

Breast Cancer: The Triple-Negative Problem

Joyce O'Shaughnessy, M.D., spent 10 years at NCI, initially as a Clinical Associate, then as a Senior Investigator and Special Assistant to NCI Director, Samuel Broder, M.D., and finally as a Senior Investigator in NCI's Intramural Breast Cancer Research Program. O'Shaughnessy is now a Medical Oncologist with Texas Oncology and the Baylor-Sammons Cancer Center in Dallas, Texas. She is also Co-Chair of the Breast Cancer Research Program at U.S. Oncology, a practice management company that operates clinical trials across its national network through a structure that resembles NCI Clinical Trials Cooperative Groups. A major focus of her clinical research is on triple-negative breast cancers.

Triple-negative breast cancers are defined by what they are lacking—they do not have the three molecular receptors known to fuel most breast cancers: estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). Metastatic, triple-negative breast cancer has a very poor prognosis, with a median survival of only about one year, and there is no standard-of-care therapy.

Triple-negative cancers share similarities with hereditary *BRCA1*-related breast cancers, namely dysregulation of *BRCA1*, which leads to defects in repair of double-stranded breaks in DNA. Thus, we and others have wondered whether we could develop therapeutic strategies that exploit this defect in DNA repair. Poly-ADP ribose polymerase (PARP) inhibitors were identified as agents that could further disrupt DNA repair in breast cancer cells, thus rendering

them particularly vulnerable to DNA-disrupting chemotherapeutic agents like gemcitabine and carboplatin.

We recently conducted a phase 3 clinical trial of these standard chemotherapeutic agents with and without the PARP inhibitor, iniparib. We saw a promising signal of iniparib benefit in second and third-line patients but, disappointingly, the overall population did not benefit. We believe that this inhibitor may provide even greater overall benefit if we can identify the right subset of patients. As with many cancers, a particular challenge these days is to better define the subtypes of triple-negative breast cancer. Not all of them have the same DNA repair problems; not all of them even have the same cell types of origin.

Working with Populations

I am involved in a wide variety of clinical trials for high-risk, potentially lethal breast cancers.

The majority of my work involves patients with triple-negative breast cancer because it is such a large unmet medical need.

I have developed a particular interest in correlative tissue biomarker studies for triple-negative breast cancer. A few years ago, my colleague Lisa Carey, M.D., and I reported data at the San Antonio Breast Cancer Symposium that the epidermal growth factor receptor inhibitor, cetuximab, showed some activity in breast cancers that are triple negative. We are working on a follow-up study with an intensive biomarker discovery component, in which we hope to understand how to predict the really long benefit—the multiyear remissions—that we have seen in a subset of patients.

One of the reasons I came to Texas Oncology is because I felt they were very prescient in starting community-based clinical research

back in the late 1980s. Although large clinical trials were once the domain of NCI and the academic medical centers, currently, accrual to larger phase 3 trials, even within the NCI cooperative groups, mostly comes from the community setting. And U.S. Oncology has at least 10 practices that do collaborative phase 1 work, making many of those investigational agents available outside the academic setting. I remember a time in the early 1990s when I looked around and realized that there was just a tremendous amount of research going on in the community. In part, I attribute that proliferation to the NCI's training of so many talented Oncology Fellows who are able to carry on the principles of clinical research outside of academia.

Working with Individuals

In addition to conducting large-scale clinical trials, I am also engaged in a project with the Translational Genomics Research Institute (TGen) in which we harvest and analyze transcriptome data from patients' metastatic triple-negative breast cancer tissue. We are not just describing the mutational abnormalities; we are using this data to identify the most productive targetable mutations in an individual patient and then treating the patient with corresponding investigational drugs or off-label agents.

For example, we found clear indications of important mutations in the phosphatidylinositol 3 (PI3) kinase pathway in the first patient whose tumor we sequenced, and on the basis of those mutations, I made a referral for her to start on a phase 2 study of a promising PI3 kinase inhibitor. This is a patient I have been caring for, for years—she was diagnosed about four years ago, received preoperative chemotherapy followed by a mastectomy, and then found that the cancer recurred two years later in her lungs, lymph



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nodes, and chest wall. She has since been treated on two clinical trials, but her cancer has progressed each time. Between those therapies, we harvested tissue and it has taken a few months to get the sequencing results. But now, she is being treated with an agent that specifically targets a driving mutation in her cancer.

Where We Go from Here

The standard cytotoxic agents are, by themselves, only going to cure a small minority of newly diagnosed patients. To me, a cure is not necessarily a complete eradication of the disease at a microscopic cellular level; it is never seeing that life-threatening breast cancer again in a woman's lifetime. This may involve long-term therapies—already, breast cancer patients may take anti-estrogen therapies for a decade or

more. I think about the current AIDS therapies, which basically suppress but do not eradicate HIV and which provide convergent combination therapies focused on one or two essential HIV enzymes.

I am encouraged by the fact that we are increasingly differentiating among the several different types of breast cancers, we are understanding some of the driving biological factors in these cancers, and we now have some solid leads for therapeutic interventions. Clinical research in breast cancer is dramatically different from what it was during my early years at the NCI. In those days, when we did clinical trials, it didn't matter what subtype of breast cancer you had. If you had breast cancer, you could enroll. So, I am definitely encouraged by our advances in the last two decades, but we still have miles to go.