

# Taking Cancer-Drug Toxicity to Heart

Researchers unravel the mechanisms of heart failure and search for biomarkers of risk

It's a big problem driven by a big success.

Doxorubicin (Adriamycin; Pfizer) and other anthracyclines effectively treat leukemias, lymphomas, and several types of solid tumors, including breast cancer. The success of these chemotherapies is one driver of the dramatic improvements in survival rates for childhood cancers since the 1970s.

Sadly, the drugs have been linked to subsequent heart failure in cancer survivors. A 2009 study noted that more than 7.5% of children treated with anthracyclines will develop heart failure within 30 years. Adults aren't immune to the problem: For example, 1% to 2% of breast cancer patients treated with anthracyclines develop drug-related heart failure; others may have asymptomatic cardiomyopathy, pushing the true incidence of heart failure even higher.

Although some risk factors have been identified, no one knows exactly which patients will develop a problem, says Maryam Lustberg, MD, a medical oncologist specializing in breast cancer at Ohio State University in Columbus, OH. "It's really anyone's guess," she says.

## ANTHRACYCLINES IN ACTION

Doxorubicin induces double-strand breaks and cancer cell death primarily by intercalating into DNA and by blocking the activity of the topoisomerase II (TOP2) enzymes TOP2 $\alpha$  and TOP2 $\beta$ , preventing DNA replication.

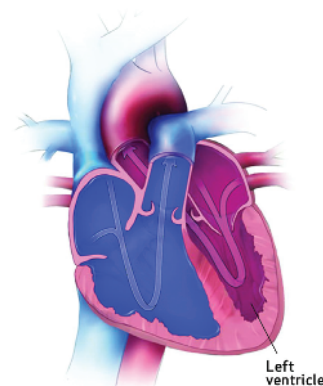
However, researchers aren't sure how doxorubicin exerts its cardiotoxic effects. The most widely studied theory argues that doxorubicin treatment leads to significant increases in reactive oxygen species, damaging cardiomyocytes via the redox cycle, says Steven Lipshultz, MD, a professor of pediatrics and director of the Batchelor Children's Research Institute at the University of Miami Miller School of Medicine in Florida. Doxorubicin also forms complexes with intracellular iron, producing harmful free radicals, he adds.

Last October, a group at the University of Texas MD Anderson Cancer Center in Houston published a study concluding that doxorubicin-induced cardiotoxicity is mediated by TOP2 $\beta$ . They examined the effects of doxorubicin in mice with normal cardiomyocytes and in mice with cardiomyocytes in which *Top2b* had been deleted. They found marked upregulation of apoptotic genes and activation of the DNA damage response, mitochondrial dysfunction, and repression of oxidative phosphorylation in the cardiomyocytes with intact *Top2b*, but not those without *Top2b*, says Edward T.H. Yeh, MD, chairman of the cancer center's cardiology department and senior author of the study.

Molecularly targeted agents may also cause complications. For example, a 2012 retrospective study involving 12,500 breast cancer patients found that the risk of heart failure and/or

cardiomyopathy is 4 times greater in women who take trastuzumab (Herceptin; Genentech) compared with women who receive no chemotherapy or monoclonal antibodies.

Agents targeting VEGF, such as the monoclonal antibody bevacizumab (Avastin; Genentech), and certain tyrosine kinase inhibitors, such as sorafenib (Nexavar; Onyx Pharmaceuticals and Bayer Health Care) and sunitinib (Sutent; Pfizer), can cause hypertension, thrombosis, and heart failure, says Javid Moslehi, MD, codirector of the cardio-oncology program at Boston's Brigham and Women's Hospital and Dana-Farber Cancer Institute (DFCI).



A normal heart (above) pumps enough oxygenated blood to meet the body's needs. In heart failure, which can be caused by some cancer drugs, the heart enlarges, its muscular walls thin, and the left ventricle pumps ineffectively.

## STEPS TOWARD PREVENTION, MONITORING

Aiming to protect the heart, Lipshultz and others tested the iron-chelating drug dexrazoxane (Zincard; Pfizer) in rats treated with anthracyclines. They found that it could inhibit formation of anthracycline-iron complexes even when the animals were given large doses of anthracyclines. In follow-up studies in children with acute lymphocytic leukemia (ALL), the drug dramatically cut the incidence of heart trouble.

"Unfortunately, we don't know why dexrazoxane works in some patients and not in others," confesses Stephen Sallan, MD, senior pediatric oncologist at DFCI. "It's not the end-all, be-all, but it's all we've got when it comes to prevention."

Although patients who develop heart trouble following treatment with anticancer agents may take ACE inhibitors, beta blockers, or statins to help improve heart function, randomized controlled trials and long-term follow-up supporting the use of these drugs to prevent cardiotoxicity are lacking. For now, Moslehi says that physicians should periodically check patients' heart function with echocardiograms.

Biomarkers might help physicians determine which patients are at the greatest risk of cardiac complications after treatment. For example, in children, increased levels of cardiac troponin T, a marker of cardiac injury, and N-terminal pro-brain natriuretic peptide, a marker of cardiomyopathy, during treatment for ALL may predict who will experience changes in the heart's left ventricle 4 years later.

Additionally, Yeh and his colleagues aim to find out whether TOP2 $\beta$  blood levels could indicate who will be most sensitive to doxorubicin's cardiotoxic effects—and whether altering therapy based on biomarkers will improve outcomes. "We want to be sure that cancer patients will have healthy hearts to enjoy their lives after treatment," Yeh says. —Suzanne Rose ■

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