Temple researchers show targeted cancer drug may stunt heart's ability to repair itself

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Scientists for the first time have evidence showing how a widely used type of "targeted" cancer drug can be dangerous to the heart.

Studying mice with the equivalent of a heart attack, researchers found that the drug sorafenib (Nexavar) – which inhibits proteins called tyrosine kinase receptors (RTKs), and is used in kidney and liver cancer treatment – can interfere with heart stem cell activity, affecting the heart's ability to repair itself after injury. The findings suggest that sorafenib and other similar drugs that target these kinds of protein receptors may raise the risk for heart attack for some cancer patients with underlying heart disease, as well as affect the heart's ability to repair damage. By understanding how these cancer drugs can affect the heart, scientists and clinicians may be able to devise new treatment strategies to lessen such potentially damaging effects of often vital cancer drugs.

"The goal is not to take the drug off of the market – it's a very good and useful drug that cancer patients need. We're trying to understand how this cancer drug and others like it can affect the heart, and what types of individuals might be at risk for problems," said senior author Steven Houser, PhD, Professor and Chair of Physiology at Temple University School of Medicine and Director of Temple's Cardiovascular Research Center. "Our results are beginning to provide a clearer picture of some of the potential physiological mechanisms at play."

Dr. Houser, first author Catherine Makarewich, a graduate student, and

their co-workers reported their findings November 5, 2012 at the Late-Breaking Basic Science Session at the American Heart Association's Scientific Sessions in Los Angeles.

Sorafenib is a member of a broad class of anticancer drugs called targeted therapies that halt cancer growth, rather than necessarily trying to eliminate the disease. Termed a "multi-kinase" inhibitor, sorafenib blocks the activity of a range of protein enzymes and specific targets in the cell that can contribute to the development and growth of cancer. In this case, sorafenib inhibits several RTKs, including c-kit, a receptor found on cardiac progenitor cells in heart and bone marrow, and can prevent the cardiac stem cell population from growing. Such progenitor and stem cell populations play important roles in cardiac repair.

Mortality Rates Following Induced Heart Attacks

The researchers wanted to see if they could better understand the mechanism behind these toxic effects. In the study, normal mice were given sorafenib for a week before being made to have the equivalent of a heart attack, and compared to mice that had a heart attack without receiving the drug. After one week, the mice that received sorafenib had significantly worse heart damage than the other group. Only 40 percent of those mice, versus 72 percent of the other group, were alive after one week. According to Dr. Houser, the doses were equivalent to those cancer patients would typically receive. Sorafenib by itself had no discernible effect on the mice prior to heart attack.

"Our study was to see if such a drug would put individuals with cancer and ischemic heart disease at extra risk for a heart attack," he said. "Mice given sorafenib and then made to have the equivalent of ischemic disease and a heart attack had much poorer heart function and survival. The drug put the animals at much greater risk for heart damage and death compared to animals without the drug."

Cancer patients tend to be middle-aged and older, and often have other significant health issues, including underlying heart disease. As a result, in patients with ischemic heart disease, there is already damage under repair. Drugs such as sorafenib may block or slow this repair process and increase the risk for a heart attack, Dr. Houser said.

Repair Process Inhibited

The researchers subsequently treated bone marrow stem cells, heart stem cells, and heart muscle cells (myocytes) with sorafenib in the laboratory dish. The drug blocked both types of stem cells from growing, but had no effect on normal heart muscle cells. This meant that the drug likely doesn't affect normal heart cells that were not damaged and under repair, Dr. Houser pointed out. "Injury activates the proliferation of the stem cells," he said. "We think it's something about the repair process that the drug affects."

He and his team would like to find drugs that could be taken alongside cancer drugs such as sorafenib that would reduce adverse effects on heart stem cells. At this time, they are developing a program to screen candidate agents. "Ideally, we could help physicians predict which patients are at higher risk for these effects, and find better ways to screen patients," Dr. Houser said.

The investigators next plan to test therapies to stimulate repair and protect hearts from potential damage from such cancer drugs.

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