NCI Launches an Innovative Design for a Breast Cancer Clinical Trial

A new clinical trial will use a comprehensive genetic profile to test whether early-stage breast cancer patients need chemotherapy.

The National Cancer Institute-sponsored trial is among the first to tailor a patient’s therapy to her individual genetic profile. Many researchers say this as yet unproven approach is a logical step in cancer treatment. “It’s very different. It’s very novel because it’s really testing a signature for a certain stratification of patients. It’s the first time this has really been done in a treatment trial,” said James W. Jacobson, Ph.D., of NCI in Bethesda, Md.

Designed to evaluate whether women with lymph node-negative, estrogen receptor (ER)-positive, early-stage breast cancer need chemotherapy, the Trial Assigning Individualized Options for Treatment (TAILORx) uses a 21-gene test known as Oncotype DX. The test, which has been used in several recent studies, produces a genetic profile that the researchers will then use to calculate an individual’s risk of breast cancer recurrence and assign patients to treatment groups. Several scientists think that this tailored approach may be a model for trial design in the future.

From Past to Present

These early-stage breast cancers represent about half of the cases diagnosed in the United States. Currently, women diagnosed with tumors larger than 1 cm receive a combination of hormone therapy and chemotherapy, whether they are pre- or postmenopausal. However, for patients with tumors less than 1 cm, doctors don’t know when chemotherapy is useful for preventing recurrence or when hormone therapy alone is enough. The present chemotherapy guidelines for these tumors are vague—women younger than 50 years receive chemotherapy approximately 75% of the time, whereas women aged more than 70 years receive chemotherapy only around 5% of the time.

Jo Anne Zujewski, M.D., of the National Institutes of Health, says that toxicity and other side effects make chemotherapy an undesirable treatment unless women derive a substantial benefit. “Thousands of women are receiving toxic therapies. We had to find a way to make this better.”

Enter TAILORx. The trial, launched May 23, will assess the treatment options for 11,000 patients with ER-positive, node-negative, early-stage breast cancer. It is based on results from the National Surgical Adjuvant Breast and Bowel Project (NSABP), where doctors assessed gene expression in tissue samples from similar breast cancer patients by using Oncotype DX. That study suggested that patients designated as high risk by Oncotype DX test received a large benefit from chemotherapy, whereas patients designated as low risk received little or no benefit.

Oncotype DX works by looking at the expression of 21 genes. The genes range from those commonly tested in breast cancer treatment, like ER, PR, and HER2, to less commonly tested genes including GAPDH, STK15, and cyclin B1. The test marks an improvement in the complexity of the molecular analysis used to assign therapy, Jacobson says. In past trials, the treatment groups were assigned on the basis of gene expression data from a few genes.

Doctors will use the gene expression data to calculate a patient’s chance of recurrence on a scale from 1 to 100. Patients with a recurrence score less than 18, or low-risk, will be given only hormonal therapy. A score more than 30, or high-risk, means that patients
will receive hormone therapy and chemotherapy. Patients with intermediate scores will be randomly assigned to receive hormone therapy or hormone therapy and chemotherapy combined.

“With TAILORx, we hope to gain a better understanding of the effects of chemotherapy for those patients with midrange scores, building upon what we’ve already learned in an effort to individualize treatment for all women with early-stage breast cancer,” says Soonmyung Paik, M.D., director of the NSABP division of pathology.

In addition to evaluating the benefits of chemotherapy, TAILORx will create a tissue bank of biological samples, tumor samples, blood plasma, and DNA from patients enrolled in the trial. Researchers hope to use these samples for future clinical cancer trials.

Moving Forward

In tailoring therapy to a diverse range of gene expression, TAILORx is the first trial of its kind.

“There really haven’t been any breast cancer trials conducted in the way that this one is being done. You could talk about trials measuring single markers, but this is the first time a signature of risk has been tested in this way,” Jacobson says. “I think this will be kind of a model for how trials of this type will be done in the future.”

Jacobson says that Oncotype DX marks the kind of test of multiple biomarkers that scientists may expect in future trials. Trials may assess even more biomarkers as scientists are further able to uncover the genetic and biological mechanisms behind developing cancer. “Oncotype DX is a very well-characterized, well-developed, carefully designed test. It’s of great interest.”

Others say that although Oncotype DX is a great test for assessing the use and benefit of chemotherapy in breast cancer patients, it’s nothing revolutionary. “This is not a new concept; long ago it was node negative versus positive, then we found out that hormone receptor status was important, and then we added HER2/neu expression,” says Donn Young, Ph.D., of the Ohio State University Comprehensive Cancer Center in Columbus. “Genetic markers, such as Oncotype DX, may prove to be the next step to improved care for thousands of women with breast cancer.”

Most researchers think that TAILORx will make a difference by getting patients the treatment they need and steering them away from therapies that may do more harm than good. More importantly, it will provide a definitive solution to the puzzle of how to treat a large contingent of women at intermediate risk for breast cancer recurrence.

Carolina Hinestrosa, executive vice president of the National Breast Cancer Coalition, says that the challenge now is to get women to enroll in the study.

“We have been in the mindset of ‘more is better’ in medicine…. I think once people understand that we have been overtreating patients, patients will gladly give up the toxic side effects of chemotherapy. They will gladly escape treatments that are so harsh and so difficult,” she said.

“If we have this objective way to determine who will benefit from chemotherapy, everyone is going to be better off in the end. We really believe that this will resonate with the patients.”

—Ariel Whitworth

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