

FEATURE STORY

# Beneficial Risk

BY JO CAVALLO

*Questions about the safety of approved drugs has the FDA poised to reform. But with cancer patients willing to accept a higher level of risk, what will changes mean for them?*

The numbers are daunting: When looking at all diseases, around 100,000 people die each year from an adverse reaction to a drug or medical device, and although drugs are put through intense studies to test their safety and effectiveness, more than half of the most serious adverse drug reactions, or ADRs, are discovered seven or more years after the Food and Drug Administration approves a drug, according to Research on Adverse Drug Events and Reports [RADAR], a multidisciplinary, clinically based drug monitoring program at Northwestern University's Feinberg School of Medicine in Chicago.

Since its inception, RADAR investigators have identified ADRs associated with 33 approved drugs, including the heart medication Plavix [clopidogrel] and drug-coated cardiac stents. While RADAR also focuses its investigative efforts on chemotherapy drugs and has reported ADRs on such cancer-fighting drugs as Thalomid [thalidomide], which may pose potential heart risk, they're often harder to track.

"You have to say by their very nature, cancer drugs will have a serious adverse effect because they're uniquely designed to be toxic [to cancer cells] and that's why we consider them to be the most difficult and most challenging to look at for adverse events," says Charles Bennett, MD, PhD, lead investigator of RADAR and co-director of the cancer control program at Robert H. Lurie Comprehensive Cancer Center. "Cancer drugs are meant to kill cells. You just hope that they kill more bad cells than good cells."

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The life-threatening potential of cancer, the desire of patients to have access to the latest treatments quickly, the difficulty in distinguishing between a drug toxicity and a health problem that is the result of cancer progression, and interactions between cancer drugs and medications taken for other medical problems are all reasons cited for why it’s especially difficult to identify side effects from cancer drugs.

“We understand that determining the toxicities of cancer drugs is difficult and requires a lot of basic science infrastructure. The FDA primarily looks at databases and statistical signals [to identify ADRs]. It’s really understanding the science that leads us to understanding an adverse event, rather than a statistical signal,” says Dr. Bennett.

And, experts say, there isn’t public outcry to outlaw or level more restrictions on cancer drug use because patients are more willing to roll the dice when it comes to assessing their personal level of drug risk-to-benefit ratio.

“People should realize that nothing is completely safe,” says Karen Weiss, MD, deputy director of the Office of Oncology Drug Products in the Center for Drug Evaluation and Research at the FDA. “And particularly for patients with advanced cancer, there’s a much different level of benefit to risk. The public is willing to accept greater risk the more serious the disease and the more the drug is going to be able to benefit the patient.”

Even when they know the potential danger of an agent in regards to immediate and long-term risks, Dr. Bennett says cancer patients often assess their individual risks and benefits differently from what the actual data show. “Patients often overemphasize the benefit and underemphasize the risks at the start of treatment,” he says.

## Moving Target

Formed in 1998, RADAR investigates reports of serious adverse drug events that meet its criteria: a drug or device that causes death, severe organ failure, or requires a major medical intervention such as placing a patient on a ventilator. RADAR then alerts the pharmaceutical company and sends its case reports to MedWatch, the FDA’s Safety Information and Adverse Event Reporting Program.

In some instances, these reports led the FDA to issue its strongest warning, putting a “black box” label warning on the drug. The FDA estimates about 3.5 percent of drugs are ultimately withdrawn from the market for safety reasons, but the agency couldn’t put a percentage on the number of drugs that have gotten black box warnings. (The FDA doesn’t keep a comprehensive, updated listing of drug warnings, but patients can find information on specific drugs at

[www.fda.gov](http://www.fda.gov))

It's well-known that adverse drug reactions occur more often when cancer therapies are used off-label, meaning the use is not firmly supported by scientific evidence. More than half of cancer drug use is for off-label indications, according to the National Cancer Institute, which makes predicting the unpredictable even more difficult.

The most recent cancer-related drugs to receive a black box warning are the erythropoietin drugs Procrit (epoetin alfa) and Aranesp (darbepoetin alfa). Both drugs are approved for anemic chemotherapy patients to increase the number of red blood cells, but the FDA placed a warning on the drugs in March after research found they can worsen cancer and increase the risk of death if used at higher than approved doses and for unapproved indications. The new labeling recommends doctors should only use Procrit or Aranesp to avoid the need for blood transfusions in cancer patients undergoing chemotherapy.

Black box warnings have also been placed on a number of popular drugs that treat cancer, including Avastin (bevacizumab), an agent approved for colorectal and non-small cell lung cancers that carries a rare risk of gastrointestinal perforation and hemorrhage, and Herceptin (trastuzumab), a drug approved for HER2-positive breast cancer that could cause heart damage, serious infusion reactions, and lung damage in a small percentage of patients. Indeed, studies have shown 1 to 11 percent of women taking Herceptin experience symptomatic congestive heart failure, depending on history of heart disease, prior anthracycline exposure, and prolonged exposure to Herceptin.

When GayeRene Ledford was diagnosed with HER2-positive breast cancer two years ago at the age of 56, getting rid of the aggressive cancer was the only thing on her mind. She had a mastectomy to remove the cancerous left breast and started on a chemotherapy regimen of Adriamycin (doxorubicin)—an anthracycline—and Cytosan (cyclophosphamide). When Ledford entered a clinical trial for Herceptin, a drug proven to lower the risk of recurrence after chemotherapy, she was given reading material about the clinical trial protocol, which included information about the heart risks associated with Herceptin. But, she admits, she discounted the potential problems because her fear of the cancer returning was so great.

“At first I didn't even take in [the information], because cancer was the main thing on my mind. And to be truthful, I didn't even read the literature I was given for a few weeks,” says Ledford.



GayeRene Ledford wishes she had paid closer attention to the risks of treatment. Photo by Lisa Nelson.

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Ledford, who is considered overweight and has a family history of heart disease, joined the Herceptin trial. Ten months later, her heart function had decreased so much that she was taken off the drug for a month, but finished the trial. Today, she has a permanent 10 percent reduction in heart function, and says even though she would still make the same decision to enter the trial, she would pay more attention to risk factors.

“When you’re diagnosed with cancer, it’s such an emotional time and it’s such an invasive disease that it outweighed my thoughts of heart problems. [In the future], I would definitely look at risk factors stronger than I did, and I would talk to my doctor to get more answers to find out if there was anything I could do to protect myself,” says Ledford.

But some experts say it’s difficult for patients to be able to objectively judge their treatment risk-to-benefit ratio and make a choice. “It’s a tough position to put patients in,” says Dr. Bennett. “They have a life-threatening illness and they’re facing drug risks that are real but difficult to assess. It really requires a lot of help from the doctor. There’s no natural way to frame these things where patients would actually be able to realistically evaluate their risk-benefit profile given their own dire straights.”

Patients taking potentially heart-toxic therapies should be monitored closely using both clinical exams and diagnostic tests, including echocardiograms, blood tests, electrocardiograms, or multiple-gated acquisition (MUGA) scans to spot heart problems. At the first sign of trouble, the drug may be stopped, the dose may be reduced, or the patient may be put on heart medication to either limit or

even reverse the damage.

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While cancer drugs do carry myriad potential long-term health consequences besides heart damage for survivors— such as neuropathy and secondary cancers—Patricia Ganz, MD, director of the UCLA LIVESTRONG Survivorship Center of Excellence, says those are uncommon events.

“I wouldn't want patients to think they have to be on the lookout for these things, which may be very rare,” says Dr. Ganz. “But if they're having symptoms or problems, they need to communicate with their primary physician to ask whether the symptoms are related to the drugs taken in the past or something new. Many times it's something new or unrelated.”

Dr. Ganz suggests patients keep a list of all the drugs they've taken over the course of treatment, along with the dosage schedule and total dosage to present to their doctor if a health issue does crop up. She also recommends maintaining a healthy lifestyle to reduce future health problems. “If you're smoking and have a family history of coronary artery disease, your risks for some of these things are going to be much more severe than somebody who has low risk otherwise.”

## Finding a Solution

Complications aren't just limited to cancer drug use. Three years ago, Merck voluntarily withdrew its popular painkiller Vioxx (rofecoxib) from the market after a study showed it doubled patients' risk of heart attack and stroke. And the Type 2 diabetes medication Avandia (rosiglitazone) is under similar fire as concerns grow about its risk of congestive heart failure. The controversies fueled new questions about the FDA's competence in tracking infrequent side effects on an ongoing basis well after the drug has been approved.

This past summer, Congress passed the Food and Drug Administration Revitalization Act, a bipartisan bill that reauthorizes the Prescription Drug User Fee Act, known as PDUFA, which enables the FDA to collect funds from pharmaceutical companies to supplement the cost of the drug application review process; boosts the FDA's resources for evaluating and managing a drug's safety both before and after approval; and gives the agency authority to impose fines on companies that violate a drug's safety plan or run misleading ads.

“The bill sets up a robust system to allow the FDA to have more active and more advanced interactions with established health care databases, which gives the agency a wealth of information to detect signals of drug risk at an earlier time point than is able to be done today,” says Jeff Allen, PhD, director of science

policy for Friends of Cancer Research, a nonprofit that raises public awareness on cancer research.

The bill also establishes the Reagan-Udall Foundation for the FDA, which will develop public and private partnerships to advance drug safety and improve techniques to identify which patients will benefit most from a new drug with the least amount of risk. As of press time, the FDA Revitalization Act is expected to be signed into law in September.

The new legislation comes on the heels of “The Future of Drug Safety,” a report from the Institute of Medicine that contains 25 recommendations for reforming the process of evaluating drug safety, including revamping the FDA Center for Drug Evaluation and Research to balance its drug approval process with the equally important surveillance of drugs after they’ve been approved; increasing resources in both additional funds and manpower; and ensuring the regulatory process reflects the balance of drug benefit and risk.

“The limitations imposed should match the specific safety concerns and benefits presented by the drug product,” reads the Institute of Medicine report. These are reassuring words for cancer patients worried the current spotlight on the FDA’s drug approval process may result in the overregulation of new drugs, making it more difficult for cancer patients to get quick access to new medications.

“[What is acceptable risk for cancer patients] is a huge issue and I think it’s a wake-up call for patient groups to think about because in today’s toxic climate in the media, we couldn’t get aspirin approved,” says Ellen V. Sigal, PhD, chair of Friends of Cancer Research. “We need to think about the continuum of drugs that we need—the ones that are less toxic, the ones that are more effective—and we have to think about the [drug] pipeline and how urgent it is [to get new drugs approved].”

Although the FDA’s Dr. Weiss says some of the Institute of Medicine’s recommendations about providing greater transparency and information to the public about emerging drug safety issues have already been put into place, she concedes there needs to be greater public awareness that the safety data found in a clinical trial setting in a small patient population can change once the drug is distributed to a more diverse patient group in the real-world setting.

“It’s very, very difficult to anticipate all the safety issues that could come up with a drug at the time it’s approved for marketing, and there’s tension about how much data are needed,” says Dr. Weiss. “And then once a drug goes to market, it tends to be used in larger populations with comorbidities. It’s difficult to know all about a safety profile of a drug once it’s approved and used in hundreds of thousands [of patients], because you don’t have that big set of numbers prior to approval.”

Although Dr. Weiss doesn’t know what effect, if any, the FDA Revitalization Act will have on cancer treatment, she doesn’t think there will be a downturn in approvals for new cancer medications. “There are a number of vocal cancer groups that feel drugs should be approved faster and the FDA waits too long. I don’t think cancer patients should worry that there’s going to be a slowdown in drugs that have potential to show some benefit in terms of survival or progression-free survival,” she says.

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## What's Ahead

In the future, cancer patients may not have to worry about the possibility of trading one health problem for another caused by drug toxicity. Over the next two decades, experts say the sequencing of the human genome will enable researchers to develop truly targeted molecular therapies that only kill errant cancer cells and leave healthy cells alone.

“Now that we know most tumors are derived from definable genetic mutations in very specific genes, it allows researchers to think about drug discovery in a different way,” says David Jones, PhD, senior director of early translational research at the University of Utah's Huntsman Cancer Institute in Salt Lake City. “For example, if I understand exactly the three mutations that occurred in a cell to make it a tumor, I can now start to think about drugs that specifically target the consequences of those three mutations.”

The result, says Jones, would end the current hit-and-miss approach to cancer treatment because drugs would be given to patients based on their tumor's genetic makeup, improving drug efficacy and limiting toxicity. His group is currently looking for drugs that will be effective only in cells that have mutations in the adenomatous polyposis coli gene, which is mutated in 85 percent of colon cancers.

In the meantime, Jones says, it's incumbent upon the medical profession to help cancer patients make informed decisions about risks and benefits when it comes to their treatment. “As a patient, I'd want to know everything that could go wrong [in my treatment plan] given my current health condition so I could take that into account [when making my decision].”