Is There a Role for Epidermal Growth Factor Receptor Inhibitors in Breast Cancer Prevention?

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Growth and differentiation of both normal and malignant human breast cancer cells are known to be regulated by steroid hormone and peptide growth factor receptors. Among the peptide growth factor receptors frequently implicated in breast cancer are members of the type I receptor tyrosine kinase family, which includes HER1 (epidermal growth factor receptor [EGFR]), HER2 (c-erbB-2), HER3, and HER4. Hetero- and homo-oligomerization of these growth factor receptors results in tyrosine kinase activation, receptor phosphorylation, and subsequent activation of substrates involved in cellular signal transduction. In experimental models (1–3) and clinical correlative studies (4–7), it has been shown that the peptide growth factor receptor and steroid hormone receptor pathways are closely linked to one another. Growth factor receptor activation can result in direct phosphorylation and activation of the estrogen receptor (ER) in an estrogen-independent manner and lead to a ligand-independent reduced expression of ER (3). Transfection studies in hormone-sensitive breast cancer cell lines have demonstrated that increased expression of EGFR or HER2 promotes hormone-independent growth (1–3). Moreover, increased EGFR and HER2 expression has also been associated with acquired tamoxifen resistance in breast cancer cells that were initially hormone-sensitive (8). Importantly, treatment of EGFR- or HER2-transfected breast cancer cells with an EGFR or HER2 inhibitor resulted in the reversal of endocrine resistance and restored the sensitivity toward tamoxifen (9–11). Thus, breast cancer cells appear to have the capacity to switch between proliferation that is dependent on steroid hormones and proliferation that is dependent on growth factors, depending on whether the later pathway is activated or inhibited. A better understanding of the interaction between the steroid hormone receptor and growth factor receptor pathways will allow us to improve established therapies and develop new concepts for the treatment and prevention of breast cancer.

In the current issue of the Journal, Lu et al. (12) investigate the effect of gefitinib (ZD1839 or Iressa), an orally administered, selective, and reversible inhibitor of the EGFR tyrosine kinase, on the development of ER-negative breast cancer. Their study was intended to provide a preclinical rationale for the development of the EGFR inhibitor gefitinib as a potential preventive of ER-negative human breast cancer.

The concept of breast cancer prevention originally stemmed from the results of large adjuvant tamoxifen trials, many of them carried out by the National Surgical Adjuvant Breast and Bowel Project (NSABP), which showed a statistically significant reduction in contralateral breast cancer (13). With the support of these data, the NSABP began their breast cancer prevention trial (NSABP P-1) to evaluate the role of tamoxifen in reducing the risk of primary invasive breast cancer in women at increased risk of the disease (14). In this study, 13 388 women at increased risk of breast cancer were randomly assigned to 5 years of tamoxifen or placebo. A 49% reduction in invasive breast cancer occurred (175 tumors with placebo versus 89 tumors with tamoxifen); this reduction was mainly among ER-positive tumors (130 such tumors in the placebo group and 41 in the tamoxifen group). The results of more recent trials, such as the Multiple Outcomes of Raloxifene Evaluation (MORE) and the International Breast Cancer Intervention (IBIS) trials confirmed the effectiveness of antiestrogens such as tamoxifen and raloxifene in reducing the risk of breast cancer (15,16). In all of these studies, however, the reduction was confined to ER-positive tumors. It is in this precise situation that gefitinib appears to be specifically suitable for the chemoprevention of ER-negative breast cancer, because increased expression of EGFR or HER2 has been linked to the development of estrogen independence in preclinical experiments (1–3,8) and in clinical correlative studies (17–19).

The current work of Lu et al. (12) demonstrates that gefitinib statistically significantly delayed the formation of ER-negative tumors in an MMTV-c-erbB-2 transgenic mouse model (median time to tumor development was 230 days in untreated mice versus 310 days in treated mice; P<.001). The inhibition of HER2-driven tumor formation by an EGFR inhibitor is, however, somewhat surprising at first glance. Gefitinib is a small molecule inhibitor with specificity for the EGFR tyrosine kinase. Gefitinib inhibits the isolated EGFR and HER2 tyrosine kinase with 50% inhibitory concentrations of 0.033 μM and 3.7 μM, respectively (20). In intact cells, however, HER2 is known to be the preferred co-receptor for EGFR, HER3, and HER4 (21,22). The results of recent studies suggest that gefitinib interferes with HER2 function in intact cells by the formation of inactive unphosphorylated EGFR–HER2 heterodimers (23), which potentially explains the activity of an EGFR inhibitor in a HER2-driven tumor model. HER2 also increases the overall level of activated EGFR by both enhancing its recycling and reducing its internalization. Thus, EGFR inhibitors should be more effective in cells that overexpress HER2 than in cells that do not overexpress HER2, where EGFR recycling is reduced and internalization is enhanced (24).

Lu et al. (12) further demonstrate a strong growth-inhibitory effect of gefitinib in normal human epithelial cells (HMEC and 184) and nontransformed immortal cells (MCF10A and 184B5). The capability of gefitinib to block the proliferation of normal epithelial cells was also confirmed in tissue biopsies of the MMTV-c-erbB-2 transgenic mouse model. Gefitinib treatment resulted in increased expression of the cell cycle inhibitor p27 in normal mammary glands and tumor tissue by 49% and 50%, respectively, resulting in reductions of cell proliferation of 20% and 42% in normal mammary glands and tumor tissue, respec-

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tively. The effect of gefitinib on proliferation of normal or precancerous breast cells supports its role as a chemopreventive agent, because it decreases the rate of proliferation in normal epithelial breast cells that are at risk for transformation. However, the mechanisms of a chemopreventive effect of gefitinib could be more complex because the mammary epithelium is organized into two layers, a luminal epithelium and a basal myoepithelial layer. EGFR expression is found predominantly in cells of the basal myoepithelial layer and is much higher in these cells than in the luminal cells (25). The normal mammary epithelial cell lines used in the experiments of Lu et al. display characteristics of basal myoepithelial cells, which express high levels of EGFR and low levels of ER and require EGF for growth in vitro (26). Gefitinib completely inhibited the growth of these normal mammary epithelial cell lines, which suggests that gefitinib may block an early step in the initiation of a subset of hormone-independent breast cancers with a basal myoepithelial phenotype. In addition, gefitinib might also interfere with the initiation of tumors of luminal origin, because EGFR signaling appears to play an important role in the regulation of breast epithelial progenitor cells that give rise to both basal myoepithelial and luminal mammary epithelial cells (27,28).

Although the presented preclinical results support the development of gefitinib as a chemopreventive agent, its future development may be challenged by the following two issues. First, the development of tamoxifen as a preventive agent was based on comprehensive efficacy data derived from numerous large adjuvant clinical trials, and development was further supported by extensive information on its short-term and long-term side effects. Comparable efficacy and toxicity data, however, are not yet available for gefitinib. Gefitinib has mostly been studied in non–small-cell lung cancer, where partial responses occurred with oral doses of 250 mg/day in 12.0% of the patients after they had received at least two chemotherapy regimens (29) or in 18.4% of the patients after they had received one or two chemotherapy regimens (30). In breast cancer patients, efficacy data are currently limited to two phase II studies—one that reported one patient with a minor response and three patients with stable disease of more than 6 months among 34 patients with metastatic breast cancer (31) and another that reported two patients with partial responses and three patients with stable disease of more than 6 months among 19 patients with tamoxifen-resistant metastatic breast cancer (32). Thus far, gefitinib has been evaluated in patient populations unselected for the relevance of the EGFR-signaling pathway. However, two other targeted therapies—trastuzumab (Herceptin) and imatinib mesylate (Gleevec)—were assessed in patients with tumors known to overexpress or to express the target that contributed to the malignant phenotype (33,34). It is quite likely that EGFR inhibitors demonstrate antitumor activity for only a subset of patients in whom EGFR is pathogenetically involved in tumor formation or growth. Before we develop gefitinib as a chemopreventive agent, further research is needed to find and validate predictive factors that can be used to identify patients and healthy women likely to respond to gefitinib as a therapeutic and chemopreventive agent.

As a chemopreventive agent, gefitinib would be given to healthy women at risk for the disease most likely over a period of several years. The success of a preventive drug, however, will ultimately be defined by its risk-to-benefit ratio. Gefitinib has been generally well tolerated in the various clinical trials in which it has been tested. Mild (Common Toxicity Criteria—National Cancer Institute grade I/II) adverse events, however, were reported frequently. The most common side effects of gefitinib were rash, pruritus, dry skin, or acneiform rash, which occurred in 62% and 75% of the patients treated with 250 and 500 mg/day, respectively (29). Mild diarrhea occurred in 56% and 70% of the patients at 250 and 500 mg/day, respectively (29). Although these toxicities were generally mild, manageable, noncumulative, and completely reversible with cessation of the drug, these side effects might cause healthy women to stop taking gefitinib as a chemopreventive agent. In addition, a rare but potentially life threatening adverse event—interstitial lung disease—has been reported with the drug. This potential side effect associated with the use of gefitinib is reported to occur in 1%–2% of patients (35). Importantly, the incidence of interstitial lung disease among 23,000 patients in the U.S. expanded access program was reported to be lower [0.3% (36)] and no case of interstitial lung disease was reported in the U.S. phase II study of 216 patients (29). Although interstitial lung disease is a very rare adverse event, its extremely infrequent occurrence may represent an important challenge for the broad use of gefitinib as a chemopreventive agent in healthy women.

We agree with Lu et al. (12) that tyrosine kinase inhibitors are very promising agents to be studied as chemopreventive agents for breast cancer; however, a better understanding of the molecular pathways associated with clinical response would allow a more accurate and targeted selection of women who may maximally benefit from such prevention strategies. This clearly is an important area that merits further study. The preclinical data in the current report underscore the potential importance of this area of translational research.

References


