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## Negative, Negative, Negative!

One never heard of triple-negative breast cancer 5 years ago. Papers would distinguish estrogen receptor (ER)-positive from ER-negative, and HER2-positive from HER2-negative cancers, but somehow we failed to make the intellectual leap to thinking of ER-, progesterone receptor-, and HER2-negative tumors as a distinct category from a biologic or therapeutic standpoint.

Now, that has all changed. The change has occurred in part because of the burgeoning genomics literature, which suggests that triple-negative breast cancer is actually something positive, a special biologic category (now called the basal or basaloid subtype) that plays by its own rules. In part, the new interests reflect our realization that BRCA1 tumors are typically triple-negative. The realization that young black women are preferential targets for this disease has also attracted notice. And finally, I suspect, the new interest represents simple human curiosity, the yearning of scientific explorers to plant a flag on the last remaining large piece of *terra incognita* on the breast cancer map.

The naming of things has a power all its own. It focuses interest and energies, in this particular case, on a group of cancers that lacks the easy biologic targets that have made ER-positive and HER2-positive disease treatable entities. Knowing that the subtype exists (if it is just one subtype, which may not be the case) motivates researchers to investigate it in the clinic and in the laboratory.

In the clinic, triple-negative breast cancer is currently treatable with 2 classes of systemic therapy: chemotherapy and antiangiogenic therapy. Chemotherapy is the adjuvant mainstay and is certainly effective for many women. Indeed, much of the progress achieved with adjuvant chemotherapy in breast cancer may be focused in these patients, with their proliferation gene signature and rapid growth phenotype. Some preclinical evidence suggests the possibility of preferential chemosensitivity for DNA-damaging agents, though this remains unproven. Antiangiogenic therapy, administered with chemotherapy, appears to offer significant progression-free survival benefit in the first-line metastatic setting and is moving into the adjuvant setting.

Still, clinicians and patients yearn for more, and more may be on the way from the laboratory. Preclinical data suggests the possibility that new classes of agents affecting DNA repair (eg,

PARP inhibitors) might benefit the fraction of triple-negative tumors with *BRCA1* mutations, and perhaps more. Such agents are entering clinical trials. They are pioneers in this new territory, with many more to follow. It has not escaped the notice of the pharmaceutical and biotech industries that these cancers represent an unmet medical need, leading to an explosion of focused trials. This is quite a change from even 3 or 4 years ago, when no focused therapeutic trials existed in this area.

In addition to the obvious need for new agents, other questions exist in the triple-negative universe. Calling a tumor "triple-negative" is not a particularly useful definition. Can pathologists and molecular pathologists define these tumors in operationally useful terms? Can we get a better handle on the etiologic and chemopreventative aspects of these tumors? Are there populations of patients with triple-negative breast cancer who will not require adjuvant therapy, and can we develop proteomic or genomic signatures that will identify such patients? What is the role of breast stem cells in triple-negative breast cancer? Are there current chemotherapeutic agents that don't work for these cancers and, therefore, should be avoided? All good questions—all to be answered in the fullness of time.

Triple-negative disease represents something of a black hole for patients, given the current lack of targeted therapies or even a significant scientific literature. This may be changing as well. The Triple Negative Breast Cancer Foundation now offers a useful Web site for patients ([www.tnbcfoundation.org/tnbc/home.asp](http://www.tnbcfoundation.org/tnbc/home.asp)) and has recently sponsored (with the Komen for the Cure Foundation) a symposium for researchers in the area. No doubt, the interest of concerned advocates will help to inspire and focus researchers as it so often has in the past.

Will "negative, negative, negative" become something positive in the near future? Is the next tamoxifen- or trastuzumab-equivalent just around the corner? No one can say. But it is already clear that triple-negative breast cancer is no longer a hidden scourge. It is in our sights, a target for all.

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