

# Childhood cancer drugs cure now, may cause problems later, research shows

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Will a drug used to treat childhood acute lymphoblastic leukemia and other pediatric cancers cause heart problems later in life?

UB associate professor of [pharmaceutical sciences](#), Javier G. Blanco, PhD, who sees his work as a bridge between research and clinical practice, has focused recent efforts on trying to answer this question.

Blanco and colleagues' recent study in the [Journal of Clinical Oncology](#) looked for the underlying genetic answers to why some [childhood cancer survivors](#) who were treated with anthracyclines -- powerful antibiotics like Adriamycin and Daunomycin -- developed cardiomyopathy, such as [congestive heart failure](#), later in life.

"Anthracyclines are effective drugs used to treat a variety of pediatric cancers, they are also used to treat [breast cancer](#) and other malignancies in adults," Blanco says. "After cancer, survivors can develop cardiac toxicity anywhere from one year to more than 15 years after the initial chemotherapy with anthracyclines. The window separating the effectiveness of these drugs from their toxicity is narrow. The dosage has to be precise to achieve a [therapeutic effect](#) without toxicity."

Blanco explains that the key to individualizing any drug treatment comes down to understanding the way an individual is genetically coded to respond to the drug once it enters the body, and then adjusting the dose accordingly.

Working closely with Smita Bhatia, MD, MPH, chair of the Department of Population Sciences at City of Hope National Medical Center in California and senior author of the study, Blanco and a team of researchers decided to look at how the drug was broken down by enzymes encoded by specific genes.

The study, which began seven years ago, compared DNA genotypes of 170 childhood [cancer survivors](#) diagnosed with anthracycline-related cardiomyopathy to a control group of 317 survivors without heart disease.

Using the candidate gene approach, Blanco and his team were able to identify a tiny [gene variant](#) related to the risk of cardiotoxicity.

"We pinpointed the genetic difference or polymorphism that makes an enzyme work faster or slower in patients," said Blanco, "slower is better."

They zeroed-in on carbonyl reductases (CBR1 and CBR3) -- two enzymes that break down anthracyclines into cardiotoxic alcohol metabolites. Blanco notes that in mouse models, higher levels of CBRs or faster enzymes dictate higher levels of these metabolites -- and more cardio toxicity.

The research showed that the risk of cardiomyopathy was significantly increased among individuals with two copies of the "G" version of the CBR3 polymorphism when exposed to low-to-moderate doses of anthracycline.

Blanco says that while the results of the study validated the findings of an earlier study in a totally independent cohort of cancer survivors, further study is required.

"We have to be careful," says Blanco. "So far, we are showing an association, not yet causation. Our next step will be to conduct a prospective study -- where we don't study individuals who were exposed to anthracyclines in the past but follow them in real time as they are receiving the drug and after."

What does this mean for children who are taking or have taken anthracyclines?

"If we stop using anthracyclines we will not be able to cure up to 90 percent of the children who suffer from [acute lymphoblastic leukemia](#)," Blanco says. "Parents must continue to have their children's health monitored long after the cancer is cured to identify cardiac problems if they develop."

Provided by University at Buffalo

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