ALK Gene Amplified in Most Inflammatory Breast Cancers

By Rabiya S. Tuma

Inflammatory breast cancer (IBC) is a rare form of the disease that differs substantially from noninflammatory breast cancer in presentation and response to therapy. Despite those differences, researchers have uncovered few molecular characteristics that distinguish IBC from noninflammatory breast cancer, and IBC treatment generally relies on standard breast cancer regimens.

Now, Frederika Robertson, Ph.D., professor of experimental therapeutics at the University of Texas M. D. Anderson Cancer Center in Houston, and colleagues report that ALK gene amplification is a common feature of IBC tumors and that small-molecule ALK inhibitors are effective in mouse xenograft models. On the basis of those preclinical data, clinical investigators have started enrolling IBC patients in a phase I trial testing an experimental ALK inhibitor, Robertson reported at the AACR–NCI–EORTC Molecular Targets and Cancer Therapeutics Conference in San Francisco.

“This disease is so difficult that if we can find something like the ALK amplification and can inhibit it, we should try it in a clinical trial,” said Beth Overmoyer, M.D., from the Breast Oncology Center at the Dana–Farber Cancer Institute in Boston, who was not involved in the work.

Uncovering a New Target

Robertson’s discovery came as part of a larger effort in which her team was using genomic and proteomic tools to characterize the biology of IBC (see “Elucidating an Uncommon Disease: Inflammatory Breast Cancer,” J. Natl. Cancer Inst. 2011;103:1358–60). During a proteomic pathway analysis, Robertson’s collaborators Lance Liotta, M.D., Ph.D., and Emanuel Petricoin, Ph.D., codirectors of the Center for Applied Proteomics and Molecular Medicine at George Mason University in Manassas, Va., noticed that the ALK pathway was as activated in three different IBC cell lines as it was in ALK-driven non–small-cell lung cancer models.

Later genomic experiments showed that the ALK gene is amplified in the IBC cell lines and in nine of the 12 patient tumors analyzed. Thus far, the team has not detected activating mutations in the ALK gene, which are common in non–small-cell lung cancer.

“This may be a very prevalent genetic change in IBC,” Robertson said. “But we really believe that if we had not been doing this tandem proteomic–genomic approach, we might have missed it. So we really need to use all of the resources that we have.”

Crizotinib (Xalkori), a small-molecule inhibitor of ALK that the U.S. Food and Drug Administration recently approved for lung cancer therapy, arrested growth of IBC cells in culture and activated the cell death pathway. Moreover, xenograft IBC tumors were resistant to paclitaxel but sensitive to low doses of crizotinib, which caused tumor shrinkage.

Quick Move to Patient Trials

Given the preclinical data and the unmet treatment needs in IBC patients, Massimo Cristofanilli, M.D., chair of the medical oncology department at Fox Chase Cancer Center in Philadelphia and a collaborator on the preclinical studies, opted to enroll IBC patients in an ongoing phase I study testing LDK378. “Taking advantage of the phase I trial gives us the opportunity to test this drug very early on in patients with this disease,” he said.

Thus far, three IBC patients have enrolled in the trial, though Cristofanilli said it was too early to comment on responses. The research team is considering a larger trial specifically for IBC patients but have not yet settled on a detailed plan. The collaborators are interested in crizotinib and have been talking with Pfizer, which owns the drug, according to Robertson.

An Aberration Apart

“The disease is so aggressive clinically—and patients usually respond so poorly to therapies used in the usual form of breast cancer—you would expect there is a major driver or different kinds of drivers that are responsible for this clinical behavior,” Cristofanilli said. However, until now, investigators have largely focused on genetic abnormalities known to affect noninflammatory breast cancer. For example, a high frequency of TP53 mutations occurs in IBC; approximately 40% of IBC tumors express high levels of HER2; and triple-negative disease, which lacks expression of hormone receptors and HER2, is more common in IBC than in noninflammatory breast cancer. “But we have never had something unique for IBC compared with other forms of breast cancer,” Cristofanilli continued. “I think this is a promising finding because there are drugs that are available to target this aberration.”

Overmoyer agrees. Although she thinks it is too early to say whether this is a breakthrough, any new information about the biology is welcome. “It is very important to understand what differentiates this disease
from noninflammatory breast cancer," she said in a phone interview.

“This is the type of disease where we don’t know all that much, and the treatments we have are not all that successful,” Overmoyer said. “So given the fact that [Robertson] has the data, we should go forward with a larger clinical trial—and you don’t need a lot of patients to see if the drug is going to hit its target.” Given the relatively accessible nature of IBC tumors, she said investigators should be able to get pre- and post-treatment biopsy samples and analyze them for changes in gene expression and tumor phenotype. “If you are really hitting the target in a human being, you’ll know quickly.”

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