MedicalXpress

# Another 'smart' cancer drug can have toxic effects on the heart

December 14 2007

Another FDA-approved targeted cancer drug, sunitinib (Sutent, Pfizer), may be associated with cardiac toxicity, report researchers at Children's Hospital Boston, Dana-Farber Cancer Institute (Boston), and Thomas Jefferson University (Philadelphia). Their collaborative study, led by Ming Hui Chen, MD, MMSc, a cardiologist at Children's who specializes in the cardiac health of cancer patients, appears in the December 15 issue of The Lancet, accompanied by an editorial.

Sunitinib is one of several new "smart" cancer drugs called tyrosine kinase inhibitors that targets specific signaling molecules inside cancer cells that aid cancer spread. Another "targeted" cancer therapy, imatinib (Gleevec, Novartis Pharmaceuticals), was reported last year in Nature Medicine to be associated with heart failure in patients with chronic myelogenous leukemia.

Sunitinib was originally thought to be relatively free of cardiac side effects. However, a new retrospective analysis, focused on cardiovascular events, revealed a risk for heart failure, myocardial infarction and hypertension in 75 adult patients with imatinib-resistant, gastrointestinal stromal tumor (GIST) receiving multiple cycles of sunitinib in a phase I/II trial at Dana-Farber.

Of the 75, six (8 percent) developed symptoms consistent with moderate-to-severe congestive heart failure, and two had heart attacks. In all, eight (11 percent) had some kind of cardiovascular event while receiving sunitinib at FDA-approved or lower doses. Patients with preexisting

coronary artery disease were more likely to develop cardiac problems. Nineteen percent of the 36 patients receiving the FDA-approved dose had decreases in left ventricular ejection fraction, a measure of the heart's pumping ability.

In addition, 47 percent (35 of 75) developed hypertension. "Hypertension is a common side effect with certain cancer drugs, but the degree of hypertension – both the percentage of affected patients and the magnitude of increase in systolic blood-pressure – was notable," says Chen, who is also affiliated with Brigham and Women's Hospital, Dana-Farber Cancer Institute and Harvard Medical School.

Two patient biopsies revealed abnormalities in the heart cells' mitochondria (the structures responsible for energy production). Further studies, led by Maria Rupnick, MD, of the Children's Hospital Boston Vascular Biology Program, and Thomas Force, MD, from the Center for Translational Medicine and Division of Cardiology at Jefferson, examined heart-muscle cells from mice who had received the equivalent of a human dosage of sunitinib alone, and found direct evidence of cardiotoxicity.

"Early identification of cardiac side effects is an important part of keeping patients on life-saving cancer therapy over the long-term," says Chen. "In this study, the cardiac dysfunction and hypertension were usually medically manageable. Most importantly, patients were most often able to resume sunitinib therapy following temporary withholding of drug, addition of cardiac medications and/or dose adjustment."

"This sunitinib study highlights potential concerns with agents that are 'multi-targeted,' meaning they inhibit multiple factors involved in cancer progression," adds Force, who led the study of imatinib patients published in Nature Medicine last year. "Some of these factors may also play important roles in maintenance of proper heart function, and their

inhibition by cancer drugs could have adverse effects on the heart."

"The most important element of this new work is the close, creative collaboration between our medical oncology and cardiology teams," says George Demetri, MD, a co-author on the paper and director of the Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School. "As our molecular targeting involves more pathways, we can inform one another's fields and identify side effects early by working together across traditional disciplinary boundaries."

"We are hopeful," Chen concludes, "that this type of multidisciplinary approach, from the patient's bedside to the basic cell biology laboratory, will lead to further pharmaceutical advances that will make these 'smart' cancer drugs even smarter."

Children's has a long history of researching the cardiovascular effects of cancer drugs. In children, such side effects are especially important to manage so they can survive the cancer in good health well into adulthood. In 1991, for example, Children's cardiologists published the seminal finding that doxorubicin therapy for childhood leukemia can lead to clinically important heart disease.

Source: Children's Hospital Boston