Search for New Treatments Intensifies for Triple-Negative Breast Cancer

By Vicki Brower

Many physicians consider triple-negative breast cancer (TNBC) the most difficult type to treat, and some patients think it is a death sentence. This subtype of breast cancer is extremely aggressive, has limited treatment options, and carries a high risk of recurrence and death. Unlike breast cancers that express hormone receptors for estrogen and/or progesterone and over-express the HER-2/neu protein, TNBC is negative for all three proteins, so it cannot be treated with drugs specifically targeted at them. Although TNBC accounts for only 15% of breast cancer, it causes a disproportionate number of deaths, particularly among young, black, and Hispanic women, and those with BRCA1 and BRCA2 mutations.

But a spate of recent studies has some experts feeling more optimistic. “Triple negative breast cancer is now receiving a tremendous amount of research,” said Lisa Carey, M.D., medical director of the UNC Breast Center of the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill. That research includes the development of new molecular targets and drugs aimed at them, including poly(ADP–ribose) polymerase (PARP) inhibitors, which drew national attention after this year’s meeting of the American Society of Clinical Oncology. Analyses of larger breast cancer trials are yielding clues about possible drug combinations for TNBC. And promising leads are coming from basic and translational laboratories, according to Harvard’s Eric Winer, M.D., who heads the breast oncology center at the Dana–Farber Cancer Institute in Boston.

“I believe that we are on the verge of important discoveries that will have a lasting impact on the care we deliver to women with triple-negative breast cancer,” Winer said.

Paradoxically, TNBC cells are initially more sensitive to DNA-damaging effects of chemotherapy than are other breast cancer types. Chemotherapy kills TNBC cells more effectively than it does other cancer
cells because TNBC cells are particularly deficient in their ability to repair DNA. Nevertheless, relapse and overall survival are worse in TNBC.

For the same reason that chemotherapy works, TNBC cells are sensitive to PARP inhibitors, which produce double-stranded DNA breaks from which cells cannot recover. Researchers at the American Society of Clinical Oncology’s annual meeting reported that in a phase II randomized trial, the PARP inhibitor BSI-201, combined with chemotherapy, improved median overall survival in TNBC compared with chemotherapy alone (see News, J. Natl. Cancer Inst. 2009;101:1230–2). A phase III trial with BSI-201, sponsored by BiPar Sciences, a subsidiary of Sanofi-Aventis, opened in July.

**Vaccines**

PARP inhibitors, although furthest along in the pipeline, are not the whole story. One alternative strategy is to target TNBC with therapeutic vaccines. Andrew Simpson, Ph.D., scientific director of the Ludwig Institute for Cancer Therapy, New York, and colleagues reported in July in the *Proceedings of the National Academy of Sciences* that CT-X genes, which are normally expressed only in germ cell development, are expressed in TNBC. One of them in particular, called MAGEA3, is expressed in about 40% of women with TNBC. Because MAGEA3 is not active in the adult female body, but “turned on” only in cancer, it is an excellent target for a therapeutic vaccine, Simpson said.

Vaccines targeted at the MAGEA3 gene product, which is also known to be expressed in lung cancer and melanoma, are now being tested in phase II and phase III studies, respectively, by GlaxoSmithKline. “We therefore hope to persuade the company to conduct trials in TNBC,” Simpson said.

Another candidate target of an immunotherapeutic vaccine is the MUC-1 antigen, which is expressed in the vast majority of breast cancers, including TNBC, as well as in ovarian, lung, and prostate malignancies. Last year, Joseph Baar, M.D., Ph.D., director of breast cancer research at the Case Comprehensive Cancer Center in Cleveland, Ohio presented data at the 2008 San Antonio Breast Cancer Symposium to show that 92% of 53 analyzed TNBC tumors expressed MUC-1. “While both normal breast cells and cancerous TNBC cells express MUC-1, cancer cells express a different form of MUC-1, so it should be possible to target only cancerous cells with this variation,” Baar said.

A MUC-1 vaccine developed by University of Pittsburgh researchers is also being tested in pancreatic and prostate cancers. Working with them, Baar has developed a vaccine based on this antigen, which will begin testing later this year in early-stage TNBC patients following primary therapy with surgery, radiation and chemotherapy. In the new study, Baar will vaccinate up to 37 early-stage patients up to six times in order to raise an immune response against MUC-1. His aim is to eventually develop the vaccine as a long-term preventive therapy for TNBC. “We want to determine if it is possible to reduce relapse for women with TNBC who have completed primary treatment but who have a high risk of recurrence,” he said.

**More Targets**

Another potential target in TNBC is the epidermal growth factor receptor, EGFR (or HER-1), which plays a role in cell differentiation, proliferation, and survival. To date, trials with EGFR inhibitors have shown only modest activity in TNBC, so researchers have tried combining them with other targeted drugs and chemotherapy.

Two years ago, Carey and colleagues reported that the EGFR inhibitor cetuximab (Erbitux) combined with carboplatin produced better response rates than cetuximab alone in a randomized phase II trial. Recurrence, however, was rapid.

Other trials under way with EGFR inhibitors include a phase II study of erlotinib (Tarceva) as a single agent at the University of Texas M. D. Anderson Cancer Center in Houston. Another trial, at the University of Kansas, is combining erlotinib with chemotherapy in TNBC patients.

Researchers have also identified the Src oncogene as a potential target in breast cancers, including TNBC. Src and its family members play a crucial role in cellular growth and proliferation, angiogenesis, invasion, and metastasis, according to Carmelo Bengal, M.D., of the University of Modena, Italy. At last year’s San Antonio Breast Cancer Symposium, Richard Finn, M.D., Bengal, and colleagues reported that in a phase II trial of 43 advanced TNBC patients, the Src inhibitor dasatinib (Sprycel) produced only “modest” activity as a single agent.

“We were disappointed because preclinical work indicated that dasatinib [substantially] inhibits this subtype of breast cancer,” Bengal said. He added that combining dasatinib with other agents, such as doxorubicin, taxanes, and/or angiogenesis inhibitors, might improve results.

Angiogenesis inhibitors have shown some promise. In an analysis of a trial in metastatic breast cancer, comparing paclitaxel alone to paclitaxel with bevacizumab (Avastin), the drug slowed clinical activity in patients with estrogen- and progesterone-negative cancer, most of whom were also HER2/neu negative, according to Kathy Miller, M.D., principal investigator and associate professor of medical oncology at the University of Indiana in Indianapolis. Overall, patients in the trial had an increase in progression-free survival but not overall survival. The trial results were published in 2007 in the *New England Journal of Medicine*, in which Miller reported receiving consulting and lecture fees from Roche. Two other metastatic breast cancer trials showed similar activity with bevacizumab in a subgroup of estrogen- and progesterone receptor–negative patients.

Despite these leads, an effective treatment specific to TNBC—what Finn calls the holy grail—remains elusive. Current guidelines, such as those from the National Comprehensive Cancer Network, simply recommend the same chemotherapies as those used for other breast cancers, excluding the treatments aimed at the three receptors that are “negative” in TNBC.

“There is no question,” Winer said, “that the treatment of triple-negative disease remains a major clinical challenge.”