A CURE FOR THE GENE BLUES

Women who harbor the BRCA gene mutations have renewed hope, thanks to a new drug now in clinical trials. It’s a pill, it’s potent, it’s portable, and it targets breast and ovarian tumors. By Idelle Davidson

It is a cool morning and Barbara Shellow is sipping a hot drink at a small table outside a coffeehouse. Glancing at her, you would never guess she has been through illness and the side effects of cancer treatment. Rather, she is rosy cheeked and robust. Everything about her suggests calmness and steadiness—from her hearty laugh to her unhurried manner and casual dress in a blue jean skirt and plaid top. “It must be my Wisconsin roots,” she says. “I’m from rural stock.”

Maybe her Midwestern heritage is also what accounts for Barbara’s no-nonsense outlook on life. “I have always known from the very beginning that if I just put one foot in front of the other,” she says, “somebody was going to be behind me with the next thing.” Then she rummages through her purse and pulls out what for her is that next thing: a baggy with four ordinary looking capsules. “I tell my grandkids that they are my magic pills.”

Those little capsules are called olaparib. Although not quite magic, Barbara hopes they will make her cancer disappear. Barbara is one of a small group of patients at Cedars-Sinai Medical Center participating in an international trial of the drug for women who carry the BRCA2 (breast cancer 2) gene mutation. Barbara actually has cancer of the peritoneum, which is the lining of the inside wall of the abdomen, but it is treated similarly to ovarian cancer. In 2000, she was also diagnosed with breast cancer.

With the discovery in the mid-1990s of the BRCA1 (breast cancer 1) and BRCA2 genes, researchers correlated the disease-causing mutations in these genes to the risk for developing breast or ovarian cancer. BRCA gene mutations are highly hereditary, especially in Ashkenazi Jewish, French-Canadian, and Icelandic heritage populations.

Researchers are now hoping to find a drug that directly targets breast and ovarian cancers in women who harbor a BRCA1 or BRCA2 gene mutation. That group includes 10 percent of women with ovarian cancer and 5 percent of women with breast cancer. Fewer than 10 percent of cancers are hereditary or genetic.

The functional aspects of the cell are controlled by and through proteins, not genes. This explains why most targeted cancer drugs on the market, or those being developed, are directed at proteins or enzymes, not genes. That is the case with olaparib.

In 2008, scientists from the United Kingdom and The Netherlands reported that the drug, in a clinical trial designed to test toxicity levels, also interfered with tumor growth in BRCA-positive ovarian and breast cancers. It did so by inhibiting an enzyme called PARP (Poly ADP-ribose polymerase). After the toxicity levels and proper dosages were established, 20 major cancer centers enrolled patients in Phase II of the trial, including the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai.

“BRCA genes are involved in repairing DNA, so when someone has inherited an abnormal copy of one of those genes, there is a tendency for DNA damage to develop in that person’s cells,” explains medical oncologist M. William Audeh, MD, who was principal investigator of the
In Search of the Perfect Personalized Prescription

The key to determining who will have a positive reaction to a chemotherapy drug and who will have a negative or no reaction lies in a field called biostatistics.

Today, patients who combat cancer with chemotherapy can expect one of three possible outcomes: The treatment works and the cancer recedes or is eliminated. The treatment has no impact. Or it causes such severe side effects that the patient must interrupt therapy. The reason, says André Rogatko, PhD, is that different patients respond to drugs differently. “Someone with a slow detoxification metabolism might retain a drug longer, so it becomes toxic,” Dr. Rogatko explains. “Or, if you have a fast metabolism, the drug might never reach the cancer.” As associate director of biostatistics at the Samuel Oschin Comprehensive Cancer Institute, Rogatko oversees biostatistical support for diverse cancer research efforts developing and testing new forms of statistical analyses.

Dr. Rogatko leads a team that studies how genetics, pharmacokinetics, and clinical variables affect a patient’s response to chemotherapy. “We want to calculate the perfect personalized dose of medicine for each patient—enough to be effective but not toxic,” he says. Determining optimal customized doses requires researchers to gather and analyze enormous quantities of genetic and other information using high-throughput screening—a sophisticated, computer-driven biological data processing technique.

“The benefits of our efforts are that this strategy could change the way clinical trials are done worldwide,” Dr. Rogatko says. “If we could determine in advance how someone will respond to a drug, we could test new therapies faster, more effectively, and with fewer toxic side effects.”

Phase II trial at Cedars-Sinai. “The PARP enzyme is one of the remaining DNA damage repair mechanisms. If you knock out or inhibit the enzyme with this drug, then the cancer cells with the damaged DNA cannot be repaired and they die,” says Audeh, an expert in hereditary cancers and medical director of the Samuel Oschin Cancer Center and the Wasserman Breast Cancer Risk Reduction Program at Cedars-Sinai.

Think of your body as a busy highway, and the vehicles on this highway are your cells. Normally, if a car (a cell) gets damaged (turns into a cancer cell), a mechanic (the PARP enzyme) would step in and fix it. Yet in many people with cancer, their mechanic (a mutated version of PARP) is not doing a good job and allows damaged cars back on the road, where they are destined to break down.

The drug olaparib (the PARP inhibitor) prevents the mutated version of PARP from allowing these damaged vehicles back on the road. For people with the mutation, a medical breakthrough cannot come too soon. “The lifetime risk of developing a breast cancer in women carrying the BRCA mutation is between 55 and 90 percent. For ovarian cancer, it is between 25 and 44 percent,” says Dr. Audeh. “Compare that to the average woman’s risk of ovarian cancer, which is less than 2 percent. So even though it is not a very common cancer, the risk is extremely high in this population.”

The fact that olaparib comes in the form of a pill is a huge advantage. Many chemotherapy drugs are given by infusion. Patients must be in a
hospital setting and hooked up to a machine for hours as the drugs are injected slowly into a vein. The physical and emotional side effects of the treatment can be extremely challenging.

According to Dr. Audeh, olaparib is nontoxic to healthy cells, and no major side effects have been observed. Although the results from the multi-center Phase II trial have not been released yet, he hopes the study drug may help shrink the cancer or stop it from growing. A Phase III trial opening later in 2010 should make the drug available to more enrolled patients.

Also involved in the Phase II trials was Beth Y. Karlan, MD. An internationally renowned expert in gynecologic oncology, she is the director of the Women’s Cancer Research Institute at the Samuel Oschin Comprehensive Cancer Institute. Dr. Karlan specializes in ovarian cancer surgery and has spearheaded translational research efforts that have contributed to innovative ovarian cancer treatment strategies. She was principal investigator of a study comparing the safety and efficacy of olaparib with the chemotherapy drug doxil in BRCA 1 and BRCA 2 patients with advanced and recurring ovarian cancer.

“We are doing extensive molecular research to better understand the correlation between genetic profiles and tumor behavior,” she says. “We sequence many of the genes in these tumors to understand why tumors recur, how they acquire resistance to chemotherapy, and why they occur at different ages in different individuals. For example, we have seen that in women with BRCA 1 mutations, the median age at which ovarian cancer occurs is 42, but for BRCA 2 that age is 61. That’s a 20-year difference. Why is that?”

“Karlan, who also directs the Division of Gynecologic Oncology in the Department of Obstetrics and Gynecology and the Gilda Radner Hereditary Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, is a national advocate for gynecologic cancers awareness and detection. She has testified before Congress to increase funding for ovarian cancer research.

Cedars Sinai is one of the institutions selected by the National Institutes of Health to contribute biospecimens to The Cancer Genome Atlas (TCGA) project, and Dr. Karlan serves on TCGA’s steering committee and ovarian cancer working group. The project’s goal is to build the genome map of all cancers, eventually leading to new targeted treatments and prevention methods.

“I often sit with families where one sister has just been diagnosed with ovarian cancer and another one has survived breast cancer, yet they have the same BRCA mutation and grew up in the same household,” says Dr. Karlan. “By studying penetrance (the proportion of individuals with the mutation who develop cancer), we think we will be able to predict the
type of cancer and the age of onset and find ways to prevent or detect them better. This understanding will also give women the tools to make better-informed decisions. Ultimately, this knowledge, combined with the development of targeted drugs like olaparib, may help us reach the point where cancer can be viewed as a lifetime condition to be managed much in the manner as HIV/AIDS is managed today.”

Barbara Shellow has been taking olaparib since July 2007 and has been in remission since October of the same year. That is good news, indeed, considering that since her diagnosis of stage 4 peritoneal cancer in 1997, and then her second diagnosis of breast cancer—also in remission—Barbara has endured numerous surgeries and four or five different regimens of intravenous chemotherapy. “What I am most happy about is not having to sit in that chemotherapy room for hours at a time and put up with nerve damage and thinning hair and all those awful side effects, one of which had me circling the drain,” she says.

So far, Barbara has had no side effects directly related to olaparib. She hopes to remain on the study drug for as long as possible. “I feel like I was in the right place at the right time for this clinical trial,” she says. “And I owe it all to Dr. Karlan. I can’t thank her and her team enough for that.” Barbara picks up the baggy of pills, gives it a little pat, and drops it in her purse. “I am living a normal life again,” she says.  

**Herceptin: The Targeted Drug Archetype**

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