Targeted Therapies Have Cancer in the Crosshairs

By Dan Gordon

A diagnosis of breast cancer is never good news. But for Louise Cooper, an elementary school teacher in her mid-40s who ran marathons and traveled to foreign countries to participate in grueling adventure-racing competitions, the news was especially jarring. She had a particularly aggressive form of the disease that, treated conventionally, was almost guaranteed to recur and, eventually, spread to other parts of her body.

But Cooper was fortunate in one sense: Her diagnosis came in June 1998, just as an entirely new approach to preventing recurrence of her disease was becoming available. Cooper began receiving the drug Herceptin® at UCLA's Jonsson Comprehensive Cancer Center that October. The following spring she resumed her athletic endeavors, completing a marathon in March and the 135-mile Badwater Ultramarathon through Death Valley in July, in which Cooper was the second woman to finish (time: 40 hours).

"I wasn't weak at all," Cooper recalls, five years after starting treatment on the drug that, she is convinced, saved her life. "On the contrary, I was building back my strength."

Although advances in conventional treatments have resulted in small incremental survival benefits for most common tumors, cancer researchers have long believed that the future of treatment rests in targeted therapies—"smart" drugs that, unlike the non-discriminating chemotherapy approach, take aim at the proteins, enzymes and pathways unique to cancer. This strategy, seemingly more rational and less toxic, was widely heralded in 1998 after Herceptin provided an early proof of principle, slowing tumor progression in women with extra copies of the HER-2/neu gene. Herceptin was approved by the U.S. Food and Drug Administration the same year, and is now standard treatment for the 20 to 25 percent of breast cancer patients who, like Cooper, fit the genetic profile.

Gleevec®, a pill for chronic myeloid leukemia (CML), is another targeted therapy that has been lauded as a success, both as proof of principle and in the clinic setting.

Approved by the FDA in May 2001, Gleevec is a signal transduction inhibitor, a class of drugs that can interfere with cell signaling pathways implicated in tumor development. The drug attacks a mutant protein in a cancer-causing gene linked to CML. Much of the pioneering work done to link the gene and its mutant protein to CML was performed at UCLA's Jonsson Cancer Center, and cancer center researchers were among the first in the world to test Gleevec on patients.

According to the most recent data, 95 percent of patients have full hematologic responses to Gleevec, meaning their white blood cells counts return to normal levels. About 70 percent have the disease disappear completely from the bone marrow, where CML originates, said Dr. Charles Sawyers, a professor of hematology/oncology and the principal investigator for the early Gleevec studies at UCLA's Jonsson Cancer Center.

"This level of response is unheard of in any cancer with a single drug," Sawyers said. "It may not be a cure, but it is very, very impressive."

"We still have a long way to go, but I am very encouraged. For the first time in 20 or more years, we have different pathways that we can tackle and new drugs that we hope will make an impact."
—Dr. Diane Prager

In the five years since Herceptin was approved, a handful of other targeted therapies, like Gleevec, have won FDA approval. More are progressing through clinical trials, including several at UCLA's Jonsson Cancer Center, where Dr. Dennis Slamon conducted much of the investigational work that led to Herceptin. Despite gains that have often been less than spectacular—along with some disappointments—UCLA researchers remain steadfastly optimistic about the future of the approach as it moves beyond its infancy.

"We've taken combinations of chemotherapy as far as we can, and if you look at how far we've come with it since the early 1970s, it's not a huge jump," said Slamon, director of the Revlon/UCLA Women's Cancer Research Program and director of Clinical/Translational Research at the cancer center.

On the other hand, he says, the results with Herceptin and several of its successors demonstrate that the targeted approach, properly executed and often in combination with chemotherapy, holds far greater potential.

"If we can decipher the pathways, we can come up with very effective therapeutics," Slamon said.

The strategy that, along with Herceptin and Gleevec,

arguably has attracted the most public attention targets not the cancer cells but the blood vessels that deliver oxygen and nutrients to these cells, enabling them to thrive.

A tumor can't grow larger than a pinhead unless it establishes an independent blood supply through the process of angiogenesis. Angiogenesis inhibitors operate on the principle that cutting off the new blood supply at the molecular level can starve, or even kill, the cancer. That's the idea behind the experimental drug Avastin®, a monoclonal antibody that targets the Vascular Endothelial Growth Factor (VEGF), a dominant angiogenesis protein.

"We have now had enough examples to show that if we identify the target, prove that it's driving the tumor, correctly identify the patients who have it and develop a drug that hits that target and stays around long enough to inactivate it, we can make a major impact." —Dr. Dennis Slamon

When combined with standard chemotherapy in a Phase II trial, Avastin proved superior to chemotherapy alone in treating advanced colorectal cancer.

"The Avastin group did better regardless of the endpoint we used—whether it was response rate, time to tumor progression or survival," said Dr. Fairooz Kabbinavar, associate professor of hematology/oncology and Jonsson Cancer Center researcher, who headed the trial and has studied the drug in both the lab and the clinic for the last decade.

Kabbinavar found similar effects—including a 33 percent improvement in median survival, as well as statistically significant improvements in response rates and time to tumor progression—in a Phase III trial of nearly 1,000 patients, the results of which were presented at this year's meeting of the American Society for Clinical Oncology.

"I have become a firm believer in this class of drugs," said Kabbinavar. "There was a lot of hype a few years ago and the enthusiasm of quite a few researchers was dampened when some of the anti-angiogenic agents failed to live up to that hype. Avastin has shown that targeting VEGF is a very sound and relatively less toxic strategy that can complement the existing therapies."

Other Jonsson Cancer Center researchers are combining targeted drugs, based on the rationale, supported by laboratory findings, that doing so will bring more benefits than either drug could provide alone. One Phase II trial at UCLA focuses on breast cancer patients indicated for treatment with Herceptin. Rather than being administered with chemotherapy, Herceptin is combined with Tarceva, which blocks the Epidermal Growth Factor Receptor (EGFR), a protein found on the surface of many tumor cells.

"There are multiple contributors to breast cancer and its ability to spread, and targeting just one of these contributors is probably not going to be enough to be clinically meaningful for most cases," said Dr. Mark Pegram, director of the Women's Cancer Program Area for the Jonsson Cancer Center.

"This is a departure from earlier targeted approaches, both in its use of two targeted therapies in combination and because, if effective, it would offer patients a treatment option that would allow them to avoid chemotherapy," added Dr. Carolyn Britten, an assistant professor of hematology/oncology, a Jonsson Cancer Center member and the principal investigator for the Herceptin and Tarceva study.

Both Britten and Pegram are studying several other targeted approaches in clinical trials, including a Phase I study that pairs Herceptin with Avastin for HER-2/neu-positive advanced breast cancer patients. That two-front strategy, based on research in Slamon's lab showing that HER-2 can promote angiogenesis, aims to cut off the tumor's blood supply at the same time that Herceptin is targeting the HER-2 receptor over-expressed in certain breast cancers.

By the time Jan Lesser was diagnosed with stage IV non-small cell lung cancer in February 2000, she had two tumors in her lungs, two in her liver and one in her brain the size of a golf ball. She was 46 and had three children, ages 15, 12 and 10.

After surgical removal of the brain tumor, she went through three unsuccessful rounds of chemotherapy and radiation. In November 2000 she joined a UCLA clinical trial of Iressa®, a once-a-day pill that blocks the EGFR pathway. By the end of December, her tumors had all shrunk by two-thirds, and two months later, they were no longer showing up on CT scans.

"These last three years have been magic," said Rick Lesser, who recently celebrated 25 years of marriage with his wife. In an open letter to family and friends to mark the occasion, he wrote: "The side effects have been extremely minimal. When Jan says she feels 'down' it means she's been SCUBA diving;

when she feels 'out of breath' it's because her trainer has been running her too long."

"Almost all non-small cell lung cancers have receptors for the EGFR pathway, which appears to be important for growth of this cancer, and we know from the laboratory that Iressa seems to block the EGFR pathway," said Dr. Diane Prager, associate professor of hematology/oncology and the Jonsson Cancer Center member who headed the Phase II trial of Iressa at UCLA.

As Jan Lesser's experience illustrates, Iressa has also proved easy for patients to tolerate.

In the trial led by Prager, patients whose disease had progressed after two previous types of chemotherapy were given Iressa. Approximately 10 percent responded with tumor shrinkage of 50 percent or more, and the disease was stabilized in 40 percent of patients, roughly the same proportion that showed improvement in symptoms.

"If you compare it with second-line chemotherapy, Iressa stacked up pretty favorably," said Prager.

A separate trial yielded less encouraging results—Iressa was paired with chemotherapy as a first-line treatment for lung cancer, with no significant impact on survival or response rate. Still, the dramatic effect in even a small percentage of patients who otherwise would have little hope was enough to convince the FDA to approve the drug in May of this year.

"We still have a long way to go, but I am very encouraged, said Prager, who is involved in several other trials of targeted agents for non-small cell lung cancer. "For the first time in 20 or more years, we have different pathways that we can tackle and new drugs that we hope will make an impact."

The most pressing challenge, Prager said, is to determine how to predict who will respond to a medication such as Iressa.

"This is called a targeted therapy, but we don't really know which patients should be targeted, because just having the receptor for this drug on the cell doesn't predict success," she said.

Indeed, notes Pegram, when targeted drugs produce disappointing results, there's a good chance it's because they are not properly aimed.

"The ability to select the right patients and to understand why some from a particular group respond while others do not is critical," he said. "If we would have done Herceptin studies in patients who weren't HER-2 positive, we would have never recognized its benefit."

The crafty nature of cancer makes the job of finding and hitting the right targets extremely challenging.

"By its nature, cancer is genetically unstable, so the cancer cells can change their blueprint much more easily than normal cells," said Slamon.

But he is as confident as ever in the strategy he and his colleagues are pursuing to defeat their formidable foe.

"We have now had enough examples to show that if we identify the target, prove that it's driving the tumor, correctly identify the patients who have it and develop a drug that hits that target and stays around long enough to inactivate it, we can make a major impact," Slamon said. ✯

A Guide to the Targeted Therapy Arsenal

Herceptin®

Treats: Advanced-stage breast cancer patients whose cancer has spread and who have a genetic over-expression of HER2, a growth factor found on some cancer cells. This over-expression results in an aggressive form of the disease and occurs in about 20 to 25 percent of breast cancer patients.

How it works: The drug binds onto HER2, blocking the reaction needed to tell the cells to multiply. It is used with standard chemotherapy drugs.

Status: Approved by the FDA in 1998 and is being tested in earlier stage breast cancer patients.

Gleevec®

Treats: Chronic myeloid leukemia, or CML. Also being tested, with good results, against a rare cancer called gastrointestinal stromal tumor.

How it works: The drug interrupts the process that allows mutant white blood cells to overproduce.

Status: Approved by the FDA to treat CML in May 2001.

Iressa®

Treats: Non-small cell lung cancer, which makes up about 80 percent of all lung cancer.

How it works: It is an inhibitor of Epidermal Growth Factor Receptors. It binds onto receptors found on the surface of a cancer cell, preventing the cell from reproducing.

Status: Approved May 2003 as a last line therapy for patients with advanced lung cancer.

Avastin®

Treats: Cancers of the lung, breast, colon and kidney.

How it works: Avastin inhibits a vascular growth factor, called VEGF, preventing tumors from developing the blood vessels they need to grow and thrive. Without blood, the tumor may die.

Status: The FDA granted fast-track review status to Avastin in June. It may be approved within months.

Tarceva

Treats : Lung, pancreatic and breast cancers.

How it works: Binds to Epidermal Growth Factor Receptors (EGFR) found on the surface of many types of cancer cells, blocking signals that order cells to reproduce.

Status : In clinical trials

Sources: National Cancer Institute, American Association for Cancer Research, American Cancer Society