A Big Trial for a New Technology: TransBIG Project Takes Microarrays Into Clinical Trials

Researchers already use the tools made possible by genomics and proteomics to categorize otherwise indistinguishable tumors and to correlate molecular features with the likelihood of treatment response or with prognosis. But as useful as those techniques are for providing research information, such tools have not been put to the test in prospective clinical trials.

That, however, is about to change. A European consortium plans to initiate a prospective randomized controlled trial early in 2005 in which cancer therapy will be determined in part by microarray gene expression analysis. The trial will test whether a gene expression pattern is more effective than common clinical-pathological criteria at determining which node-negative breast cancer patients can safely bypass adjuvant chemotherapy.

Doctors now use the classic disease and patient characteristics—tumor size, lymph node status, pathological grade, hormone receptor status, and age—to determine whether to recommend that a woman should receive adjuvant chemotherapy. However, even the consensus guidelines from the National Comprehensive Cancer Network, the National Cancer Institute, and the St. Gallen conference do not agree on how to treat young women with node-negative breast cancer, said Martine J. Piccart-Gebhart, M.D., head of Molecular Pathology at the Jules Bordet Institute in Brussels, Belgium. In the United States, 95% of such patients are eligible for adjuvant chemotherapy, and 85% are in Europe.

Although adjuvant therapy has been shown to reduce the relative risk of recurrence by about 35% in both node-negative and node-positive cancers, the absolute reduction in risk is not equivalent between the groups. For node-positive patients, the risk of recurrence drops from an absolute risk of 65% to 42% with adjuvant therapy, Piccart-Gebhart said. By contrast, the absolute risk reduction is only 7%, from 20% to 13%, in node-negative patients.

"Remember this is an average risk," Piccart-Gebhart said. "Accumulating evidence shows that a subset of patients have a much larger benefit, while others have a much lower benefit."

Retrospective Analysis

Given these data, Laura J. van’t Veer, Ph.D., head of Molecular Pathology at the Netherlands Cancer Institute in Amsterdam, and colleagues set out to determine whether they could more accurately distinguish which patients are at high risk of recurrence by using gene expression profiling.

The team started with a microarray containing approximately 25,000 genes and found about 5,000 genes that were differentially expressed. They identified an expression profile consisting of 70 genes that was able to predict disease recurrence in women who had node-negative cancer, were younger than 55 years of age, and whose tumors were smaller than 5 centimeters in diameter.

When they validated this 70-gene profile on samples from 295 breast cancer patients who were treated between 1983 and 1994, they confirmed the profile’s ability to identify women at low risk of recurrence. Notably, none of the women in the node-negative sample were eligible for adjuvant chemotherapy at the time of their diagnosis (prior to the St. Gallen consensus). Yet those placed in the low-risk category by the microarray analysis had a 96% probability of overall survival and 87% likelihood of disease-free survival for 10 years, whereas those with a high-risk profile had a 50% overall survival and 48% probability of disease-free survival for 10 years. Thus, the microarray pattern was able to identify patients who were at low likelihood of recurrence in the absence of adjuvant therapy. "We purposely developed a model to predict the highest accuracy the patients in the low-risk group," van’t Veer said.

Additionally, the gene profile method assigned more women (40%) to the low-risk category than did either the St. Gallen (15%) or the NIH (7%) criteria. This means, said both Piccart-Gebhart and van’t Veer, that if the expression profile were used to determine treatment, a large number of women would be saved the trauma of chemotherapy without substantially increasing the risk of recurrence for the population as a whole.

Multicenter Confirmation

Before proceeding with a randomized prospective trial, several laboratories from a large translational research consortium called TransBIG—a network involving about 40 partners in 21 countries that is the "sister" to the Breast International Group (BIG)—will complete a retrospective analysis to determine whether van’t Veer’s results are reproducible in a more diverse population and in a multicenter setting.

This retrospective analysis, coordinated by Christos Sotiriou, M.D., from the Jules Bordet Institute, is already under way, with 168 samples coming from four centers in France, the United Kingdom, Sweden, and The Netherlands. Researchers in Belgium, The Netherlands, and France are performing the microarray analyses. The TransBIG consortium expects the results from this validation early this summer.
If these data are consistent with the Dutch group’s results, TransBIG will launch a 5,000-patient prospective randomized trial called MINDACT, which stands for molecular-based adjuvant trial for node-negative breast cancer patients. The MINDACT trial design is still being finalized by BIG and the European Organization for the Research and Treatment of Cancer (EORTC), the TransBIG partner and BIG member group that will manage the trial. The current plan is for patients who consent to participate, and for whom there are properly processed biopsy samples, to be randomly assigned to one of two arms. In the control arm, physicians will evaluate patients by using standard histopathological and clinical criteria and will treat them with adjuvant therapy as appropriate. In the experimental arm, the researchers will analyze the tumor samples with the 70-gene profile and determine treatment based on whether the patient falls into the high- or low-risk categories.

On the basis of previous data, about 20% of the women in the control arm are expected to fall into the low-risk category, while 40% of the patients in the microarray-determined arm are expected to be low risk. These women will be offered endocrine therapy if appropriate but will not receive adjuvant chemotherapy. Women who are determined to be at high risk of recurrence based on either set of criteria will be treated with adjuvant chemotherapy and endocrine therapy as appropriate.

The primary goal of the trial is to determine if there is any inferiority of treatment outcome during a 5-year follow-up in the microarray arm compared with controls, while treating 20% to 25% fewer women with chemotherapy. An independent monitoring committee will assess the number of recurrence events in the two low-risk groups at 1- and 3-year follow-ups as well as patient safety.

Community Counsel

During presentations at the recent American Association for Cancer Research in Orlando, Fla., numerous scientists, including Piccart-Gebhart, called for increased use of molecular markers and molecular diagnostics in the clinic. However, many of these researchers also emphasized the need for standardization in the technologies and testing platforms, an issue that should be addressed by the ongoing retrospective phase of TransBIG’s project.

Several scientists noted that tools such as these are a rapidly evolving technology. The MINDACT results will not be available until sometime in 2010, given the 5-year follow-up required for the data to mature. With this long lead time, researchers must consider whether the platforms and study design being tested will remain relevant when the study is completed.

“There is a danger in starting a trial too soon,” said Larry Norton, M.D., director of breast cancer programs at Memorial Sloan-Kettering Cancer Center in New York. “Most trials accrue patients slowly, not in the first 6 months.” If the level of sophistication of the technology or questions increases dramatically in a year or two, and accrual follows the typical pattern, he worries that the data will end up being meaningless. That said, he points out that the only way anyone is really going to know if microarrays will work in a clinical setting is to do a well-designed trial.

“I think this is a very timely trial,” said Edison T. Liu, M.D., executive director of the Genome Institute of Singapore and a former adviser on the MINDACT trial. “I have always been disappointed that we aren’t using molecular strategies to prospectively stratify [breast cancer patients] more, even before microarrays. This is where we need to be,” he said in reference to the ongoing TransBIG effort. He also noted that there is a big difference between designing a two-arm trial to test the efficacy of a molecular diagnostic and simply laying such a technique on top of an otherwise finished trial that was designed to test something else, as is commonly done. This direct clinical test using a two-arm trial, Liu said, is the only way to know if it will work.

Moving Forward in The Netherlands

While the larger international consortium is working to replicate van’t Veer’s work, her own group is moving forward with a test to assess the clinical value of the technology and its cost-effectiveness.

The Netherlands Health Insurance Council, which is a government body that oversees private insurance companies and determines what they must reimburse for, and The Netherlands Cancer Institute are cosponsoring a study to look at whether and how physicians will use microarray data during clinical decisions. The agencies also want to learn whether the test saves money by lowering the overall cost of chemotherapy by reducing the number of patients who take it.

The team is currently working on a pilot study with 75 breast cancer patients, half of whom have already been recruited. In this trial, the physician evaluates the patient as he normally would, using standard criteria. In addition, biopsy samples are analyzed using the 70-gene microarray pattern, and the risk category information is provided to the physician. It is up to the doctor and the patient to decide how to use that information, although the doctor is asked to report back and tell the researchers whether it influenced their decision-making process.

Thus far, both patients and doctors have been very enthusiastic about the opportunity to participate and gain access to the extra information. “We have doctors from other hospitals calling to ask if they can participate,” van’t Veer said. Five hospitals are participating, and all of the tissue samples are analyzed in a central laboratory. If the pilot continues to do well, the trial will expand to include 3,000 more patients and more hospitals.

“It would be a crime not to prospectively test this technology,” said Daniel D. Von Hoff, M.D., director of the Arizona Health Sciences Center’s Cancer Therapeutics Program in Tucson, Ariz. “Many patients are already asking for such tests. This could be one of the most significant findings on the way to personalized medicine.”

—Rabiya S. Tuma