

"It's my belief that a year from now, everyone will be checking for HER2 amplification in gastric cancer the way we test it now in breast cancer," Wainberg said.

While only about 25,000 to 30,000 Americans are diagnosed with gastric cancers every year, the disease is a significant problem worldwide.

Gastric cancers remain one of the most common forms of cancer diagnosed worldwide, with approximately 870,000 new cases and 650,000 deaths every year.

"This is definitely a cancer type where we very much need newer and more effective therapies," Wainberg said.

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