US cancer researchers go abroad for trials

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By Emily Anthes and Scott Allen, Globe Staff | December 29, 2007

It was one of the biggest advances in cancer treatment this year, a drug combination that potentially adds years to the lives of patients whose colon cancer has spread.

But the research that led to the finding could never have been conducted in the United States, because most Americans wouldn't have been willing to participate in a trial, like this one, where there was a strong chance that they would be assigned to a group that did not get the experimental chemotherapy.

"We wouldn't even try it," said Dr. A. William Blackstock, a North Carolina radiation oncologist who serves on a federally funded committee that promotes cancer research.

Thirty-six years after the United States declared "war" on cancer, scientists are increasingly fighting its battles in other countries, where doctors have an easier time persuading patients to take part in experiments and ethical rules for human research are sometimes looser. About 43 percent of all US-regulated clinical trials are now conducted outside the country, according to a new study by the Tufts Center for the Study of Drug Development.

The move offshore reflects a numbers problem in the United States: Though more than 1.4 million people were diagnosed with cancer in 2007, fewer than 5 percent of them enrolled in clinical trials of experimental drugs. Many don't enroll because they are wary of potential side effects or fear that the drugs could turn out to be ineffective or inferior to conventional treatments. In contrast, others worry about being assigned to a comparison group that doesn't get the experimental treatment. And some aren't aware of trials for their specific condition.

Such low participation is one reason it can take 15 years, or longer, to develop new cancer treatments. Four-fifths of US clinical trials are delayed because researchers can't find enough people to fill them.

When Barbara Holtz, of Wayland, was diagnosed with breast cancer in 2001, even physicians in her own family advised against participating in a clinical trial because of the risks of taking an unapproved drug. She ultimately decided to participate in the trial anyway, largely because she wanted to contribute to science.

"One of my commitments here is my faith in the scientific process, my belief in wanting to move science along," she said.

Even though Holtz had to drop out of the study because of concern about the drug's impact on her heart, she said the experience was positive and that she'd do it again - a sentiment that is typical of people who take part in drug trials. They report getting excellent care in surveys, and some say the experimental treatments they received were superior to conventional care.

But analysts who track cancer research say that faltering public confidence in the drug industry, which pays for most human tests of cancer drugs, is likely to hold down participation rates.

"We have seen a real erosion of public trust in the clinical trial enterprise," said Ken Getz, founder of the Center for Information & Study on Clinical Research Participation, a Dedham-based nonprofit group. "Only 14 percent of the American public believes that pharmaceutical companies are honest - that puts them on par with the tobacco and used-cars industries. That's really a dramatic change for the worse."

This public skepticism comes at a time when the demand for patients to test cancer medications is exploding.

Not only has the number of anti-cancer drugs under development grown from 400 in 2001 to 650 last year, but federal regulators are also pressing researchers to include more patients so that trials more reliably pinpoint possible side effects. As a result, the number of patients needed to fill industry-sponsored trials for all kinds of medications grew from 2.8 million people in 1999 to 19.8 million in 2005, according to BBK Worldwide, a patient recruitment company in Newton.

Also, because trials are usually aimed at patients suffering a very specific form or stage of cancer and who meet strict eligibility requirements, the vast majority of volunteers are rejected.

In Boston, where so much clinical research takes place and ads for volunteers line the inside of subway cars, patients

are more likely to volunteer, Getz said, but, even here, trials aren't necessarily any easier to fill, because there are so many researchers competing for the available cancer patients and patients can typically enroll in only one trial at a time.

The shortage has forced researchers to look increasingly abroad, where patients are more likely to sign up because experimental cancer treatments give them a chance to be treated at top medical centers and get more aggressive care. Trials with recruits from other countries fill 40 percent faster than those limited to patients in the United States, according to BBK, and trials carried out in developing nations cost less, too, since the investigators and support staff are not paid as much as their American counterparts.

But the globalization of trials carries ethical risks. Poor, less-educated people in developing nations are more vulnerable to manipulation. For instance, "in India, physicians exert far more influence over a patient decision than you're going to see in most parts of the US," said Joan Bachenheimer, the cofounder of BBK, suggesting that some subjects may feel pressured to participate.

And it can be harder to assure quality control in developing nations, although officials at the US Food and Drug Administration hold foreign-based scientists to the same scientific and ethical standards that they would in the United States.

In Europe, where the problems of developing nations don't apply, researchers say they find that patients are more willing to accept risk for science than in the United States.

In France, a study of patients whose colon cancer had spread to their livers was challenging to organize because it required desperately ill people to risk forgoing the experimental chemotherapy if they were randomly assigned to a comparison group of patients who would get surgery but not the drug combination. It took several years and help from medical centers across Europe and Australia, but, in the end, the team, led by Paris surgeon Bernard Nordlinger, recruited 364 patients willing to take part. That allowed him to demonstrate that chemotherapy before and after liver surgery boosted patients' survival chances by 25 percent.

By comparison, Blackstock of Wake Forest University Baptist Medical Center said his National Cancer Institute-funded committee has struggled to design a similar study that American patients - and their doctors - would support.

To increase American participation, Getz and Bachenheimer both say the medical community must increase awareness of clinical trials and explain to the public that participants fare as well as patients receiving conventional treatment, and sometimes they do better. Currently, three-quarters of the general public say they have "little to no knowledge" of trials or how to take part.

Terry Barter, 59, enrolled in a clinical trial at the Dana-Farber Cancer Institute to avoid the invasive stem-cell transplant his first two oncologists recommended. Every two weeks for five years, Barter, who had been diagnosed with multiple myeloma, an incurable blood cancer, made the 40-mile drive from his home in Berlin to Boston to be examined and have blood drawn for the study.

But the sacrifice, he says, was worth it.

Before the trial, his doctors had told him that he had only two years to live if he didn't get a stem-cell transplant. He went to Italy and bought himself a Corvette. But the experimental drug he took drove his cancer into remission. It's now been seven years since his diagnosis.

"I did all these things I wanted to do before I left this Earth," he said. "And now it looks like I'm not leaving." ■