The New Generation of Targeted Therapies for Breast Cancer

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The article by Drs. Syed and Rowinsky is well written and comprehensive. They introduce several biologic pathways that are important in breast cancer and focus on new pharmaceutical agents designed to disrupt these pathways. Patients and physicians hope that agents that target the tyrosine kinase signal transduction pathways, block tumor angiogenesis, modulate apoptosis, and inhibit histone deacetylation will be effective, nontoxic therapies for breast cancer. These molecularly targeted approaches hold promise, but delivering on this promise requires that we move beyond histologic characterization of the disease and rethink the design of clinical trials.

Molecular Pathology

The most common histologic type of invasive breast carcinoma is infiltrating ductal carcinoma. This diagnosis, however, is achieved by default, in that such cases of breast cancer do not have specific histologic features that allow them to be categorized as lobular, tubular, mucinous, medullary, or inflammatory. Indeed, some pathologists use the term "infiltrating ductal carcinoma of no special type." Some of these cancers express receptors for estrogen, progesterone, and HER2; others will not. Decades of clinical trials have demonstrated that women with metastatic disease with estrogen-receptor (ER)- and progesterone-receptor (PR)-negative tumors have less than a 10% likelihood of responding to endocrine therapy. Those without 3+ overexpression of HER2 have a low likelihood of responding to trastuzumab (Herceptin). Thus, two of our most successful targeted therapies fail patients with tumors that are negative for the target. Molecular profiling has the potential to refine the pathologic diagnosis of breast cancer, improve prognostic accuracy, and predict which patients will respond to specific therapies.[1] Genomic analysis of human breast cancers, using complementary DNA microarrays reveals that what was morphologically a single entity is, in fact, several different subtypes of breast cancer.[2] The ability to analyze the expression of thousands of genes simultaneously will help us identify a molecular signature for tumors that will predict which pathways are driving cancer growth and which should be targeted for optimal response. Imatinib mesylate (Gleevec) therapy in chronic myelogenous leukemia provided stunning therapeutic benefit primarily because patients receiving therapy were positive for the target of the drug. In order for this success to be repeated in the development of targeted therapies for breast cancer, our biologic understanding and pathologic classification of the disease will have to advance as rapidly as our choice of agents for study. Molecularly targeted therapies offer the opportunity to dissect the pathways that permit cancer growth. The fact that these pathways are redundant and interrelated likely explains the failure of single agents such as gefitinib (Iressa) to produce significant response rates in patients with advanced breast cancer. It is time to design clinical trials to evaluate not only whether a new agent is effective in some women with breast cancer, but also which women will benefit, which will not, and why. Clinical investigators must partner with patients and pharmaceutical sponsors to investigate the modulation of targets of therapy, develop diagnostic tools for these targets, and identify how targets in one pathway interact with those in another. Patients enrolling in these clinical trials will need to be educated about the importance of granting permission for specialized analysis of their tumor samples, and how the information gained will improve therapy for all diagnosed with breast cancer. Clinical Trial Design

Molecular diagnostic and therapeutic breakthroughs are challenging our current clinical research methodologies. Careful selection of patients with disease expressing the target of therapy is necessary to prevent unrecognized molecular heterogeneity from resulting in an underpowered, falsely negative study of a new agent.[3] The traditional therapeutic end points of clinical trials
include increasing overall survival, regressing tumor lesions in association with clinical benefit, and palliating disease-related symptoms. Studies evaluating molecularly targeted agents also need to determine whether the pathway targeted is modulated by the drug. Most breast cancer growth results from multiple genetic aberrations, and targeting a single pathway is unlikely to result in a dramatic response. Rather, responses are likely to require combinations of targeted therapies that block various interrelated signals in multiple pathways. Assessing a new agent's ability to modulate its target is an additional important end point of the clinical trial evaluating its efficacy. The biologic pathways important in carcinogenesis and disease progression are clearly complex, interactive, and can become resistant to therapy via multiple mechanisms. This challenges us to define effective combinations of targeted therapy. Preclinical work has identified cross-talk between the HER2- and ER-signaling pathways as a potential mechanism of resistance to tamoxifen. However, numerous retrospective reviews have yielded mixed results regarding the impact of HER2 overexpression on response to tamoxifen therapy. The impact of HER2 may be modulated by the ER-coactivator AIB1 (SRC-3). Signaling through the HER2-receptor pathway activates AIB1 by phosphorylation. Analysis of the relationship between ER, HER2, and AIB1 in a series of patients treated with adjuvant tamoxifen reveals that patients with high HER2 expression and high AIB1 levels had poor disease-free survivals, whereas those with high HER2 but low AIB1 expression had favorable disease-free survivals.[4] The mixed results regarding tamoxifen resistance in ER-positive and HER2-overexpressing tumors may result from analysis of patients heterogeneous for AIB1. Dissection of the HER2- and ER-receptor crosstalk pathways supports the combination of endocrine therapy and inhibitors of signaling through the HER1 and HER2 pathways, such as gefitinib (Iressa)

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