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Hazardous to Your Heart

BY JAMIE SPENCER

Protecting the heart from toxic side effects of cancer therapy.

At the dizzying moment when a patient first receives a diagnosis of cancer, the side effects of treatment to fight the disease may seem insignificant. That was certainly true for Adriana Jenkins, who found out in 2001 at age 31 that she had inflammatory breast cancer and the disease had already spread to her lymph nodes and chest wall.

“Quite honestly, my situation was so dire,” she says now, “if they had said hydrochloric acid would help, I’d have spread it all over my body.” Instead, she entered a trial for Herceptin® (trastuzumab). But after 12 weeks of treatment, despite her cancer responding well, she had to withdraw from the trial because of potentially dangerous changes in her heart rhythm.



Adriana Jenkins was removed from a Herceptin study after experiencing injury to her heart. Photo by David Gordon.

While many side effects of traditional chemotherapy are well-known, such as nausea, hair loss and fatigue, other problems associated with targeted cancer agents, including those affecting the heart, may be much more serious. Drugs can

prevent or reduce the severity of cardiac toxicity, and advancements in anticancer therapy are attempting to lower the risk even more.

A Critical Organ

The heart is the body's workhorse, pumping blood throughout the circulatory system to bring oxygen and other nutrients to tissues and organs. When the heart is healthy, its four chambers coordinate to keep blood flowing through the valves into the blood vessels, all while its electrical system keeps the heart pumping in a steady rhythm.

But when the heart is damaged by certain types of cancer treatment, disturbances can occur. The effects can be acute, occurring shortly after the start of treatment or months after the last dose, or late, occurring years after treatment is over. And unlike the more visible side effects of treatment, such as hair loss, heart side effects are often silent, though symptoms can include shortness of breath, dizziness, irregular heartbeat or swollen feet or ankles.

“The old adage ‘do no harm’ doesn’t always work in the treatment of cancer,” says Michael Ewer, MD, a cardiologist at M.D. Anderson Cancer Center in Houston. “Some cancers have to be treated aggressively, and the price we pay sometimes is a cardiac effect.”

Rare But Serious

Only a small percentage of patients who undergo drug therapy or radiation experience cardiac toxicity, and the percentage and severity can vary with different drugs. When discussing cardiac toxicity, doctors say it's important for patients to understand the difference between a cardiac event, which can be a minor degree of injury that produces no symptoms, versus serious heart damage that can lead to congestive heart failure or other dangerous heart conditions.

Cardiac toxicity was recognized as early as 1967, when reports surfaced of heart failure in children who received Adriamycin® (doxorubicin) to treat leukemia. Since then, other cancer therapies have been recognized as potentially harmful to the heart.

Drugs known as anthracyclines, which include Adriamycin as well as Cerubidine® (daunorubicin), Idamycin® (idarubicin) and Ellence® (epirubicin), are known for their potential cardiac toxicity. Anthracyclines treat a variety of cancers, including breast cancer, sarcoma, lymphoma and leukemia. While serious heart damage is rare in patients receiving anthracyclines—ranging from 2 to 7 percent—the risk increases with each dose, so oncologists carefully monitor a patient's total anthracycline dose received over a lifetime to minimize the risk of permanent heart damage. Other heart-toxic drugs often used in combination with other cancer drugs are 5-fluorouracil, or 5-FU, and cisplatin.

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—Michael Ewer, MD

And then there is Herceptin, a targeted drug used to treat the 25 to 30 percent of breast cancer patients with HER2-positive breast cancer. While Herceptin works well to reduce breast cancer recurrence and risk of death, studies have shown anywhere from 1 to 11 percent of women who take the drug experience symptomatic congestive heart failure. Investigators who reported the 11 percent statistic clarified in their study, published in late 2006 in the *Journal of Clinical Oncology*, that the elevated percentage wasn’t surprising since a significant number of patients had a history of heart disease, prior anthracycline exposure and prolonged exposure to Herceptin (an average of 21 months).

“There is a concern that if patients develop heart trouble [on Herceptin], they might need to limit something that can help them,” says Charles Geyer, MD, director of Breast Medical Oncology at Allegheny General Hospital in Pittsburgh who investigated the cardiac toxicity of Herceptin. But there are ways to optimize its benefits, he says, and although some therapies carry heart-toxic risks, their cancer-fighting benefits may tip the scales. “We don’t want people to be afraid of Herceptin.”

In addition to drug therapy, radiation directed at the chest, spine or upper abdomen may cause cardiac injury. But changes to methods of delivering radiation in recent years, such as using lower doses and reducing exposure to heart tissue, have reduced the risk.

Certain pre-existing health problems can increase the risk of heart damage. People with heart disease, high blood pressure, diabetes or who are either very young or elderly are at increased risk. All of these factors must be weighed when making decisions about treatment.

Preventing Heart Complications

With so many cancer patients surviving long after treatment, the enduring consequences of therapy have become more of a concern. “We didn’t used to have long-term cancer survivors,” says Carolyn Runowicz, MD, chair of the National Cancer Advisory Board and director of the Neag Comprehensive Cancer Center at the University of Connecticut Health Center in Farmington. “It’s been an evolution.”

In addition to strategies to reduce the dose of radiation to heart tissue, reducing the overall dose of medication or administering the drug differently can cut the risk of heart problems. With Adriamycin, giving the drug by a continuous infusion rather than in a large single dose can reduce its toxic effects.

When Dr. Runowicz faced decisions about her own breast cancer treatment in 1992 when she was in her early 40s, she questioned whether she should take Adriamycin. “There were not a lot of data yet about the benefits of Adriamycin on survival, so we didn’t know the effect,” she says. “But I decided I’d rather have heart disease at 60 than be dead at 45 or 50. In my mind, it was worth it.”

Fifteen years later, new drug formulations can lower the risk of complications. A form of Adriamycin called liposome-encapsulated doxorubicin, or Doxil®, appears to reduce cardiac toxicity by enveloping the drug within a bubble of fat, allowing it to be slowly released. This allows a higher dose to be given with less severe side effects.

Heart-protective drugs have been developed to reduce the harmful effects of therapy. Zinecard® (dexrazoxane) has been shown to lower iron levels in the blood, reducing the level of free radicals that can damage heart tissue. Zinecard also allows more patients to be treated with extended doses of Adriamycin.

Another approach to protect the heart from therapy involves ACE inhibitor medications, such as enalapril, typically given to people with high blood pressure or heart failure. These drugs slow the progression of left ventricular dysfunction that results from some chemotherapies.

Monitoring the Heart

Patients receiving potentially cardiotoxic cancer therapy should be carefully monitored both during and after treatment. An echocardiogram (heart ultrasound) is the primary tool used to monitor heart health, but other tests may also be done, including blood tests, electrocardiograms or multiple-gated acquisition (MUGA) scans, which produce a moving image of the heart muscle.

M.D. Anderson Cancer Center’s department of cardiology recently sponsored a panel discussion of oncologists and cardiologists to discuss how to best monitor a patient’s heart function. Concerning the issue of whether to use non-invasive echocardiogram or time-consuming yet generally more precise MUGA, the panel determined either imaging method was acceptable depending on the expertise of the radiologists and cardiologists at a particular cancer center.

Following treatment, survivors should have a yearly checkup to identify any long-term consequences of cancer therapy. Those at higher risk for heart complications may need more frequent monitoring.

An early and often missed warning sign of heart damage, says Dr. Ewer, is a pulse rate that goes up and stays up after minor exertion, such as climbing stairs. “By the time patients are short of breath, there may be more serious cardiac effects,” he says.

If heart problems occur, stopping the drug may reverse the effect. Treating the heart problem can also help the heart to heal. The previously mentioned *Journal of Clinical Oncology* study found that most of the metastatic breast cancer patients who suffered some degree of heart damage while taking Herceptin saw an improvement in heart function after stopping the drug and receiving cardiac treatments, such as beta-blockers and ACE inhibitors. These patients were then

able to resume Herceptin therapy.

In Adriana Jenkins' case, after being pulled from the Herceptin trial, she was eventually able to go back on the drug after having a mastectomy. "I was devastated when I was pulled from the trial," she says. But now, almost six years later, her heart is healthy and she's cancer-free.