Study suggests newer breast cancer drug may protect heart

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By uncovering how one breast cancer drug protects the heart and another does not, Duke University Medical Center researchers believe they may have opened up a new way to screen drugs for possible heart-related side effects and to develop new drugs.

The Duke researches compared the actions of two breast cancer drugs in experiments involving human cells and rats. The drugs in question were the older drug trastuzumab, whose trade name is Herceptin, and the newer drug lapatinib, whose trade name is Tykerb.

The results of the study appear early online in the journal *Proceedings of the National Academy of Science*.

The main side effect of trastuzumab is that it can damage heart muscle cells. Heart abnormalities have been detected in 2 to 7 percent of women taking the drug, and about one in ten women cannot take the drug because preexisting heart problems put them at greater risk for heart damage. To date, there appear to be fewer cardiac effects associated with lapatinib therapy.

Both drugs are prescribed to women whose cancerous breast cells have HER2 genes that are overactive. Approximately one in four women with breast cancer have this overactive gene, which is associated with increased cancer recurrence and worse outcomes. Lapatinib was approved earlier in March for use in women who have not responded to trastuzumab therapy.

“Trastuzumab revolutionized the treatment of HER2-positive breast cancers and represents an effective therapy for some women with one of the most aggressive forms of breast cancer,” said Duke oncologist Neil Spector, M.D., first author of the paper.. “However, now we have two agents that go after the same target and both have an effect against the cancer, but one appears to have a greater potential – based on this preliminary work – for causing cardiovascular damage.

“It is important to be clear that we are reporting findings from pre-clinical experiments, so while they suggest a difference between these two agents, it would be over-interpreting the study to conclude that women taking trastuzumab should consider any treatment change,” Spector said. “However, it may be important to conduct well-controlled clinical trials to answer this question.”

In addition to its association with breast cancer, HER2 is also essential for the early development and later sustenance of heart muscle cells. It appears that trastuzumab’s mechanism for blocking HER2 is different.

“We found that lapatinib activates a critical pathway that protects heart cells from ‘committing suicide’ as a result of stress,” Spector continued. “Heart muscle cells require a tremendous amount of energy to function properly and are therefore extremely sensitive to energy deprivation as a consequence of reduced oxygen or nutrient supply. In addition, heart muscle cells appear to be sensitive to the death promoting effects of inflammation.

“Our experiments in isolated human heart muscle cells indicate that lapatinib activates a pathway that protects cardiac muscle cells from the death-promoting effects of mediators of inflammation, which are activated in cancer patients, particularly those who have received chemotherapies that damage heart tissue,” Spector said. “In contrast, trastuzumab does not activate this protective pathway.”

With clinical trials currently investigating the combination of lapatinib with trastuzumab, there is a possibility that the effects of lapatinib in cardiac muscle cells might protect the heart against potential toxicity associated with trastuzumab, Spector added.

More broadly, Spector said that these findings of how lapatinib bestows cardiovascular protection during times of stress – whether from chemotherapy or heart muscle cells deprived of oxygen during a heart attack -- could be used in other situations.

“Using this system, we could theoretically screen drugs that are in the development phase to see what their effects may be on heart muscle cells,” Spector said. “We may be able to select the drug candidates that have the fewest cardiovascular side effects and theoretically would be safer for patients. This way, we could find out about some of these potential problems long before the drugs even make it to market.”

Additionally, Spector said there is the potential for the development of similar drugs that can be used as protective agents in situations where the heart is stressed for periods of time, such as during heart attacks, coronary artery bypass surgery or angioplasty. Such a drug could even be used to preserve cardiac function in hearts being harvested for transplant, he said.

Source: Duke University Medical Center

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