Tamoxifen: Dr. Jekyll and Mr. Hyde?

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Without regard to patient selection, other than the eligibility requirements for entry into the studies, worldwide overviews of prospective clinical trials demonstrate that adjuvant tamoxifen reduces the annual odds of death for women with invasive breast cancer by approximately 15% over 10–15 years (1). These data raise the provocative question: Should all patients with invasive breast cancer receive tamoxifen? Application of tamoxifen, irrespective of selection factors, would result in overtreatment of an enormous number of women who would not benefit to ensure the benefits for those who do. Although acceptance of tamoxifen treatment is very high, the ability to measure its target, the estrogen receptor (ER), has permitted application of this drug to those most likely to benefit: patients whose tumors express ER (1,2). Thus, ER is one of the few tumor markers that is recommended for routine clinical use by the American Society of Clinical Oncology (3).

However, tamoxifen is not ideal. Even among women with ER-positive breast cancer, only 40–50% of patients benefit, suggesting that a substantial fraction of ER-positive cancers are resistant to this drug. Moreover, tamoxifen causes both common side effects and occasional life-threatening toxicities (1,4). These observations raise a second question: Why does tamoxifen not seem to work in nearly one-half of women whose tumors appear, at least by ER measurement, to be estrogen dependent?

The answer to this question may be found in an emerging understanding of the biology of the ER and other steroid hormone receptors (5). Preclinical and clinical data over the last 20 years have demonstrated that tamoxifen is not, as originally designated, an “anti-estrogen” (6). Rather, tamoxifen has been designated a “selective estrogen receptor modulator” (SERM). This class of drugs has variable agonistic and/or antagonistic activities, depending on the type of ER (alpha versus beta) and on the coactivator and corepressor milieu in which they bind to the ER (7). Thus, it is possible that, by acting as an agonist within certain hormone-dependent breast cancers, tamoxifen, like Dr. Jekyll, might become a “Mr. Hyde.” This hypothesis is supported by in vitro studies that demonstrate that estrogen-dependent breast cancer cell lines, which are initially growth inhibited by tamoxifen and other SERMs, can become growth dependent on these same agents after long-term exposure to low concentrations (8,9). If these results hold true clinically, then it may be that a major form of resistance to tamoxifen in certain ER-positive cancers occurs because this agent acts as an estrogen, as it does in bone and liver tissue, rather than an anti-estrogen (10).

What is the mechanism of this strange transformation from Jekyll to Hyde? Once again, we turn to emerging biology. Recently published results suggest that breast cancer cell lines may become SERM dependent, in part, by modifying NF-xB activity and the Fas/Fas ligand system, thus increasing proliferation and decreasing apoptosis (9). In this issue of the Journal, Shou et al. report a series of intriguing laboratory studies that may provide further insight into the phenomenon of tamoxifen duality in hormone-dependent breast cancers (11). They have compared the biology of a HER-2–transfected variant of the most widely used estrogen-dependent human breast cancer cell line, MCF-7, with its HER-2–negative parent, in the setting of estrogen, estrogen depletion, and tamoxifen. HER-2 is one of four transmembrane proteins that belong to the epidermal growth factor receptor (EGFR) family. Three of these four proteins (HER-1, -3, and -4) bind extracellular peptide ligands, all four form homo- or heterodimers, and three of the four (HER-1, -2, and -4) transmit signals through an intra-cytoplasmic tyrosine kinase domain (12). Several retrospective clinical studies have suggested that patients with ER-positive, HER-2–positive breast cancers are less likely to benefit from endocrine therapy than patients with ER-positive, HER-2–negative tumors (13). Embedded within these studies was an observation from one investigation that has often been overlooked or dismissed as artifact: patients with HER-2–overexpressing tumors who were assigned to adjuvant tamoxifen had higher rates of recurrence and mortality than those who did not receive the agent (14,15).

In this regard, Shou et al. (11) have confirmed previously demonstrated phosphorylation “cross-talk” between these very disparate steroid hormone receptor (ER) and peptide growth factor receptor (EGFR) systems (16). [See figure 6 in Shou et al. (11), for a diagrammatic model of current understanding of this cross-talk.] Among other interesting results within this article, there are two important observations. First, in the HER-2–transfected cells, tamoxifen acted like an estrogen agonist by every measure studied. Second, the EGFR inhibitor gefitinib—presumably by inhibiting HER-2-to-ER crosstalk—restored the ER antagonistic properties of tamoxifen. These results are consistent with those of other investigators who have reported enhancement of tamoxifen activity in ER-positive, HER-2–positive cultured cells by treatment with trastuzumab, a monoclonal antibody that binds the extracellular domain of HER-2 (17).

Are these data clinically relevant? All but one of the experiments were performed in a single cultured cell line or its transfected derivative. Thus, the question remains as to whether these results can be extrapolated to other cell lines, and, more important, to the vastly heterogenous clinical situation. Nevertheless, the study has two potential clinical implications. First, recent studies have suggested that newer agents might be more effective than tamoxifen against hormone-dependent breast cancers yet retain (or even improve on) its favorable toxicity profile. Perhaps the most important of these is a class of agents known as aromatase inhibitors (anastrozole, letrozole, and exemestane). These agents prevent the peripheral and tumoral P450 aromatase

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activity that is required to convert precursors to estradiol, thus depleting estrogen-dependent breast cancers of their required ligand. Clinical investigations have demonstrated that these agents are at least as effective, if not more so, than tamoxifen in both the metastatic and adjuvant settings (18–24). Aromatase inhibitors are bereft of toxicities associated with estrogenic activity of tamoxifen and other SERMs, such as increased thrombosis and uterine cancer risk. However, they are clearly associated with problems related to estrogen depletion, including high rates of osteoporosis and bone fracture, which are of major concern in the group of patients most likely to receive them: postmenopausal women (25). Clinicians are therefore faced with the dilemma of choosing between these newer agents and the old standby, tamoxifen, weighing what appears to be modestly higher efficacy and lack of both thrombogenicity and uterine carcinogenesis of the newer agents with the established activity, proven reduction in osteoporosis, and many more women-years of experience of tamoxifen (25).

Given the choice between a SERM or an aromatase inhibitor in the adjuvant setting, the preclinical studies by Shou et al. (11) suggest that one might elect to recommend the latter in patients with ER-positive, HER-2 positive breast cancers to avoid the potential estrogen agonist activity that might be associated with tamoxifen. This concept is far from confirmed. However, it is supported by results from the retrospective clinical study discussed above (14,15), as well as by recently reported preliminary correlative science studies of HER-2 in large randomized clinical trials comparing tamoxifen with anastrozole and tamoxifen with letrozole in both classic and neo-adjuvant settings (26,27).

The second clinical implication of the results of Shou et al. (11) is that clinical trials of the combination of tamoxifen with gefitinib (and perhaps trastuzumab as well) in ER-positive, HER-2-positive breast cancers are justified. If successful, this strategy might provide the antineoplastic benefits of the aromatase inhibitors but retain the bone-sparing effect of the SERMs. Results from three phase II studies of single-agent gefitinib in unselected patients with metastatic breast cancer have been generally disappointing using classic phase II criteria for “success” (28–30). However, in each study, a few objective responses or disease stabilizations were observed. Coupled with recent reports that, in non–small-cell lung cancer, responses to gefitinib were seen almost exclusively in patients with apparent activating mutations in EGFR (31,32), the results by Shou et al. (11) suggest that this drug may yet have a role in the treatment of breast cancer, if we can be clever about its use.

Like Dr. Jekyll, tamoxifen has clearly contributed immensely to the well-being of patients. Like Mr. Hyde, cloaked in the disguise of an agonist rather than an antagonist for its receptor, it may also have harmed some. It is imperative that we now take advantage of the advances in understanding of the biology of these two receptor systems to efficiently select optimal treatment and even further reduce mortality of patients with breast cancer. These steps can be taken only by conducting well-designed clinical trials founded in translational science, such as the study reported by Shou et al. (11).

References

(21) ATAC Trials’ Group T. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmeno-


NOTES

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