Individualized Care for Patients with Cancer — A Work in Progress
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During the past two decades, molecular biologists have been dissecting the heterogeneity of human cancer — a diversity that oncologists have long appreciated, especially because patients who have similar stages and grades of cancer and whose tumors have similar histologic features have a broad range of clinical outcomes. Some cancers respond to treatment; others do not. Some patients have a recurrence of cancer; others are cured.

Molecular markers promise the ability to estimate prognoses and predict responses to particular treatments with greater precision than is possible with clinical findings. With further refinement of molecular diagnostics, the care of patients with cancer might be individualized: treatment would be reserved for patients at greatest risk of recurrence, and therapy would be chosen according to its ability to target the abnormalities of a particular cancer while minimizing the effects on normal tissues. Individualized treatment of cancer would require the development and careful validation of robust markers that not only meet critical clinical needs but also lend themselves to ready application in the community.

In this issue of the Journal, Paik et al. report the development of a biomarker for predicting the recurrence of breast cancer after hormonal adjuvant therapy. The authors have identified a critical clinical need in the care of patients with breast cancer. Several studies have shown that the addition of adjuvant chemotherapy to hormonal therapy improves the survival of both premenopausal and postmenopausal women with estrogen-receptor–positive breast cancer. However, the magnitude of the benefit is more modest among women older than 50 years. Current guidelines recommend chemotherapy for most women with a primary breast cancer larger than 1 cm in diameter, regardless of the status of the axillary lymph nodes. However, less than 20 percent of patients with negative axillary nodes will have a recurrence within 10 years after treatment with tamoxifen. Consequently, chemotherapy may be given to a majority of women who might be cured with locoregional treatment and tamoxifen alone. More precise prediction of risk could spare patients the toxicity of chemotherapy.

In a carefully considered series of studies designed specifically to address this problem, Paik et al. identified 21 genes that can be detected by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) analysis from a larger panel of genes that have been implicated in the pathogenesis of breast cancer. This approach is in contrast to prognostic tests for breast cancer that depend on the pattern of expression of large numbers of genes in microarrays. By focusing on a small number of distinctive genes, Paik et al. found that patients could be grouped into categories of risk with rates of distant recurrence at 10 years of 6.8 to 30.5 percent. The group at lowest risk would, presumably, not require chemotherapy, since the advantage in survival would be offset by a similar rate of life-threatening short-term or long-term toxic effects.

The biomarker panel was developed in a logical
sequence of analyses, facilitated by the availability of high-throughput, real-time RT-PCR, which can be performed on sections of paraffin-embedded, formalin-fixed tissue. Some 250 candidate genes were selected from the literature, genomic databases, and the results of DNA-expression arrays performed on fresh-frozen tissues. Gene expression was correlated with breast-cancer recurrence in patients who had participated in three independent breast-cancer studies, including patients in the tamoxifen-only group of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-20. A panel consisting of 16 cancer-related genes and 5 reference genes was selected, and an algorithm was used to compute a “recurrence score” for each tumor sample. Tissue from the tamoxifen-treated group in NSABP trial B-14, for which mature clinical data were available, served as a validation set, permitting the correlation Paik et al. now report.

These studies underscore the value of maintaining banks of tissue from large, well-executed clinical trials for prompt validation of new biomarkers. Remarkably, adequate RT-PCR profiles were obtained from more than 98 percent of the paraffin blocks, which had been stored for more than a decade. Since paraffin sections are available from virtually every patient with breast cancer, this technology could be moved rapidly from the research laboratory to community hospitals.

Before use of the recurrence score is applied to general patient care, however, additional studies are needed. Does the recurrence score predict prognosis in women who are not exposed to systemic therapy? Using the same assay and analysis, Esteva et al. found no correlation with local or distant recurrence in 149 selected patients with node-negative breast cancer who had not received adjuvant systemic therapy. It could be hypothesized that the utility of the assay is restricted to estimating the prognosis of patients who are receiving tamoxifen and thus that it can predict the response to antiestrogen therapy. The absence of estrogen receptors in a tumor is an excellent predictor of resistance to tamoxifen. Conversely, only 20 to 50 percent of patients with an estrogen-receptor–positive tumor have a response to tamoxifen therapy. Therefore, a new test with improved predictive value might be a useful addition to the care of women with breast cancer.

Another interpretation of the study by Esteva et al. is that the promising results reported by Paik et al. may be difficult to replicate. Additional retrospective analyses of patients in the control groups of large studies as well as patients who receive tamoxifen as adjuvant therapy will help to place the utility of the test in perspective. In performing these studies, use of multiple laboratories would confirm the general applicability of the assay. Since aromatase inhibitors are being used increasingly widely for primary adjuvant therapy in postmenopausal patients, it will be important to confirm that the recurrence score applies to all forms of hormonal adjuvant treatment. Although prospective trials would be ideal, additional retrospective studies might provide reassurance that this very promising panel of biomarkers accurately predicts recurrence in women with receptor-positive, node-negative breast cancer who receive hormonal adjuvant therapy.

Are there other potentially useful applications of this 21-gene panel in the management of breast cancer? There is much interest in identifying accurate predictors of the response to chemotherapy, and preliminary work with gene-expression profiles appears promising. The panel evaluated by Paik et al. includes not only estrogen-induced genes, but also genes related to proliferation and the cell cycle. Therefore, this panel might predict responsiveness to chemotherapy, a hypothesis that could be tested retrospectively in large, randomized trials with the use of stored paraffin blocks. Ongoing work with RT-PCR analysis based on a larger number of genes than those included in the calculation of the recurrence score suggests that the response to preoperative chemotherapy can be predicted with this technique. Since RT-PCR can be successfully performed on stored material, the practical advantages of this approach over microarray-based analysis that can be performed only on fresh tissue are obvious. This is an exciting work in progress. Additional validation in independent laboratories with the use of biopsy specimens from other clinical trials should provide complementary information to help determine the role that the recurrence score might play in the care of patients with primary breast cancer.

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